Comparison of Clevidipine Versus Sodium Nitroprusside for the Treatment of Postoperative Hypertension in Cardiac Surgery Patients

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ABSTRACT

Objective: To evaluate the efficacy and safety of clevidipine (CLV) versus sodium nitroprusside (SNP) for the treatment of hypertension (HTN) in postoperative cardiac surgery patients at a community hospital.

Methods: This single-center, retrospective, cohort study included cardiac surgery patients treated with CLV or SNP for postoperative systolic blood pressure (SBP) control. The primary efficacy outcome was defined as the mean number of times the SBP rose above 140 mm Hg. Secondary outcomes included a comparative cost analysis and a safety analysis.

Results: Forty patients were included in each arm. Patients who received CLV had a higher incidence of SBP readings greater than 140 mm Hg ($p < .05$). There were no differences in safety outcomes, number of patients who received as-needed (PRN) antihypertensives, or mean number of PRN antihypertensives required. There were differences in infusion duration (22.4 hours CLV vs 15.6 hours SNP; $p = .035$), number of infusions dispensed (2.8 CLV vs 1.3 SNP; $p = .001$), and length of hospital stay (12.33 days CLV vs 7.65 days SNP; $p = .013$). However, CLV was less expensive based on the AWP cost at the time of review.

Conclusions: Although a difference in blood pressure control was seen between CLV and SNP, the safety profiles were similar between the 2 drugs. In addition, CLV remained less expensive than SNP for postoperative BP control.

Key Words—blood pressure, cardiac surgery, clevidipine, hypertension, postoperative, sodium nitroprusside

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Acute hypertension (HTN) is a common complication that affects many postoperative cardiac surgery patients. If left untreated, postoperative HTN can cause serious neurological, cardiovascular, and renal complications, making proper management crucial.¹ The best treatment options for this condition are short-acting, intravenous medications that are easily and quickly titrated to the patient's blood pressure (BP) goal.¹⁻³ Sodium nitroprusside (SNP) and clevidipine (CLV) are 2 agents commonly used in clinical practice to treat HTN in postoperative cardiac surgery patients.

Sodium nitroprusside has been a standard treatment option for postoperative HTN in cardiac surgery patients due to its rapid onset and short duration of action. However, the concern for cyanide and thiocyanate toxicity, as well as the need for extensive monitoring, makes newer agents such as CLV more preferable treatment options.^{1,4,5} Due to its pharmacokinetic profile, inactive metabolites, and resulting low-risk of toxicity, CLV use in postoperative cardiac surgery patients has been evaluated in several phase III clinical trials.^{6,7} The Efficacy Study of Clevidipine Assessing its Post-operative Anti-hypertensive Effect

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in Cardiac Surgery (ESCAPE-2) trial, the Evaluation of Clevidipine In the Perioperative Treatment of Hypertension Assessing Safety Events (ECLIPSE) studies, and a trial conducted by Powroznik et al have evaluated the use of SNP and CLV in postoperative cardiac surgery patients.^{2,3,8} These trials indicate that CLV is a safe and efficacious treatment option in postoperative cardiac surgery patients with acute HTN. Since its reintroduction to market, CLV has been utilized as an alternative agent to SNP for patients with renal and hepatic impairment due to its efficacy and safety profiles.^{6,7} This trial aims to assess the efficacy, safety, and cost of CLV compared to SNP for treatment of postoperative HTN.

PATIENTS AND METHODS

This single-center, retrospective, cohort study evaluated patients at a 489-bed community hospital. The trial was approved by the institutional review board before data collection began. Due to the retrospective nature of the study, informed consent was not necessary.

Inclusion and Exclusion Criteria

Physicians in the cardiovascular recovery (CVR) unit began routinely prescribing CLV for use in postoperative cardiac surgery patients on April 3, 2013. Electronic medical records were reviewed for patients who received CLV or SNP for postoperative BP control after this date. Patients were evaluated until September 30, 2014. There were many fewer patients who received CLV than SNP, as CLV was new to the institution at the time of this study. As such, all postoperative cardiac surgery patients 18 years of age or older who received CLV and met inclusion criteria were included in the study. An equal number of SNP patients were then consecutively and chronologically included. Patients were excluded if they were pregnant, received a radial artery graft, underwent pulmonary or thoracic surgery, had permanent ventricular pacing, or received both CLV and SNP concurrently for more than 30 minutes at any point during their hospital stay. In addition, patients who received SNP solely for intra-operative vein baths were not included in this study, as the medication was not utilized for postoperative BP control. The software utilized to gather patient data could not group patients with SNP orders based on indication of the drug.

Baseline Demographics

Baseline demographics included, but were not limited to, patient's age, gender, height, weight,

admitting alanine aminotransferase (ALT) and aspartate aminotransferase (AST), ethnicity, pre-anesthesia induction BP and heart rate (HR), admitting serum creatinine (SCr), admitting triglycerides, admitting international normalized ratio (INR), type of cardiac surgery, duration of the cardiac surgery (hours), and past medical and surgical history. Medication information included treatment duration (hours), number of infusions of CLV or SNP dispensed, infusion rates of CLV or SNP, number of dose titrations, and use of concomitant medications that could cause hypotension, hypertension, or renal or hepatic dysfunction.

Definitions

Data were collected for the entire duration of each patient's hospital stay, both in the intensive care CVR unit and after transition to a step-down floor. Systolic blood pressure greater than 90 mm Hg and less than 140 mm Hg was defined as within goal. Hospital protocol for postoperative cardiac surgery patients dictates initiation of an antihypertensive agent for SBP readings greater than 140 mm Hg. Similarly, vasopressor support is initiated for SBP readings less than 90 mm Hg. In addition, this BP range falls within the target postoperative BP range (75-145 mm Hg) used in the ECLIPSE trials.² Vital signs are measured and recorded every hour in the CVR unit. The initial infusion rate for CLV ranges from 1 to 2 mg/h. The infusion rate can be doubled at short 90-second intervals, initially. As the BP approaches goal, nurses are instructed to lengthen the time between titrations to every 5 to 10 minutes and notify a physician if/when the infusion rate reaches 21 mg/h. The initial recommended infusion rate for SNP is 0.25 mcg/kg/min. Nurses are instructed to titrate infusion rates by at least 0.25 mcg/kg/min every 5 minutes until the desired mean arterial pressure (MAP) is achieved or a maximum rate of 10 mcg/kg/min is reached. If additional BP control is needed, intravenous labetalol and metoprolol are used.

Cardiac surgery procedures included aortic aneurysm repair; aortic, mitral, or tricuspid valve repairs; aortic, mitral, or tricuspid valve replacements; on- or off-pump coronary artery bypass graft (CABG); and transcatheter aortic valve replacements (TAVR).

All inpatient medications were screened for effects on BP, renal function, and liver function. A comprehensive list of medications that can cause hypotension, hypertension, acute renal dysfunction, and acute liver dysfunction can be found in the eAppendix.

Based on the 2012 KDIGO guidelines, renal dysfunction was defined as a postoperative increase in SCr to 1.5 times the admitting SCr value.⁹ Acute hepatic dysfunction was defined as a postoperative ALT and/or AST elevation greater than or equal to 3 times the upper limit of normal (AST >123 units/L and ALT >162 units/L).¹⁰ Hypertriglyceridemia was defined as a triglyceride level greater than 500 mg/dL, as this level is significant to warrant discontinuation of CLV or a reduction in concurrently administered lipids due to an increased risk of pancreatitis.⁴ In addition, per the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, a triglyceride level of greater than 500 mg/dL warrants modification to medication therapy.¹¹

