Examining the Use of Sodium Nitroprusside in Coronary Artery Bypass Grafting: Is the Benefit Worth the Cost?

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Abstract

Purpose: Sodium nitroprusside is a vasodilator frequently used in the coronary artery bypass grafting (CABG) setting. However, the price of a 50-mg vial of sodium nitroprusside increased from \$5.00 in 2003 to up to \$900 in 2016. The purpose of this review is to help health systems balance high-quality patient care with economic responsibility. **Methods:** A MEDLINE literature search was performed using the search terms “nitroprusside” and “coronary artery bypass.” All English-language trials in human subjects assessing the use of sodium nitroprusside in the setting of CABG were evaluated. The references of these studies were also reviewed. **Results:** In the setting of CABG, sodium nitroprusside attenuates conduit vasospasm and reduces the incidence of inflammation, atrial fibrillation, and acute kidney injury after surgery. However, other vasodilators are more effective at maintaining postoperative blood pressure at goal. **Conclusions:** Despite its cost, sodium nitroprusside may be an appropriate agent to use during CABG operations, but other agents should be considered for treatment of postoperative hypertension.

Keywords

coronary artery bypass, CABG, sodium nitroprusside, vasodilators, postoperative atrial fibrillation, postoperative hypertension

Introduction

US drug costs are increasing at an alarming rate. In 2014, spending on prescription drugs increased by 12.6%, a remarkable increase from previous drug spending growth, which averaged about 2% per year from 2008 to 2012.¹ With the increased economic burden of many drugs, health systems must reevaluate the use of expensive medications, ensuring the utilization is evidence-based and pharmacoeconomically sound.

One medication which has recently seen an increase in cost is sodium nitroprusside, a potent short-acting systemic arterial and venous vasodilator. In 2003, the average wholesale price (AWP) of a sodium nitroprusside 25 mg/1 mL vial (2 mL) was \$5.00. By 2017, the AWP increased to \$360.00 to \$900.00 depending upon the manufacturer.² