COST-EFFECTIVENESS OF INTRAVENOUS NICARDIPINE VERSUS SODIUM NITROPRUSSIDE FOR POSTOPERATIVE HYPERTENSION AFTER CARDIAC SURGERY

BY

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ABSTRACT

Postoperative hypertension after cardiac surgery is common and associated with substantial morbidity. Both sodium nitroprusside (SNP) and nicardipine (NIC) are effective in its management. SNP is inexpensive, but associated with labile blood pressure (BP) control, cardiac ischemia, and metabolite toxicity. NIC is well tolerated and provides stable BP control, but is limited by high acquisition cost. We conducted a cost-effectiveness analysis from an institutional perspective of NIC versus SNP in subjects experiencing postoperative hypertension after cardiac surgery.

A retrospective, cohort study identified subjects who underwent coronary artery bypass grafting (CABG) and/or valve surgery at our institution between 2007-2009. We included adults experiencing postoperative hypertension requiring ≥30 minutes of either NIC or SNP. Institutional-specific data from the Society of Thoracic Surgeons and University HealthSystem Consortium national databases and our financial and electronic medical records were used. The number of infusion rate changes divided by the infusion duration was calculated. We considered ≥ 1 dose change/hour to represent excessive dose changes and presumably uncontrolled blood pressure. The rate per 100 subjects in each group who avoided excessive dose changes served as the efficacy variable for the economic model. Direct postoperative costs were calculated. Data were compared with t, Wilcoxon Rank Sum, Chi-square, or Fisher's exact tests as appropriate. Log-binomial regression was used to control for surgery type and severity of illness.

Of the 112 subjects identified, 72 received NIC and 40 SNP. Demographics including hypertension history, number of preoperative antihypertensive agents, surgery type, and postoperative length of stay were not significantly different. NIC required significantly fewer

dose changes/hour (1.2±1.6) versus SNP (1.7±1.8, p=0.004). After controlling for surgery type and severity of illness, the risk of excessive dose changes was 60% higher in those subjects prescribed SNP compared to those prescribed NIC (adjusted relative risk = 1.60, 95%CI, 1.10-2.34, p=0.0147). In the entire cohort and each specific surgery type, NIC remained cost-effective when compared to SNP.

NIC use may be limited due to decisions based solely upon acquisition costs. We found that NIC resulted in less frequent dose changes and was cost-effective when compared to SNP in the treatment of post-cardiac surgery hypertension.

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INTRODUCTION

In the United States, 552,000 open-heart surgical procedures are performed annually (2006 data), including coronary artery bypass grafting (CABG), valve replacement or repair, and thoracic aortic procedures.[1] Of these procedures, 253,000 patients underwent 448,000 CABG procedures as a treatment for severe coronary artery disease.[1] The mean inpatient hospital charge for CABG is $112,337 (2007 data). CABG is associated with an in-hospital mortality rate of 1.95%.[1] Whereas, 104,000 involve surgical valve procedures that have a mean inpatient charge of $157,888 (2007 data). The in-hospital mortality rate for those undergoing valve surgery is 4.7%.[1] Despite significant advancements in these procedures, morbidity associated with the operations remains substantial.

One of the most common complications of cardiac surgery is hemodynamic instability. Patients are rarely normotensive early after surgery. Approximately 22%-54% of patients develop postoperative hypertension which is primarily due to an increased systemic vascular resistance.[2-7] Postoperative hypertension may be life-threatening and is associated with significant morbidity, including myocardial ischemia or infarction, poor ventricular function, hemorrhage, cerebrovascular accidents, and renal failure.[7-13] Risk factors for postoperative hypertension are poorly characterized but are reported to include preoperative factors such as history of hypertension, diabetes, vascular disease, advanced age, and renal disease.[14] Intraoperative risk factors include surgery type, technique and duration as well as anesthesia technique and agents used.[14] Postoperative risk factors include: pain, anxiety, hypothermia, anesthetic emergence, hypoxia, hypercarbia, endotracheal tube placement, bladder distension, antihypertensive agent withdrawal, hypervolemia, hypovolemia, myocardial ischemia, drug

interactions, increased intracranial pressure, pulmonary embolism, vasopressor therapy, and brochodilator use.[14]

The management of postoperative hypertension involves removal or treatment of potential underlying etiologies (e.g. treatment of pain or anxiety, raising core body temperature, etc) and frequently necessitates the use of intravenous antihypertensive agents. Several intravenous drug choices are available for this indication including: beta-blockers, hydralizine, fenoldopam, enalaprilat, nitrates, and calcium channel blockers. As a result of their strong vasodilatory actions and rapid onset of action, sodium nitroprusside (SNP) and nicardipine (NIC) are most frequently used to treat postoperative hypertension following cardiac surgery.[14]

SNP is a potent vasodilator that affects both the arterial and venous side of the circulatory system. The parent compound is metabolized by the blood vessels to nitric oxide which activates the guanyl cyclase-cyclic guanosine monophosphate (GMP) pathway leading to potent vasodilation.[15] This leads to significant reductions in systemic vascular resistance, mean arterial pressure, pulmonary vascular resistance, and cardiac preload. These changes typically result in an increase in cardiac output. Administration of SNP usually begins with a starting dose of 0.25-0.5 mcg/kg/min continuous infusion, which is increased every 5 to 10 minutes in increments of 0.5-1 mcg/kg/min until the blood pressure is within a desired range.[16] The product labeling suggest a maximum infusion rate of 10 mcg/kg/min, however, in clinical practice infusion rates infrequently exceed 5 mcg/kg/min due to the risk of acute cyanide toxicity (which is a byproduct of SNP metabolism).[14-17]

Like SNP, NIC is also a potent vasodilator; however, NIC differs from SNP in that it selectively dilates the arterial side of the circulatory system.[17] NIC is a dihydropyridine calcium channel blocker which prevents calcium ions from entering vascular smooth muscle cells.

Vascular smooth muscle contraction depends upon extracellular calcium ion movement into these cells through specific ion channels. Unlike the non-dihydropyridine calcium channel blockers verapamil and diltiazem, NIC has minimal effect on cardiac conduction or inotropy.[14,15,18] NIC causes a significant reduction in systemic vascular resistance, mean arterial pressure, and an increase in cardiac output. Unlike SNP, pulmonary vascular resistance and cardiac preload are not usually altered by NIC. For a more gradual reduction in blood pressure, a continuous infusion of NIC is typically initiated at 5mg/hour and increased by 2.5 mg/hour every 15 minutes up to a maximum infusion rate of 15mg/hour. Following obtainment of the desired blood pressure the NIC infusion rate is often decreased to 3 mg/hour to avoid hypotension. For a more rapid reduction in blood pressure the time between infusion rate changes can be decreased from every 15 minutes to every 5 minutes. Clinically, and in early clinical trials, NIC has been administered as a 2.5 mg IV bolus (repeated every 10 minutes for up to 12.5 mg total) and then transitioned to a continuous infusion for maintenance of blood pressure.

The ideal drug to treat postoperative hypertension would be potent, titratable, available in an intravenous formulation, have a rapid onset of action, and a short elimination half-life.[14,19] While SNP possesses these characteristics, and has been used frequently for this indication, it carries with it other less desirable properties. For example, after administration of SNP many patients experience excessive preload reduction as a result of strong venous dilation; this may precipitate hypotension and require volume resuscitation to normalize blood pressure.[14-17] As a consequence of the hypotension, patients may also experience a reflex tachycardia, creating increased oxygen demands on the heart.[15,17] Shunting in the pulmonary and coronary systems, which causes worsening of tissue oxygenation, has also been experienced with SNP use.[4,14,15,17] Conceivably, this would prolong the required duration of mechanical ventilation. Lastly, the

potential for patients to accumulate toxic metabolites during administration of SNP has an unacceptably high prevalence.[16,17]

More recently, intravenous NIC has been considered an effective alternative to SNP.[19-28] While NIC possesses the same desirable properties of an ideal agent for postoperative hypertension, it lacks the adverse effects of SNP described above.[18] Investigations comparing NIC and SNP have concluded that the drugs possess an equivalent ability to reduce blood pressure.[19-28] However, NIC has been associated with a more rapid time to obtainment of the goal blood pressure.[19-28] Additionally, once the blood pressure goal is achieved studies have concluded NIC requires significantly less dose changes, indicating a more stable blood pressure during NIC use.[19,22,26,28] Also of clinical importance is the fact that NIC has not been associated with excessive venous dilation or reflex tachycardia.[19-28]

LITERATURE REVIEW

To date, four small clinical trials have compared NIC to SNP for the management of hypertension in patients undergoing coronary artery bypass grafting (CABG).[20-24] van Wezel and colleagues conducted a randomized, open-label, single center, controlled trial of subjects undergoing isolated and elective CABG. The results of this study are published as two separate manuscripts.[20,21] They conducted an extensive hemodynamic assessment and an electrocardiographic and enzymatic screening for myocardial ischemic changes after sternotomy. Subjects were excluded if they had a left ventricular end-diastolic pressure >12 mmHg, a left ventricular ejection fraction <50%, atrioventricular conduction defects, unstable angina, or were to undergo any other cardiac surgical procedure (e.g. valve replacement, etc.). One-hundred and twenty patients were eligible for inclusion and were administered intravenous NIC (n=40), SNP (n=40), or no study drug (n=40). Active drug was initiated prior to surgery 10 minutes after

intubation, at an initial infusion rate of 3 mcg/kg/min for NIC and 1 mcg/kg/min for SNP. Infusion rates were adjusted to maintain blood pressures between 80 to 120% of the (post-intubation) baseline blood pressure. Infusions were not discontinued until after sternotomy. Hemodynamic and electrocardiographic assessments were conducted 10 minutes after intubation (baseline), just prior to incision, and after sternotomy and the pericardial sack was opened.

Baseline demographics, including age, weight, left ventricular end diastolic pressure, severity of coronary artery disease, oral preoperative medication use, and preoperative hemodynamics, were similar between groups. Subjects administered NIC received a mean (±SD) infusion rate of 2.9±0.9 mcg/kg/min (7.1 mg/hr for a 70kg patient) for a mean (±SD) duration of 33±7 minutes. Subjects administered SNP received a mean (±SD) infusion rate of 1.7±0.5 mcg/kg/min for a mean (±SD) duration of 30±4 minutes. Among the control patients, 43% (17/40) required the unplanned administration of SNP (after sternotomy and assessment) to control perioperative hypertension. Compared to baseline, improvements in the post-sternotomy hemodynamics were noted in subjects receiving SNP and NIC. These groups both experienced significantly lower mean arterial blood pressures (MAP), systemic vascular resistance (SVR), significantly higher cardiac index (CI), and no changes in pulmonary capillary wedge pressures (PCWP). In contrast, the control group did not experience improvements in MAP, SVR, CI, but experienced a significant increase in PCWP. After sternotomy the percent of subjects who experienced changes on electrocardiogram consistent with myocardial ischemia differed between groups. Ten percent (4/40) of those receiving NIC, 25% (10/40) of those receiving SNP, and 28% (11/40) in the control group experiencing this adverse event. Post-sternotomy creatine phosphokinase-MB (CKMB) was measured in subjects and found to be elevated (>70 IU/L) in 2.5% (1/40) of subjects in the control and NIC groups, and 5% (2/40) in the SNP group. The

authors concluded that SNP and NIC were equally effective at controlling hypertension after sternotomy, however, myocardial ischemia occurred in half as many patients treated with NIC when compared to those receiving SNP or no antihypertensive drug therapy.

David and colleagues conducted a randomized, open-label, multi-center trial of subjects undergoing isolated CABG.[22] The primary study objective was the percent of subjects reaching a predefined MAP goal of <90 mmHg within 50 minutes after initiation of treatment for postoperative hypertension. To be eligible for enrollment, subjects had to experience an elevation of MAP >100 mmHg within 3 hours after isolated CABG. Subjects were excluded if they had: left ventricular end-diastolic pressure >15 mmHg, left ventricular ejection fraction <45%, frequent or severe arrhythmias, required any other cardiac surgical procedure (e.g. valve replacement, etc.), NYHA class III or IV heart failure, severe liver failure, or had renal failure. Seventy-four subjects were eligible for inclusion and were randomized to treatment within 10 minutes of being admitted to the intensive care unit, subsequently, 36 subjects were administered intravenous NIC, and 38 subjects received SNP. Infusion rates were adjusted per protocol to maintain MAP at 85±5 mmHg. Subjects receiving NIC, were administered 2.5mg IV boluses (every 10 minutes up to 12.5 mg) and transitioned to an initial continuous infusion between 2-4 mg/hr. SNP was administered as a continuous infusion starting at 0.5 mcg/kg/min up to a maximum dose of 6 mcg/kg/min.

Baseline demographics, including age, gender, weight, body surface area, left ventricular ejection fraction and other hemodynamic parameters, history of myocardial infarction or hypertension, severity of coronary artery disease, and cardiopulmonary bypass or aortic cross clamp time were similar between groups. Subjects administered NIC received a mean (±SD) infusion rate of 6.6±5.1 mg/hour and subjects administered SNP received a mean (±SD) infusion

rate of 1.43±0.74 mcg/kg/min. Of those who were randomized to NIC, 92% (35/38) reached the primary outcome (MAP<90 within 50 minutes) within 26±24 minutes. Whereas, 82% (29/36, p>0.05 compared to NIC) of those randomized to SNP reached the primary outcome within 36±16 minutes (p<0.01 compared to NIC). Those subjects receiving SNP experienced a significant increase in heart rate (SNP=+13 bpm, NIC=+2 bpm, p<0.001) after drug initiation, and elevations in pulmonary artery pressure (PAP), right atrial pressure (RAP) and PCWP. Those given NIC experienced an increase in cardiac index and a decrease in SVR compared to those receiving SNP. NIC provided more stable blood pressure control with 51±24% of MAP readings being within the pre-specified range goal (80-90 mmHg), compared with 36±16% of those receiving SNP being within this range (p=0.058). The number of dose changes made after reaching the dosing plateau (dose stable for 20 minutes) was significantly lower in the NIC group (1.1±1.6) compared to the SNP group (2.7±2.6, p<0.01). Subjects receiving NIC experienced severe hypotension (defined as MAP <70 mmHg) less frequently (20%) than those in the SNP group (85%). Presumably due to the arterial selectivity, those in the NIC group required less postoperative blood (924±644 mL versus 1306±901 mL, p=0.08) and total fluid intake (2410±934 mL versus 3003±1095 mL, p=0.05) compared with the SNP group. The authors concluded that SNP and NIC were equally effective at reducing hypertension after CABG, however unlike SNP, NIC provided more stable blood pressure control, less severe hypotension, and had a positive impact on several other clinically important variables that benefit myocardial oxygen balance.

Combes and colleagues conducted a randomized, open-label, single center trial of subjects undergoing CABG.[23] The primary study objective was the effectiveness of either NIC or SNP in lowering MAP <85 mmHg. To be eligible for enrollment, subjects had to experience an

elevation of MAP >95 mmHg for 10 minutes after CABG. Subjects were excluded if they had cardiac, renal or hepatic failure. Twenty subjects were eligible for inclusion and were randomized to treatment. Four subjects treated with SNP required discontinuation of therapy secondary to severe hypotension and thus, 6 subjects were administered intravenous SNP, and 10 subjects received NIC and were eligible for analysis. Subjects receiving NIC, were administered 2.5mg IV boluses (every 10 minutes up to 12.5 mg) and transitioned to an initial continuous infusion between 2-4 mg/hr. SNP was administered as a continuous infusion starting at 0.5 mcg/kg/min up to a maximum dose of 6 mcg/kg/min.

Baseline demographics, including age, weight, body surface area, hemodynamic parameters, history of hypertension, number of bypass grafts, and cardiopulmonary bypass times were similar between groups. Subjects administered NIC received a mean (±1 SD) infusion rate of 3.3±0.7 mg/hr and subjects administered SNP received a mean (±1 SD) infusion rate of 4.5±2.4 mcg/kg/min. On average, those randomized to NIC experienced a statistically significant decrease in MAP within 15 minutes of drug initiation (decrease in MAP from 105±17 to 97±15, $p<0.05$), whereas those randomized to SNP did not experience a statistically significant decrease in MAP until 60 minutes of drug initiation (decrease in MAP from 110±13 to 93±14, $p<0.05$). For the first 60 minutes after drug initiation, NIC provided a significantly lower MAP when compared to SNP. This difference was no longer statistically significant at the 60 minute, 6, 12, and 24 hour assessments. Systemic vascular resistance index was also significantly lower in the NIC group compared to the SNP group at the 15, 30, 45, and 60 minute time points. With exception of one patient in the SNP group experiencing a myocardial infarction, no other patients experienced ischemia. The authors concluded that SNP and NIC were effective at reducing

hypertension after CABG, however unlike SNP, NIC provided more timely blood pressure control and less severe hypotension.

Kwak and colleagues conducted a randomized, open-label, single center trial of subjects undergoing CABG.[24] The primary study objective was the effectiveness of either NIC or SNP in maintaining systolic blood pressure (SBP) between 120-140 mmHg. To be eligible for enrollment, subjects had to experience an elevation of SBP >150 mmHg within 6 hours after CABG. Subjects were excluded if they had neurologic or renal abnormalities, a left ventricular ejection fraction < 40%, required treatment preoperative with vasodilators, or needed reoperation after CABG secondary to hemorrhage. Forty-seven subjects were eligible for inclusion and were randomized to treatment. Twenty-six subject were administered intravenous NIC, and 21 subjects received SNP. Curiously, both NIC and SNP were initiated at 2 mcg/kg/min (8.4 mg/hour for a 70kg patient) as a continuous infusion for 10 minutes, despite the equipotency of NIC and SNP having never being previously described. If the SBP was higher than 140 mmHg, the infusion was increased by 1 mcg/kg/min every 10 minutes until the subjects were within the 120-140 mmHg goal range. If the SBP decreased below 120 mmHg, the infusions were held; if the SBP dropped below 100 mmHg, phenylephrine was used to increase blood pressure.

Baseline demographics, including age, gender, body surface area, history of myocardial infarction, baseline hemodynamics, and use of beta blockers, angiotensin-converting enzyme inhibitors, or nitrates were similar between groups. Subjects administered NIC received a mean cumulative dose (±SD) of 25±21 mg over a mean duration of 183±150 minutes. Subjects administered SNP received a significantly larger mean cumulative dose (±SD) of 55±58 mg ($p<0.001$) over a significantly longer mean duration of 554±457 minutes ($p<0.001$). The prevalence of hypotension requiring intervention with phenylephrine was higher in the NIC

group with 23% (6/26) needing intervention, compared with 5% (1/21) in the SNP (p=N/S). According to the authors, this was potentially the result of a relatively high average infusion rate of NIC at 8.4 mg/hr. Ten minutes after the initiation of the infusion, those receiving either NIC or SNP experienced a statistically significant decrease in SBP compared to the pre-infusion SBP ($p<0.05$). At this same study time point, those receiving NIC experienced significant improvements in CI, SVI, and SVR when compared to the SNP group ($p<0.05$). In contrast with the result of van Wezel and colleagues, Kwak et al did not observe a clinically significant increase (e.g. >70 IU/L) in CKMB after drug initiation, suggesting a lack of ischemic event occurrence. While the CKMB values 60 minutes after the initiation of the infusions were higher ($p<0.05$) than baseline, none of the post infusion CKMB values exceeded 25 IU/L. The authors concluded that both SNP and NIC decrease SBP effectively, however the onset in which NIC provides benefit is faster than SNP and the required duration of infusion is shorter with NIC.

To date, the largest clinical trial investigating the management of postoperative hypertension after cardiac surgery with intravenous dihydropyridine calcium channel blockers and sodium nitroprusside was conducted by Aronson and colleagues.[25] This study did not compare SNP and NIC head-to-head but rather evaluated a new agent, clevidipine (CLV), which is an ultra-short acting dihydropyridine calcium channel blocker (similar to nicardipine). The Evaluation of CLevidpine In the Perioperative Treatment of Hypertension Assessing Safety Events trial (ECLIPSE) consisted of three prospective, randomized, open-label, multi-center trials of subjects undergoing cardiac surgery, during which CLV was compared to nitroglycerin (NTG), SNP, and NIC. The primary objective of the study was to compare the safety of CLV to these three commonly used perioperative antihypertensive drugs. The safety assessment utilized a composite endpoint of death (all cause), stroke (hemorrhagic or ischemic), myocardial

infarction, and renal dysfunction. The secondary endpoint included an assessment of the efficacy of the drugs magnitude and duration of blood pressure excursions above or below a predefined SBP range. To accomplish this, the study evaluated the area under the curve (AUC) of the blood pressure excursions, normalized per hour. This was analyzed as the summation of the integrated SBP-time curve excursions, capturing the product of magnitude (mmHg) and duration (minutes) of blood pressure outside the predetermined SBP ranges. The SBP ranges were 65-135 mmHg intraoperatively (from chest incision to closure), and 75-145 mmHg preoperatrively and postoperatively. A post-hoc analysis was conducted to evaluate tighter blood pressure ranges (raising the lower end of the blood pressure range by 10, 20, and finally 30 mmHg) and to control for confounders of the risk of death. Eligible subjects were >17 years old, schedule to undergo cardiac surgery including on or off-pump CABG, minimally invasive CABG, and/or valve replacement or repair. Subjects were excluded if: they were females of childbearing potential, had a cerebrovascular accident ≤ 3 months before randomization, were intolerate/hypersensitive to calcium channel blockers, sodium nitroprusside, or nitroglycerin, allergic to the lipid vehicle of clevidipine, required permanent ventricular pacing, were participating in another clinical trial within 30 days of study start, or had a condition deemed by the investigator to place the patient at risk for participating. In the CLV vs NTG sub-study, 268 patients received CLV and 278 NTG. In the CLV vs SNP sub-study, 296 patients received CLV and 283 SNP. In the CLV vs NIC sub-study, 188 patients received CLV and 193 NIC. Active drug was initiated at the discretion of, and titrated to a range deemed appropriate by, the study physician at the subjects' institutions. All antihypertensive medication use was recorded. CLV was initiated at an infusion rate of 0.4 mcg/kg/min and was titrated as tolerated in doubling increments every 90 seconds up to a rate of 3.2 mcg/kg/min. Rates higher than 3.2 and up to 8

mcg/kg/min were tolerated for only 2 hour durations secondary to lipid load restrictions, which could not exceed 2.5 g/kg/24h. The administration of NTG, SNP, and NIC were not regulated by the clinical trial protocol and were to be administered as they normally would in clinical practice.

Baseline demographics, in all three sub-studies were similar between groups. A history of hypertension requiring medication was common among all participants, and was significantly higher (96% versus 89%) in the CLV group compared to those receiving NIC. Surgical type and complexity did not differ between groups, with CABG being the most commonly performed procedure (~75%), followed by valve only surgery (12%). The remaining subjects underwent CABG+valve or repeat cardiac surgery. With exception of the CLV versus NTG study, infusion rates, volumes, and durations were not significantly different between the groups. In the CLV versus SNP study, the use of adjunctive antihypertensive agents was higher among those randomized to SNP. The primary composite safety outcome did not differ significantly between CLV and NTG or NIC. However, the incidence of the 30 day all cause mortality was higher in the SNP group (4.7%) than CLV (1.7%, p=0.0445). Multiple logistic regression for treatment effect (CLV vs SNP) as an independent variable in a model that included influential variables such as duration of surgery, age, BP excursion AUC, and medical history did not find a significant association between drug use and mortality (OR=1.968, 95%CI 0.619-6.257, p=0.25) When all three studies were combined, CLV was shown to better maintain SBP within the pre-specified blood pressure range than the comparators. This was largely driven by wider excursions in BP in the NTG and SNP groups. When compared with NIC, CLV did not demonstrate superior control until the target range was narrowed by 30 mm Hg (i.e. 105-145 pre/postop and 95-135 intraop, p=0.0231). The authors concluded that CLV was as safe as the

NTG, SNP, and NIC in this setting and provided more stable blood pressure control only when compared to NTG and SNP.

NIC has been compared to SNP in other patient populations with similar results to the previously described studies in cardiac surgery. Halpern and colleagues published a prospective, randomized, multicenter trial comparing NIC versus SNP in 139 post-surgical patients.[19] They concluded that NIC and SNP were equally effective at reducing blood pressure, but that NIC controlled blood pressure more rapidly and required less dose changes (1.5±0.2 versus 5.1±1.4, p=0.05). Adverse effects were observed in 7% of those receiving NIC (5/71) and 18% of those receiving SNP (12/68). Dorman and colleagues published a prospective, randomized, double-blind, controlled single-center trial comparing NIC versus SNP in 60 patients undergoing carotid endarterectomy who experienced breakthrough hypertension postoperatively.[26] They found that 83% of those randomized to NIC versus 23% of those receiving SNP achieved blood pressure control within 10 minutes ($p<0.01$). After control was obtained, 41% (12/29) of the NIC subjects versus 83% (24/29) of the SNP subjects required additional titrations of their infusions ($p<0.05$). Roitberg and colleagues published a prospective, randomized, open-label, single-center trial comparing NIC versus SNP in 163 patients with subarachnoid or intracerebral hemorrhage needing blood pressure control.[27] Subjects randomized to NIC (74) required 5.7 dose adjustments per day, which was significantly less than those subjects randomized to SNP (89) who required 8.8 dose adjustments per day ($p=0.0012$), despite maintaining the same percent of time within blood pressure parameters (NIC=66% versus SNP= 69%, p=n/s). NIC subjects required fewer adjunctive medications (1.4) to maintain blood pressure control when compared to SNP subjects (1.9, $p=0.043$). Suri and colleagues published a retrospective, observational study of subjects experiencing intracerebral hemorrhage using data from Premier (a national hospital discharge

database, date range 7/05-6/06).[28] They sought to evaluate the impact of NIC versus SNP on risk-adjusted in-hospital mortality, length of stay, and total hospital costs. They concluded that after adjustment for baseline risk of mortality (using the 3M APR-DRG), subjects treated with SNP (n=530) were more likely to experience in-hospital death (OR 1.7 95%CI 1.3-2.2, p=0.0003) than those treated with NIC (n=926). After adjustment for age, baseline mortality risk, and institutional characteristics, they did not find significant differences in length of stay (NIC=7.8 days, SNP=8.0 days, p=0.50) or total hospital costs (NIC=$14,536, SNP=$14,974, p=0.63) among patients who survived to hospital discharge.

METHODS

Research Objective and Impact:

The overall objectives of this proposal were to compare blood pressure stability and cost-effectiveness of NIC compared with SNP in subjects experiencing postoperative hypertension after cardiac surgery. The expected outcome of this research was to determine if despite a higher acquisition cost, NIC remains a cost-effective therapy compared to SNP. The results of this cost effectiveness study has an important positive impact as many providers limit the use of NIC due to decisions based upon drug acquisition costs alone. Determining if NIC is a more cost-effective therapy provides further support and justification for the use of NIC in post-cardiac surgical hypertension. To accomplish the overall objective of this study the following hypothesis was tested with the specific aims outlined below.

Hypothesis:

Despite a higher acquisition cost, NIC provides more stable blood pressure control and will remain a cost-effective therapy when compared to SNP.

Specific Aims:

1) Compare the stability of blood pressure control with NIC versus SNP

2) Determine the cost-effectiveness of NIC compared with SNP in subjects experiencing postoperative hypertension after cardiac surgery.

Study Design and Setting:

Single center, retrospective, cohort study conduced in a cardiothoracic surgical service of an urban, tertiary care, teaching hospital (650 beds).

Study Subjects:

Source of subjects

During 2007 and 2008, Mid America Thoracic and Cardiovascular Surgery, Inc. at The University of Kansas Hospital performed ~550 cardiac surgical procedures annually. Among these cases, 60% were isolated CABG, 7% were isolated valve surgery, 13% were combined CABG and valve surgery, and the remaining 20% involved other cardiothoracic surgeries (e.g. thoracic aortic procedures, etc.). Since our institution's electronic medical record was initiated on 11/19/2007 subjects were enrolled if they were admitted between 11/19/2007 and 12/31/2009. Given our average cardiac surgical volume of ~550 cases annually, this study period provided approximately ~1200 subjects (550 cases/year * 2.2 years) to screen for NIC or SNP use.

Criteria for eligibility

Adult subjects (≥18 year old) were included if they underwent cardiac surgery requiring cardiopulmonary bypass (specifically isolated CABG, isolated valve, or combined CABG and valve surgery) and developed postoperative hypertension requiring treatment with either NIC or SNP. Male and female subjects from all ethnic groups were eligible for inclusion. Subjects not

receiving NIC or SNP, those exposed to either drug for less than 30 minutes, those receiving both NIC and SNP, or subjects whose medical records did not contain the necessary data for analyses were excluded.

Sampling method

Institution specific data in the University Health System Consortium database, was queried for patients in the 'cardiothoracic surgery' product line who utilized the individual resources 'NIC' or 'SNP' (n=158 met this criteria). Forty-six subjects were excluded for the following reasons: receiving both NIC and SNP (n=25), receiving < 30 minutes of NIC (n=1), receiving < 30 minutes of SNP (n=1), missing data in the electronic medical record (n=7 in the NIC group, n=6 in the SNP group), met criteria but underwent non-CABG or non-valve cardiac surgery (n=4 in NIC group, n=2 in SNP group). One-hundred-twelve subjects remained available for analysis including 72 subjects who received NIC, and 40 who received SNP.

Data Sources:

Demographics, outcomes, and financial data were obtained from the following sources: 1) institution-specific data submitted to the University Health System Consortium national database (used to identify cardiac surgery patients prescribed NIC or SNP and obtain severity of illness risk scores); 2) institution-specific data submitted to the Society of Thoracic Surgery's (STS) national database (used to obtain pre, peri, and postoperative demographics and outcomes); 3) a manual review of our institutions electronic medical record (to obtain medication and vital sign specific data), and 4) our institution's microaccounting system (to obtain activity-based direct cost).

Human Subjects Approval, Data Collection, and Fidelity:

Institutional review board approval (with waiver of informed consent) was obtained. Protected Health Information (names, record numbers, dates of birth, etc) were protected from unauthorized access and review. Data was collected using modern, password, virus, fire-walled protected mobile computers and entered into Microsoft Excel version 2007. Manual data collection was completed by a trained research assistant. A random sample of collected data from 10% of study subjects was audited for quality control.

Analyses:

Specific aim 1) Compare the stability of blood pressure control with NIC versus SNP.

Blood pressure stability was captured via two methods. The primary assessment method was the number of medication infusion rate changes per hour of exposure to the infusion of NIC or SNP. Given the retrospective design of this study, variables related to blood pressure goals (e.g. percent of time at goal, time to goal, etc.) were unobtainable as each patient is given a unique goal in clinical practice (which is often unspecified in the chart). However, an obtainable, applicable, and clinically meaningful indicator of controlled blood pressure is the number of dose changes divided by the total duration of the infusion of either NIC or SNP, excluding the time the infusion was temporarily held. A drug with a faster time to goal and ability to maintain stable blood pressure will have a lower dose change per hour ratio compared to a drug which is either less effective or that is less able to maintain a stable blood pressure. This variable was calculated by determining the difference between the start time and the end time of the NIC or SNP infusion, minus any duration of time the infusion was not administered. The start time had to

occur after ICU admission from the operating room and end prior to transfer from the ICU to the telemetry floor. To permit evaluation of this effectiveness variable using categorical and pharmacoecomonic data analyses techniques, we stratified the continuous dose change per hour variable into a binary variable split into either < 1 or ≥ 1 dose change per hour. We referred to those requiring ≥ 1 dose change per hour as having excessive dose changes and presumably unstable blood pressure control.

A secondary assessment of blood pressure stability assessed the minimum and maximum systolic blood pressure and heart rate while subjects were receiving the infusion. The mean and standard deviation of these indicators of hemodynamic stability were compared between those subjects receiving NIC and SNP. This variable was collected using a graphical display of vital signs in our electronic medical record, after determining the start, stop, and hold times of the infusions. This second assessment adds additional information since a common complication of the use of intravenous antihypertensive agents is varying degrees of hypotension. Patients frequently compensate for the sudden drop in blood pressure by rapidly and profoundly increasing heart rate. It is highly desirable to avoid these complications, early after cardiac surgery to minimize detrimental increases in myocardial oxygen demand.

Specific aim 2) Determine the cost-effectiveness of NIC compared with SNP in subjects experiencing postoperative hypertension after cardiac surgery.

This aim was evaluated by four cost-effectiveness models, using an institutional perspective, which were created with Microsoft Excel, all of which included the following variables:

- Effectiveness variable: rate per 100 subjects receiving either NIC or SNP who avoided excessive dose changes (i.e. subjects with an average dose change per hour <1).

- Cost variable: the average activity-based, direct, postoperative cost for subjects prescribed either NIC or SNP.

The four models included subjects receiving either NIC or SNP who underwent 1) any cardiac surgery (i.e. CABG, valve, or both), 2) isolated CABG, 3) isolated valve surgery, and 4) combined CABG and valve surgery. To determine if fluctuations in cost would change our results, we increased the actual postoperative cost variable by 10% for those subjects prescribed NIC (the more expensive drug) and by reducing the actual cost of SNP (the cheaper drug) by 10%. Under the condition where a drug therapy was less costly and more effective than its competitor it was considered a dominant therapy. Under the condition where a therapy was more costly but more effective, or less costly and less effective, the incremental cost-effectiveness ratio (ICER) was evaluated. If a therapy was more costly and less effective it was considered a dominated therapy. The incremental cost-effectiveness ratios for each model were calculated by dividing the difference in the cost variable by the difference in the effectiveness variables for subjects receiving either NIC or SNP using the following equation:

$$\text{ICER} = \frac{|\text{average postoperative costs of NIC subjects} - \text{average postoperative costs of SNP subjects}|}{|\text{rate per 100 NIC subjects with dose changes} < 1 - \text{rate per 100 SNP subjects with dose changes} < 1|}$$

While subject to much debate, ratios ranging from $25,000:1 to $100,000:1 have been considered cost-effective when studies have evaluated the cost per life-year gained.[29] However when comparing two specific therapeutic agents, an ICER much lower than this would be necessary to suggest cost-effectiveness. Our ICER calculated for this study represents the additional costs incurred by our institution to provide a single patient a therapy which yields more stable blood pressure requiring less than 1 dose change per hour on average. Two separate

incremental cost effectiveness ratios (ICERs) were calculated; ICER 1 that utilized the actual costs, and ICER 2 that used the varied cost data describe above.

Statistical methods - univariate analyses:

Using SAS (version 9.2), patient demographics and outcome variables were compared using standard statistical methodology. Categorical data were analyzed using contingency tables and chi-square analysis. Contingency tables containing > 20% of cells with expected counts less than 5, or any tables with expected counts ≤ 2, were analyzed with Fishers exact tests. Continuous variables were assessed for normality using SAS proc univariate output, including the Shapiro-Wilk's tests, box plots, and normal probability (quantile-quantile) plots. If data were non-normally distributed, an attempt was made to transform the data to a normal distribution using various mathematical operators (e.g. natural log, etc). Continuous, normally distributed data with equal variances were analyzed using t-tests and reported as means ± standard deviations. If the variance between groups were found to significantly differ, we used Satterthwaite's approximation to determine p values. Continuous data, which were non-normally distributed and transformation unsuccessful, were analyzed with Wilcoxon Rank Sum tests and reported as medians ± ranges.

Statistical methods - controlling confounders:

Demographics that may likely confound our categorical outcome (≥ 1 dose change per hour) were adjusted for using a multiple variable regression technique. Log-binomial regression was chosen over logistic regression due to the common frequency of our outcome (58% of those prescribed SNP experienced ≥ 1 change / hour). In the setting of a common binary outcome logistic regression overestimates the influence of independent variables on the dependent variable, whereas log-binomial regression better approximates true relative risk.[30] The following

variables with p values < 0.15 were included in the initial model as independent variables: drug (SNP or NIC), operation type (CABG or Valve or CABG+Valve), severity of illness (minor/moderate or major/extreme), risk of mortality (minor/moderate or major/extreme), history of renal failure (yes or no), history of myocardial infarction (yes or no), gender (male or female), age (in years) at the time of surgery, and weight (in kg) at the time of surgery. Drug and severity of illness remained significant predictors of the ≥ 1 dose changer per hour outcome and therefore were included in the final model. Operation type approached significance, and is likely clinically influential, so it was retained in the final model as well. Model convergence was assessed. Goodness of fit was evaluated by assessment of the Akaike information criterion (AIC) values.

Severity of illness and risk of mortality scores:

Risk scores were obtained from the University HealthSystem Consortium (UHC) database and were used to compare both severity of illness and risk of mortality between those prescribed NIC or SNP. These multivariate models are calculated by the all-patient refined diagnosis related grouper (APR-DRG) developed by Iezzoni and colleagues for 3M Health Information Systems.[31,32] The models assign an ordinal level (i.e. minor, moderate, major, and extreme) of illness severity and risk of mortality. Additionally, they provide a specific probability of mortality (expressed as a percent) for each subject in the UHC database. Independent variables included in the models are: risk of mortality subclass (for determining % probability of mortality), patient age, patient sex, transfer from another acute care hospital, transfer from skilled nursing facility, or transfer from a long term care facility, low socioeconomic status (based on Medicaid, Self-Pay, Charity as primary payer), emergent admit status, race, and several comorbid conditions defined by AHRQ. Comorbid conditions were based from the work of Elixhauser and colleagues and included: congestive heart failure, valvular disease, pulmonary

circulation disorders, peripheral vascular disorders, hypertension (complicated and uncomplicated), paralysis, other neurological disorders, hypothyroidism, renal failure, liver disease, peptic ulcer disease excluding bleeding, AIDS, lymphoma, metastatic cancer, solid tumor without metastasis, rheumatoid arthritis/collagen vascular diseases, coagulopathy, obesity, weight loss, fluid and electrolyte disorders, blood loss anemia, deficiency anemias, alcohol abuse, drug abuse, psychoses, and depression.[33] UHC adds additional variables for patients undergoing CABG or valve surgery. Additional independent model variables for patients undergoing CABG include: pre-operative intra-aortic balloon pump use, ventilator on day of admission, previous CABG, aortic stenosis, and multi-vessel CABG. Additional independent model variables for patients undergoing valve surgery include: current CABG, previous CABG, use of extracorporeal membrane oxygenator, and presence of mitral valve regurgitation.

Sample size and statistical power:

Using $n= [(z_{1-\alpha/2} + z_{1-\beta})^2 (2*\sigma^2)]/(\mu_1-\mu_2)^2$ to calculate the sample size needed for each of two groups for a two sided t-test, we must know both the mean result (μ) from each group and their respective variance (σ^2). At present there does not exist published literature describing the comparative outcomes regarding dose changes per hour between NIC and SNP after cardiac surgery. However, Neutel et al published the comparative results of a randomized controlled trial of NIC versus SNP in the treatment of severe hypertension.[34] In this paper they report a similar efficacy variable to that proposed in our study: "dose adjustments per hour required to maintain blood pressure reduction". In this research, they report 0.54±0.1 Δ/hour for NIC and 1.49±0.2 Δ/hour for SNP (mean±SEM, $p<0.05$). Converting SEM to standard deviation is necessary for sample size calculations, thus we used SD=SEM+√n to generate the following data (mean±SD): 0.54±0.469 Δ/hour for NIC and 1.49±1.63 Δ/hour for SNP. Neutel and colleagues do not report

the results of a test for equal variance between these groups, therefore in place of the above equation, we used the following sample size equation for non-equal variance or sample sizes:

$$n = \{ (z_{1-\alpha/2} + z_{1-\beta})^2 * [(\sigma^2_1 + \sigma^2_2)/k)] \} / (\mu_1 - \mu_2)^2$$

where $k = n_2/n_1$ (the proportion of subjects in each arm)

This calculation indicates that 25 subjects per group would be capable of detecting a significant difference (with α=0.05 and β=0.2) between the groups for this outcome. Given that we do not know the means and variance of other outcomes (such as length of stay) we conservatively planned to oversample subjects meeting the inclusion/exclusion criteria in the prespecified time period.

RESULTS

Baseline Demographics:

Baseline demographics are reported in Tables 1a and 1b below. In general subjects prescribed NIC tended to have more concomitant diseases such as renal failure and a history of myocardial infarction and thus were at a higher risk of mortality, however they were at a lower severity of illness at admission than the SNP subjects. Among factors reported to contribute to postoperative hypertension, subjects in the NIC and SNP groups were well balanced. Importantly, the history of hypertension, the preoperative blood pressure and heart rate, and the number of antihypertensive agents used preoperatively were nearly identical between the groups. However, patients receiving NIC had a significantly higher history of renal failure when compared to those receiving SNP (19% versus 5%, p=0.0363), which is a reported predictor of postoperative hypertension.[14] While not statistically significant, clinical differences between those receiving NIC and SNP were noted among the following variables.

- SNP subjects were 5 years older, p=0.0670

- NIC subjects weighed 4 kg more, p=0.0852
- NIC subjects preoperative serum creatinine was 0.3 mg/dL higher, p=0.0845
- NIC subjects had a higher myocardial infarction history, 21% versus 10%, p=0.1433
- Using a categorical score for risk of mortality (calculated UHC score), 32% of NIC subjects were classified as being at a major or extreme risk of mortality compared to 18% in the SNP group, p=0.1014
- Using a categorical score for severity of illness (calculated UHC score), 53% of SNP subjects were classified as being at a major or extreme category compared to 43% in the SNP group, p=0.3629
- Surgical type did not differ statistically but clinically the proportions were not ideally balanced.
    - CABG: NIC 61% versus SNP 48%, p=0.2334
    - VALVE: NIC 29% versus SNP 35%, p 0.6714
    - CABG + VALVE: NIC 10% versus SNP 18%, p=0.3711

TABLE 1a: Baseline Categorical Demographics.

Variable Description	NIC (n=72) n (%)	SNP (n=40) n (%)	p	Notes
Male gender	49 (68)	22 (55)	0.1694	[a]
Caucasian race	59 (82)	34 (85)	0.6797	[a]
Black race	10 (14)	4 (10)	0.5510	[a]
Other race	3 (4)	2 (5)	1.0000	[b]
Prior CABG surgery	2 (3)	1 (3)	1.0000	[b]
Prior valve surgery	2 (3)	0 (0)	0.5367	[b]
Prior other cardiac surgery	0 (0)	0 (0)	n/a	
Prior carotid surgery	5 (7)	2 (5)	1.0000	[b]
History of heart failure	8 (11)	3 (8)	0.7435	[b]
History of renal failure	14 (19)	2 (5)	0.0363	[a]
Postoperative renal failure	4 (6)	0 (0)	0.2949	[b]
History of myocardial infarction	15 (21)	4 (10)	0.1433	[a]
History of lung disease	31 (43)	14 (35)	0.4047	[a]
History of atrial fibrillation	7 (10)	7 (18)	0.2330	[a]
Postoperative arrhythmia	9 (13)	9 (23)	0.1674	[a]
History of hypertension	61 (85)	34 (85)	0.9687	[a]
Elective admission	37 (54)	22 (55)	0.8625	[a]
Major/Extreme severity of illness	30 (43)	21 (53)	0.3629	[a]
Major/Extreme risk of mortality	22 (32)	7 (18)	0.1014	[a]
Current surgery: CABG	44 (61)	19 (48)	0.2334	[a]
Current surgery: VALVE	21 (29)	14 (35)	0.6714	[a]
Current surgery: CABG + VALVE	7 (10)	7 (18)	0.3711	[a]
Current surgery: Carotidendarterectomy	3 (4)	1 (3)	1.0000	[b]
Elective surgical status	53 (74)	33 (83)	0.4028	[a]
Required reintubation	2 (3)	1 (3)	1.0000	[b]
Required ICU readmission	4 (6)	0 (0)	0.2949	[b]
Required >48 hours in ICU	22 (31)	8 (20)	0.2268	[a]
Admission source:				
Clinic	1 (1)	0 (0)	0.7624	[a]
ER	8 (12)	3 (8)		
Non-Facility	53 (77)	32 (80)		
Other Facility	7 (10)	5 (13)		
Primary Pay Source:	()	()		
HMO	10 (15)	9 (23)	0.5284	[a]
PPO	16 (23)	7 (18)		
Trad/Indemnity	3 (4)	1 (3)		
Medicaid / Trad/Indemnity	5 (7)	1 (3)		
Medicaid / Managed Care	0 (0)	1 (3)		
Medicare / Trad/Indemnity	27 (39)	17 (43)		
Medicare / Managed Care	0 (0)	1 (3)		
VA	7 (10)	2 (5)		
Self Pay	1 (1)	1 (3)		
Dead at discharge	1 (1)	0 (0)	1.0000	[b]
Dead at 30 days	2 (3)	0 (0)	0.5367	[b]

[a] Chi Square test used; [b] Fishers Exact test used.

TABLE 1b: Baseline Continuous Demographics.

Variable Description	Units	NIC mean	SNP mean	NIC median (min, max)	SNP median (min, max)	p	Notes
Age	years	61 (14)	66 (15)	63 (19,84)	70 (21,89)	0.067	[a]
Weight	kg	86 (17)	84 (26)	82 (47,126)	75 (46,178)	0.0852	[a]
Height	cm	172 (9)	167 (18)	174 (151,198)	168 (84,196)	0.1726	[a]
Left ventricular ejection fraction	%	52 (12)	52 (14)	53 (20,70)	55 (20,80)	0.9976	[a]
Last creatinine	mg/dL	1.4 (1.2)	1 (0.4)	1.1 (0.5,7.8)	1 (0.4,3)	0.0845	[a]
Cardiopulmonary bypass time	min	92 (40)	91 (34)	85 (38,271)	87 (39,201)	0.9768	[b,c]
Aortic cross clamp time	min	66 (24)	73 (29)	62 (28,169)	69 (26,162)	0.265	[b,c]
Initial time spent in ICU	hours	53 (63)	48 (33)	26 (13,484)	35 (21,171)	0.3723	[a]
Total time spent in ICU	hours	59 (69)	48 (33)	29 (13,484)	35 (21,171)	0.9493	[a]
Length of stay (surgery to hospital discharge)	days	6.9 (3.9)	6.1 (3)	6 (3,27)	6 (3,18)	0.8558	[a]
Expected mortality probability, using DRG	%	0.016 (0.034)	0.012 (0.015)	0.003 (0,0.19)	0.007 (0,0.075)	0.1267	[a]

[a] non-parametric data, Wilcoxon Rank Sum test used; [b] non-normally distributed data, transformed prior to analysis; [c] t-test used.

Antihypertensive Drug Use:

Preoperative and peri-infusion antihypertensive drug therapy use did not differ substantially between the groups. Specific utilization by drug class is reported in Table 2. When combined as a total number of antihypertensive drugs used before surgery, NIC subjects were prescribed 2.3±1.7 medications and SNP subjects were prescribed 2.2±1.6 medications, p=0.8341. During the infusion of NIC or SNP, the number and pharmacologic category of medications did not differ significantly between the groups with exception of the SNP group being prescribed concomitant intravenous nitroglycerin more often (98%) than NIC subjects (82%, p=0.0171). Interestingly, the duration of infusion (median hours, range) was significantly shorter for subjects prescribed SNP (7.5, 0.6-49.2) compared to NIC subjects (3.1, 0.5-19.3, p=0.0072). Further investigation revealed that significantly more SNP subjects required continuation of their intravenous nitroglycerin infusions after discontinuation of SNP, suggesting a continued need for intravenous antihypertensive management (60% post SNP infusion IV nitroglycerin use in the SNP exposed group versus 13% in the NIC group, p<0.0001). Concomitant use of inotropes during either the NIC or SNP infusions tended to be higher among the NIC group (13% use) compared to the SNP group (3%, p=0.0754). However, after the infusion of either NIC or SNP was discontinued, subjects who had received SNP required significantly more antihypertensive agents for presumed blood pressure management (required 2.6±1.5 medications) when compared to NIC subjects (required 1.5±1.3 medications, p=0.0006).

TABLE 2: Medication Use.

Variable Description	NIC (n=72) n (% use)	SNP (n=40) n (% use)	p	Notes
Preoperative centrally acting alpha agonists	5 (7)	2 (5)	1	[b]
Preoperative peripherally acting alpha agonists	4 (5)	0 (0)	0.2949	[b]
Preoperative beta blockers	49 (68)	22 (55)	0.1694	[a]
Preoperative calcium channel blockers	16 (22)	11 (28)	0.5315	[a]
Preoperative diuretics, loop	14 (19)	11 (28)	0.3266	[a]
Preoperative diuretics, potassium sparing	1 (1)	2 (5)	0.2898	[b]
Preoperative aldosterone antagonists	3 (4)	3 (8)	0.6646	[b]
Preoperative diuretics, thiazide	16 (22)	9 (23)	0.973	[a]
Preoperative renin inhibibitors	2 (3)	0 (0)	0.5367	[b]
Preoperative vasodilators	2 (3)	2 (5)	0.6159	[b]
Preoperative nitrates	13 (18)	3 (8)	0.1261	[a]
Preoperative ACE inhibitors	24 (33)	13 (33)	0.9284	[a]
Preoperative ARBs	13 (18)	7 (18)	0.9414	[a]
Mean # (SD) of preoperative antihypertensive medications	2.3 (1.6)	2.2 (1.6)	0.8341	[c]
Peri-infusion bolus (labetalol, metoprolol, enalaprilat)	6 (8)	1 (3)	0.4182	[b]
Peri-infusion centrally acting alpha agonists	0 (0)	0 (0)	n/a	
Peri-infusion peripherally acting alpha agonists	1 (1)	1 (3)	1	[b]
Peri-infusion beta blockers	18 (25)	6 (15)	0.2165	[a]
Peri-infusion calcium channel blockers	6 (8)	3 (8)	1	[b]
Peri-infusion diuretics, loop	16 (22)	6 (15)	0.3566	[a]
Peri-infusion diuretics, potassium sparing	0 (0)	0 (0)	n/a	
Peri-infusion aldosterone antagonists	0 (0)	0 (0)	n/a	
Peri-infusion diuretics, thiazide	1 (1)	0 (0)	1	[b]
Peri-infusion renin inhibibitors	0 (0)	0 (0)	n/a	
Peri-infusion vasodilators	3 (4)	1 (3)	1	[b]
Peri-infusion nitrates	59 (82)	39 (98)	0.0171	[a]
Peri-infusion ACE inhibitors	4 (6)	2 (5)	1	[b]
Peri-infusion ARBs	0 (0)	0 (0)	n/a	
Mean # (SD) of peri-infusion antihypertensive medications	1.6 (1.2)	1.5 (1.1)	0.6025	[c]

[a] Chi Square test used; [b] Fishers Exact test used; [c] Wilcoxon Rank Sum test used; n/a=not applicable.

TABLE 2: Medication Use. (CONTINUED)

Variable Description	NIC (n=72) n (% use)	SNP (n=40) n (% use)	p	Notes
Peri-infusion amiodarone	22 (31)	9 (23)	0.3612	[a]
Peri-infusion vasoconstrictors	1 (1)	0 (0)	0.454	[a]
Peri-infusion inotrope/vasoconstrictors	15 (21)	3 (8)	0.0656	[a]
Peri-infusion inotropes	9 (13)	1 (3)	0.0754	[a]
Post-infusion centrally acting alpha agonists	8 (11)	4 (10)	1	[b]
Post-infusion peripherally acting alpha agonists	1 (1)	0 (0)	1	[b]
Post-infusion beta blockers	32 (44)	24 (60)	0.1147	[b]
Post-infusion calcium channel blockers	11 (15)	11 (28)	0.1188	[a]
Post-infusion diuretics, loop	37 (51)	27 (68)	0.0988	[a]
Post-infusion diuretics, potassium sparing	0 (0)	0 (0)	n/a	
Post-infusion aldosterone antagonists	0 (0)	0 (0)	n/a	
Post-infusion diuretics, thiazide	2 (3)	1 (3)	1	[b]
Post-infusion renin inhibibitors	0 (0)	0 (0)	n/a	
Post-infusion vasodilators	3 (4)	3 (8)	0.6646	[b]
Post-infusion nitrates	9 (13)	24 (60)	<0.001	[a]
Post-infusion ACE inhibitors	4 (6)	3 (8)	0.6988	[b]
Post-infusion ARBs	0 (0)	2 (5)	0.1255	[b]
Mean # (SD) of post-infusion antihypertensive medications	1.5 (1.3)	2.6 (1.5)	0.0006	[c]
Post-infusion amiodarone	54 (75)	29 (73)	0.7723	[a]
Post-infusion vasoconstrictors	1 (1)	1 (3)	1	[b]
Post-infusion inotrope/vasoconstrictors	20 (28)	12 (30)	0.803	[a]
Post-infusion inotropes	5 (7)	4 (10)	0.7191	[a]

[a] Chi Square test used; [b] Fishers Exact test used; [c] Wilcoxon Rank Sum test used; n/a=not applicable.

Specific Aim #1: Compare the stability of blood pressure control with NIC versus SNP.

Dose change per hour:

In our univariate analysis (see Table 3), the average dose change per hour, our surrogate marker for blood pressure stability, differed significantly between the groups with subjects prescribed NIC requiring 1.2±1.6 changes per hour compared to 1.7±1.8 changes per hour required in the

SNP group (p= 0.0038). Thirty-eight percent (27/72) of NIC subjects and 57% (23/40) of SNP required ≥ 1 dose change per hour, our arbitrary cut point to indicate unstable blood pressure, which differed significantly (p=0.0489). Of interest, the average minimum and maximum infusion rate for NIC was 3.9±1.7 and 10.3±4.3 mg/hour, respectively. The average minimum and maximum infusion rate for SNP was 0.5±0.3 and 1.6±0.9 mcg/kg/min, respectively. Using log-binomial regression to adjust for severity of illness and surgery type, we found the risk of excessive dose changes was 60% higher in those subjects prescribed SNP compared those prescribed NIC (adjusted relative risk = 1.6030, 95%CI, 1.0971-2.3420, p=0.0147). No other confounders were found to significant influence our outcome.

TABLE 3: Continuous Outcomes.

Variable Description	Units	NIC mean (SD)	SNP mean (SD)	NIC median (min, max)	SNP median (min, max)	p	Notes
Total dose changes	n	7.2 (6.8)	6.7 (7)	5.5 (1,40)	4.5 (1,31)	0.287	[a]
Infusion duration	hours	12 (12.9)	5.3 (5.3)	7.5 (0.6,49.2)	3.1 (0.5,19.3)	0.007	[a]
Dose changes per hour		1.2 (1.6)	1.7 (1.8)	0.7 (0.1,10.9)	1 (0.2,10.5)	0.004	[b,c]
Intial infusion rate		5.9 (3.1)	0.8 (0.5)	5 (0.5,15)	0.8 (0.2,2)	n/a	
Minimum infusion rate		3.9 (1.7)	0.5 (0.3)	5 (0.1,10)	0.5 (0,1.5)	n/a	
Maximum infusion rate		10.3 (4.3)	1.6 (0.9)	10 (2.5,15)	1.5 (0.3,3.5)	n/a	
Activity-based direct costs (ICU adm - hosp dc)	US$	21743 (8716)	22014 (7161)	20617 (10795,48724)	20599 (10498,39730)	0.635	[b,c]

[a] non-parametric data, Wilcoxon Rank Sum test used; [b] non-normally distributed data, transformed prior to analysis; [c] t-test used.

Hemodynamic stability:

Systolic blood pressure, diastolic blood pressure, and heart rate before, during, and after the infusions of either NIC or SNP are summarized in Table 4. Blood pressure and heart rate were nearly identical in both study groups before and after the infusions of NIC and SNP. Comparison of the systolic blood pressures before the infusions between those prescribed NIC (139±22

mmHg) and SNP (134±16 mmHg) suggest that the occurrence of hypertension was not different between the groups (p=0.2197). Evaluation of the minimum systolic blood pressures during the infusion between those prescribed NIC (96±12 mmHg) and SNP (98±10 mmHg) suggest that the occurrence of hypotension was not different between the groups (p=0.3155). Finally, the maximum heart rate during the infusion between those prescribed NIC (94±17 mmHg) and SNP (91±12 mmHg) suggest that the occurrence of reflex tachycardia was not different between the groups (p=0.3148).

TABLE 4: Hemodynamic Data.

Variable Description	NIC mean (SD)	SNP mean (SD)	NIC median (min, max)	SNP median (min, max)	p	Notes
Systolic blood pressure - Prior to infusion (mmHg)	139 (22)	134 (16)	136 (74,190)	130 (105,171)	0.2197	b,c,d
Systolic blood pressure - Max during infusion (mmHg)	145 (20)	140 (18)	144 (102,190)	136 (111,190)	0.1893	b,c
Systolic blood pressure - Min during infusion (mmHg)	96 (12)	98 (10)	94 (70,140)	94 (84,123)	0.3155	b,c
Systolic blood pressure - After infusion (mmHg)	118 (21)	118 (20)	112 (92,176)	116 (81,183)	0.9970	b,c
Diastolic blood pressure - Prior to infusion (mmHg)	63 (15)	63 (10)	60 (36,117)	64 (46,90)	0.6769	b,c,d
Diastolic blood pressure - Max during infusion (mmHg)	64 (14)	65 (11)	61 (40,120)	62 (47,89)	0.6135	b,c
Diastolic blood pressure - Min during infusion (mmHg)	43 (8)	45 (9)	41 (30,76)	46 (28,67)	0.2760	b,c
Diastolic blood pressure - After infusion (mmHg)	53 (10)	55 (12)	52 (29,81)	53 (34,97)	0.2274	b,c
Heart rate - Prior to infusion (bpm)	83 (15)	83 (11)	80 (58,130)	81 (64,113)	0.8930	b,c,d
Heart rate - Max during infusion (bpm)	94 (17)	91 (12)	91 (65,141)	89 (68,120)	0.3148	b,c,d
Heart rate - Min during infusion (bpm)	73 (14)	77 (12)	74 (43,108)	79 (49,106)	0.1106	c
Heart rate - After infusion (bpm)	80 (14)	83 (12)	82 (50,114)	84 (52,106)	0.2917	c

[a] non-parametric data, Wilcoxon Rank Sum test used; [b] non-normally distributed data, transformed prior to analysis; [c] t-test used; [d] non-equal varances, Satterthwaite approximation used.

Specific Aim #2: Determine the cost-effectiveness of NIC compared with SNP in subjects experiencing postoperative hypertension after cardiac surgery.

The results of cost-effectiveness analyses for the entire cohort and for subjects undergoing isolated CABG, isolated valve surgery, and combined CABG and valve surgery are provided in Table 5. Two separate incremental cost effectiveness ratios (ICERs) are provided; ICER 1 that utilized the actual costs, and ICER 2 that used varied costs. That is, we increased the actual postoperative cost variable for those subjects prescribed NIC (the more expensive drug) by 10%

and reduced the actual cost of SNP (the cheaper drug) by 10%. In the entire cohort, NIC was an economically dominant therapy as it was more effective at a lower cost. When the costs were varied in the entire cohort, dominance was lost, however the ICER remained very low at $195:1. Therefore use of NIC rather than SNP, would require our institution to pay an additional $195 to provide a single patient NIC which yields more stable blood pressure requiring less than 1 dose change per hour on average. In the isolated CABG cohort, NIC was no longer dominant but its ICER ranged between $93:1 for the actual cost and up to $358:1 when the costs were varied. In the isolated valve cohort, NIC again was a dominant therapy when using actual costs, and had an ICER of $263:1 when the costs were varied. In the combined CABG and valve cohort, NIC was a dominant therapy when using actual costs, and had an ICER of $159:1 when the costs were varied. Caution in interpreting the results from this combined subgroup should be taken as the number of subjects who underwent combined CABG and valve surgery that met inclusion criteria was small (7 per group).

TABLE 5: Cost-Effectiveness Analyses.

	N	Mean dose change per hour	Rate per 100 subjects avoiding excessive dose changes (≥1Δ/hour)	Cost per excessive dose changes avoided	10% cost variance (increased NIC and decreased SNP)	NIC cost effective	ICER 1 (Δ actual costs) / (Δ of rate avoiding excessive dose changes)	ICER 1 (Δ actual costs) / (Δ of rate avoiding excessive dose changes)
ENTIRE COHORT								
NIC	72	1.15	63	$21,743	$23,917	Yes	dominant	$195:1
SNP	40	1.66	42	$22,014	$19,813			
Δ		-0.51	21	($271)	$4,104			
CABG ONLY								
NIC	44	1.15	68	$20,584	$22,643	Yes	$93:1	$358:1
SNP	19	1.52	53	$19,184	$17,265			
Δ		-0.36	15	$1,400	$5,377			
VALVE ONLY								
NIC	21	1.22	52	$22,966	$25,263	Yes	dominant	$263:1
SNP	14	1.44	36	$23,385	$21,046			
Δ		-0.22	16	($419)	$4,216			
CABG/VALVE ONLY								
NIC	7	0.96	57	$26,572	$29,229	Yes	dominant	$159:1
SNP	7	2.52	29	$27,536	$24,783			
Δ		-1.56	28	($964)	$4,447			

Summary of Findings:

In this population of patients undergoing CABG, valve, or combined CABG/valve surgery, NIC is associated with significantly less dose adjustments per hour than SNP when used to manage acute postoperative hypertension. When evaluated as a continuous outcome, subjects who were prescribed NIC required an average of 1.2 dose changes per hour compared to the 1.7 changes per hour required among those prescribed SNP (p=0.004). We found that 58% (23/40) of the SNP subjects required excessive dose changes (defined as ≥ 1 dose change per hour), whereas only 38% (27/72) of NIC subjects required this level of dose adjustment (p=0.0489). After adjustment for surgery type and severity of illness, SNP remained significantly associated with excessive dose changes (adjusted relative risk = 1.6030, 95%CI, 1.0971-2.3420, p=0.0147). Hypotension and reflex tachycardia are common side effects of antihypertensive agents used to manage postoperative hypertension. We did not find significant differences in the minimum systolic blood pressure or maximum heart rate while subjects were receiving NIC or SNP. Using activity-based postoperative costs and an institutional perspective; we found NIC was an economically dominant therapy in the entire cohort, in isolated valve surgery, and in the combined CABG plus valve surgery patient populations. In these patient populations, subjects prescribed NIC experienced excessive dose changes less frequently, and had a lower postoperative direct cost when compared to those prescribed SNP. In the isolated CABG cohort, economic dominance did not exist, since the use of NIC was associated with an increased cost of $1,400. Despite this, the use of NIC yielded an incremental cost-effectiveness ratio of $93:1, suggesting our institution would need to spend an additional $93 per patient to reduce the number of dose changes required among subjects prescribed NIC to less than one per hour. When costs were varied, NIC was no longer an economically dominant therapy in any cohort,

however it remained associated with low incremental cost-effectiveness ratios ranging from $159:1 to $358:1.