Outcomes

The primary efficacy outcome was defined as the mean number of times the SBP rose above 140 mm Hg. Secondary outcomes included a comparative cost analysis and a safety analysis of the following: acute renal dysfunction, acute hepatic dysfunction, hypertriglyceridemia, number of times SBP fell below 90 mm Hg, and in-hospital mortality. The occurrence of postoperative atrial fibrillation was also evaluated, as CLV can cause atrial fibrillation in rare cases. The cost of CLV and SNP was evaluated. At the time the study article was written, a 100 mL premix vial of CLV 0.5 mg/mL cost \$240.00 (AWP) and a 2 mL

vial of SNP 25 mg/mL cost \$773.39 (AWP). A lower cost of CLV, as well as the safety and efficacy benefit shown in previous studies, supports the importance of this study

Statistical Analysis

Baseline demographics, as well as primary and secondary outcomes, were analyzed using Student's *t* test for continuous data or chi-square or Fisher's exact test for categorical data. A *p* value of less than .05 indicated statistical significance. All analyses were performed with IBM SPSS Statistics (IBM, Inc., Armonk, NY) for Windows.

RESULTS

A total of 165 charts were reviewed for patients with an order for CLV or SNP from April 3, 2013 to September 30, 2014. Only 40 patients in each group were eligible based on predefined inclusion and exclusion criteria (Figure 1). Patients were well matched in regard to baseline demographics (Table 1). One significant difference between groups included a higher admitting SCr in the CLV group (1.8 ± 1.1 vs 1.1 ± 0.3 ; $p < .05$). This finding was expected, as renal dysfunction was a targeted patient group for CLV use in the CVR unit. Other differences included significantly more CLV patients with heart failure with reduced ejection fraction (HFrEF) (16 vs 6; $p = .012$), as well as significantly more CLV patients with aortic valve replacements (AVR) (14 vs 6; $p = .039$).

Figure 1. Study inclusion and exclusion. CLV = clevidipine; SNP = sodium nitroprusside.

Table 1. Baseline demographics

Characteristic	SNP (<i>n</i> = 40)	CLV (<i>n</i> = 40)
Age, years, mean $\pm$ SD	69 $\pm$ 9.3	72.1 $\pm$ 11
Male, <i>n</i> (%)	28 (70)	27 (67.5)
Ethnicity, <i>n</i> (%)		
Caucasian	37 (92.5)	31 (77.5)
Black	3 (7.5)	8 (20)
Unknown	0 (0)	1 (2.5)
Weight, kg, mean $\pm$ SD	93.1 $\pm$ 26.6	87.2 $\pm$ 20.9
Admitting SCr, mg/dL, mean $\pm$ SD*	1.1 $\pm$ 0.3	1.8 $\pm$ 1.1
Liver impairment, <i>n</i> (%)	11 (27.5)	13 (32.5)
History of atrial fibrillation, <i>n</i> (%)	9 (22.5)	10 (25)
HFrEF, <i>n</i> (%)*	6 (15)	16 (40)
Pre-anesthesia induction SBP, mm Hg, mean $\pm$ SD	138.7 $\pm$ 23	140.3 $\pm$ 21.8
Home antihypertensive medications, <i>n</i> (%)	36 (90)	38 (95)
Type of cardiac surgery, <i>n</i> (%)		
On-pump CABG	26 (65)	19 (47.5)
Off-pump CABG	1 (3)	0 (0)
Aortic aneurysm repair	7 (17.5)	9 (22.5)
Aortic valve replacement*	6 (15)	14 (35)
Mitral valve repair	5 (12.5)	6 (15)
Mitral valve replacement	3 (7.5)	4 (10)
Tricuspid valve repair	1 (2.5)	5 (12.5)
TAVR	0 (0)	1 (2.5)
Duration of surgery, hours, mean $\pm$ SD	4 $\pm$ 0.8	4.2 $\pm$ 1.5

Note: CABG = coronary artery bypass grafting; CLV = clevidipine; HFrEF = heart failure with reduced ejection fraction; kg = kilograms; SBP = systolic blood pressure; SCr = serum creatinine; SNP = sodium nitroprusside; TAVR = transcatheter aortic valve replacement.

**p* < .05.

The difference in the mean number of SBP readings greater than 140 mm Hg was significant between treatment groups in favor of SNP (3.8 vs 12; *p* = .01). To adjust for the total number of BP readings, the number of SBP readings above 140 mm Hg was divided by the total number of SBP readings recorded, giving a percentage of SBP readings above 140 mm Hg. This value was also significantly different between treatment groups in favor of SNP (12.6% vs 22.7%; *p* = .025) (Table 2).

The mean average infusion rate of CLV was 3.06 mg/h. There was also a significant difference in the mean average infusion duration between the CLV and SNP groups (22.4 hours vs 15.6 hours; *p* = .035). A longer infusion duration resulted in more SBP readings recorded, which could increase the likelihood of having more SBP readings above 140 mm Hg if the patients had poorly controlled BP.

With regard to safety, there were no significant differences between groups (Table 2). No patients in either treatment group had triglycerides greater than or equal to 500 mg/dL. There were no differences between CLV and SNP in the mean number of concomitant as-needed (PRN) antihypertensives required during the infusion (0.4 vs 0.225; *p* = .460) and number of patients who received PRN antihypertensives (7 vs 6; *p* = .762) (Table 2). In addition, all infusions of CLV and SNP dispensed were administered. However, there was a statistically significant difference between the CLV and SNP groups in the mean number of infusions dispensed (2.8 vs 1.3; *p* = .001), which coincides with the statistically significant difference in the infusion durations (*p* = .035). Furthermore, there was a difference in length of stay (days) between patients in the CLV and SNP groups (12.33 vs 7.65; *p* = .013).

Table 2. Primary and secondary outcomes

Outcomes	SNP (<i>n</i> = 40)	CLV (<i>n</i> = 40)	<i>p</i> value
Mean SBP readings >140 mm Hg, %	12.6	22.7	0.025
Mean SBP readings >140 mm Hg, <i>n</i>	3.8	12	0.010
In-hospital mortality, <i>n</i> (%)	0 (0)	4 (10)	0.116
Postoperative AST >123 units/L, <i>n</i> (%)	1 (2.5)	2 (5)	1.000
Postoperative ALT >162 units/L, <i>n</i> (%)	1 (2.5)	2 (5)	1.000
Postoperative SCr ≥1.5 times admission baseline, <i>n</i> (%)	5 (12.5)	8 (20)	0.363
Mean SBP readings <90 mm Hg, <i>n</i>	0.03	0.08	0.312
Postoperative atrial fibrillation, <i>n</i> (%)	16 (40)	19 (47.5)	0.499
Mean no. of PRN antihypertensives, <i>n</i>	0.225	0.4	0.460
Patients who received PRN antihypertensives, <i>n</i> (%)	6 (15)	7 (17.5)	0.762
Length of hospital stay (days), mean ± <i>SD</i>	7.65 ± 7.6	12.33 ± 8.8	0.013
Mean number of infusions dispensed, <i>n</i>	1.3	2.8	0.001
Mean number of titrations (↓), <i>n</i>	6.78	6.8	0.98
Mean number of titrations (↓), <i>n</i>	5.15	4.95	0.798
Mean average infusion duration, hours	15.6	22.4	0.035
Mean average infusion rate	3.06 mg/h	0.32 mcg/kg/min	—

Note: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CLV = clevidipine; PRN = as needed; SBP = systolic blood pressure; SCr = serum creatinine; SNP = sodium nitroprusside.

However, this was not unexpected with CLV use, as patients who received this infusion had more health complications at baseline.

Although patients in the CLV group had a longer mean infusion duration and higher number of infusions dispensed, CLV is still a less costly option when comparing the AWP of CLV and SNP. An average of 2.8 CLV infusions would cost \$672.00 and an average of 1.3 SNP infusions would cost \$1,005.41. The lower cost of CLV adds support for its use in postoperative cardiac surgery patients.