DISCUSSION

Despite a more favorable clinical profile, the acquisition cost of NIC is substantially higher than that of SNP. At the time of this study, our institutions' admixture (drug and fluid) cost for NIC was $220 (50mg NIC in 500 mL of 0.9% sodium chloride) compared to $5.36 for SNP (50 mg SNP in 250 mL of 5% dextrose solution). Given the higher acquisition costs but superior efficacy of NIC compared with SNP, a formal cost-effectiveness analysis is a clear knowledge gap in the existing medical literature. The rationale that underlies this research is that, presumably, a positive impact of NIC on patient outcomes could offset its higher acquisition costs by saving costs elsewhere. NIC has consistently demonstrated improved hemodynamic efficacy (e.g. faster and more stable control); which in turn is likely to influence other variables that increase costs. Presumably, faster and more stable control of blood pressure would reduce ICU (and potentially hospital) length of stay. More efficacious reductions and stability of blood pressure should also influence postoperative bleeding and blood transfusion rates, both of which significantly increase hospital costs. Lastly, given the substantially greater impact on venous dilation, SNP has been reported to increase the need for postoperative volume resuscitation.[22] Such aggressive resuscitation frequently causes a dilutional anemia and subsequently may increase blood transfusion requirements. To date, a cost-effectiveness analysis has not been conducted comparing SNP to NIC after cardiac surgery. Because cardiac surgery is a high volume procedure for many institutions, characterizing this knowledge gap is of important clinical interest to prescribers, formulary decision makers, and hospital administrators.

Comparison of Major Findings to Existing Literature:

While it is clear significant work remains in this field, the present study adds to the growing body of evidence demonstrating that NIC provides superior blood pressure control when compared to SNP. Specifically, this work concludes that subjects who were prescribed NIC required an average of 1.2 dose changes per hour compared to the 1.7 changes per hour required among those prescribed SNP (p=0.004). Admittedly, the study's retrospective design required we use a surrogate endpoint for blood pressure stability; however, we feel it represents an accurate and useful retrospective measure of blood pressure control, as antihypertensive agent infusion rates are not changed unless the blood pressure is not at a desired level. One exception exists which involves the infusion-weaning period for intravenous vasoactive drugs. Since both NIC and SNP require a "titrate to off" period, we assume the number of changes needed during this period still reflects the ability of an agent to provide control, even during the weaning phase. When evaluated using a cut point of ≥ 1 dose change per hour, we found that SNP was significantly associated with a 60% higher risk of excessive dose changes when compared to NIC, after controlling for surgery type and severity of illness. These findings are unique in that most other comparative studies of these agents are limited to isolated CABG.[20-24] Aronson and colleagues work[25] and the present study further expand our understanding of the differences between NIC and SNP use in other cardiac surgical populations involving isolated valve and combined CABG/valve surgery patient populations in addition to isolated CABG.

In comparison to previously reported studies in cardiac surgery, the infusion rates of NIC (average min/max = 3.9 / 10.9 mg/hour) and SNP (average min/max = 0.5 / 1.6 mcg/kg/min) used in our study are similar. NIC dosing in previous work ranges from 3.3 to 8.4 mg/hour and

SNP dosing ranges from 1.4 to 4.5 mcg/kg/min.[20-24] Our study differs from previously reported outcomes relative to hemodynamic instability. We did not find significant differences between NIC or SNP subjects in the minimum systolic blood pressure or maximum heart rate experienced while on either infusion. In contrast, David and colleagues reported less tachycardia and hypotension with NIC.[22] Aronson and colleagues reported subjects exposed to SNP spent more time outside a pre-specified blood pressure range than those treated with intravenous NIC or clevidipine.[25] However, Kwak and colleagues found that 23% of subjects prescribed NIC versus 5% of those prescribed SNP, required intervention with phenylephrine (an intravenous alpha-agonists which raises blood pressure) to treat hypotension experienced while receiving either infusion.[24]

Dose changes as a marker for blood pressure control and stability have been reported by four other authors.[19,22,27,33] A single publication within cardiac surgery reported a similar finding to the present study results regarding the number of dose changes per hour (present study, NIC = 1.2, SNP = 1.7, p=0.004). David and colleagues reported that after reaching a stable blood pressure plateau, NIC required 1.1 dose change per hour to maintain blood pressure compared to SNP requiring 2.7 hourly changes (p=0.01).[22] In a post-surgical patient population, Halpern and colleagues found NIC required a total of 1.5 dose changes to achieve a therapeutic blood pressure versus 5.1 changes needed in the SNP group (p=0.05).[19] In a population of patients who suffered intracerebral hemorrhage, Roitberg and colleagues found NIC required 5.7 dose changes per day versus the 8.8 changes needed in the SNP group (p=0.0012).[27] In a population of patients with severe hypertension, Neutel and colleagues reported that NIC required 0.5 dose adjustments per hour required to maintain blood pressure reduction compared to SNP requiring 1.5 ($p<0.05$).[34]

To date, one published study has compared the financial difference in hospital costs between patients prescribed NIC or SNP. Suri and colleagues published a retrospective, observational study of subjects with intracerebral hemorrhage using data from Premier (a national hospital discharge database).[28] In this study, they investigated risk-adjusted in-hospital mortality, length of stay, and total hospital costs. They concluded subjects treated with SNP were more likely to experience in-hospital mortality but did not find significant differences in length of stay or total hospital costs (NIC=$14,536, SNP=$14,974, p=0.63) among patients who survived to hospital discharge. To our knowledge, the present study is the first reported cost-effectiveness analysis comparing NIC to SNP for the treatment of postoperative hypertension. We found that NIC remains cost effective in all three surgery types investigated (isolated CABG, isolated valve, and combined CABG/valve surgeries). We reported a second set of cost-effectiveness analyses, which increased the cost of the NIC group by 10% and decreased the cost of the SNP group by 10%. This was done to determine if our results would be the same under more strained economic parameters. As a result of an aging population, patients undergoing cardiac surgery are increasingly complicated by more comorbid conditions, and in general have a higher severity of illness and risk of mortality. In turn, it follows that such a population would represent a higher cost to an institution. While economic dominance (more effective, cheaper drug) was no long present under these varied economic conditions, we still found very low incremental cost-effectiveness ratios ranging from $159:1 to $358:1. It is our opinion that many surgeons would see NIC as a financially sound investment to provide more stable blood pressure control.

Limitations:

Like all retrospective investigations, the present study contains several noteworthy limitations. While comparable in sample size to other similar published studies,[20-24] our study has a relatively small sample size, which may have presented an opportunity for type II statistical errors. Additionally, given the non-interventional design of this study, selection bias is likely present in some degree with more complex patients likely being prescribed NIC more often than SNP. We attempted to control for this using regression techniques described above. Given our retrospective study design, each patient is likely to have different blood pressure goals and specified ranges postoperatively, due to complications such as stroke or renal failure. Therefore, we were unable to use a specific blood pressure range as was done by Aronson and colleagues in their prospective work.[25] As a result, we were required to utilize surrogate markers of blood pressure stability (e.g. dose change per hour and proportion of subjects with ≥ 1 dose change per hour). While we see inclusion of various cardiac surgical procedures (isolated CABG, isolated valve, and combined CABG/valve) as a strength and opportunity to explore differences between these groups, others may prefer homogeneity in study populations. To address this concern, we included surgery type in the multiple variable log-binomial regression model. Several variables that likely influence postoperative hypertension were not feasibly captured by this dataset, including postoperative anxiety, pain, and hypoxia. It is therefore impossible for us to conclude that we have accounted for all possible confounders. Additionally, while the care of patients undergoing cardiac surgery is heavily standardized, we are unable to definitively conclude each patient received the same quality of care and practice styles by their providers.

CONCLUSIONS

NIC use may be limited due to decisions based upon acquisition costs alone. We found that NIC resulted in a reduced need for dose adjustment when compared to SNP, presumable due to more stable BP control. After controlling for surgery type and severity of illness, the risk of excessive dose changes remained significantly higher in those subjects prescribed SNP compared those prescribed NIC. Despite a higher acquisition cost than SNP, NIC proved to be cost-effective in avoiding excessive dose changes among the entire cohort, and specifically in patients undergoing isolate CABG, isolated valve, and combined CABG/valve surgeries.

Impact on Clinical Practice:

In our opinion, use of NIC should not be restricted based on drug cost. Our data suggest that in isolated valve and combined CABG/valve surgery, the use of NIC represents an institutional opportunity to reduce postoperative costs overall. In isolated valve surgery and combined CABG/valve surgery, NIC was more effective and less expensive. If providers believe spending an additional $93 per patient is financially worth reducing the number of dose changes per hour to less than 1, which presumably is a result of superior blood pressure control, then the use of NIC in isolated CABG is also justified.

Future Research:

A prospective, randomized trial, comparing the impact of NIC versus SNP should evaluate blood pressure excursions (capturing both the number, and area under the curve of the excursions) from a pre-specified blood pressure range in this population. The influence of these excursions on length of stay, postoperative costs, and 30-day mortality should be investigated.

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