DISCUSSION

Patients in the CLV group had a higher mean percentage of SBP readings greater than 140 mm Hg (Table 2), which could be attributed to poor infusion titration, target SBP readings greater than 140 mm Hg set by the physician, and/or a small patient population. Poor infusion titration could be due to poor nursing education on the use of CLV due to its recent addition to the hospital formulary at the time of this study. Poor titration of the drug versus instruction from a physician to target a higher SBP was difficult to distinguish. Paper charting was used in the CVR

unit, and this information was frequently not documented for every patient.

In addition, although the efficacy of CLV was not shown to be greater than SNP in this study, the safety of CLV is comparable to previous studies.^{2,3,8} There were no statistically significant differences between groups in terms of mortality, AST, ALT, or SCr elevation; mean number of times patients' SBP readings fell below 90 mm Hg; or occurrence of postoperative atrial fibrillation. Furthermore, no patients in either group had triglycerides greater than or equal to 500 mg/dL before or after study drug administration. These findings demonstrate that CLV is a safe option for patients, even those with renal failure. The lower cost of CLV, in addition to the safety seen in this study, adds support for its use in postoperative cardiac surgery patients.

Patients in the CLV group were shown to have longer length of hospital stay. This could be attributed to poor infusion titration, but it may also be due to the fact that patients in the CLV group appeared to be both sicker and slightly older at baseline. Patients in the CLV group had a higher SCr and higher incidence of HFrEF at admission.

There were 4 patient cases of mortality in the CLV group and no cases in the SNP group. The cases of mortality are not expected to be related to CLV use. These patients were elderly, had very long hospital stays, and had many comorbid conditions such as diabetes, heart failure, and renal failure at hospital admission.

There are several limitations to this study. This was a single-institution, retrospective chart review at a community hospital that focused on the use of CLV and SNP for treatment of postoperative HTN. The retrospective nature of the study allowed for potential error in data collection from the electronic and scanned medical records. In addition, all patients included in the study were in the CVR during the time of CLV or SNP infusions. This CVR unit utilizes only paper charting, and nursing and physician documentation was heavily relied upon. Error in documentation at the time of patient hospitalization, as well as bias when interpreting and recording data, could have occurred.

CLV utilization during the study period compared to SNP was small, which limited the study population size and could have impacted results. SNP was utilized more frequently during the time of the study, as CLV was recently reintroduced to market and was new to the institution. In addition, SNP can be used for other indications besides postoperative BP control. For example, the software utilized to pull patient data could not distinguish between those patients who received SNP solely for intraoperative vein baths and those who received the drug for BP control. Thus, those patient charts had to be reviewed and then excluded.

The study time period contained the initial experience with CLV in the CVR unit, and unfamiliarity with the medication and infusion titration could have affected the results of the study. The mean average infusion rate of CLV was very low compared to a maximum infusion rate of 21 mg/h.⁴ This rate is 7 times the mean average infusion rate seen in this study. The primary outcome results, as well as a longer infusion duration seen with CLV, could be attributed to poor titration of the drug. Better education for nurses, written titration instructions, and familiarity of CLV use will be necessary for future use of CLV at this institution.

In addition, data for other factors that can lead to elevated BP following surgery were not gathered. This could have had an effect on the results of the study if poor BP control was not caused from either

CLV or SNP, but rather from poor pain control or excess fluid after surgery. Finally, the external validity of this study may be affected due to the small, mostly Caucasian, male population.

As new medications are developed in the field of cardiology, it is important that pharmacists take the initiative to provide education to physicians and nurses on the appropriate use of therapy. This becomes especially true when appropriate titration is imperative for efficacy of the drug, as seen with CLV.

CONCLUSIONS

Although there was a difference in efficacy between the 2 agents, the safety profiles were similar between CLV and SNP. This is consistent with previous large population studies. In addition, although patients in the CLV group had longer mean infusion durations, more infusions dispensed, and longer hospital stays, this was not unexpected as patients who received CLV generally had more health complications at baseline. Finally, CLV still remained a less costly treatment option.

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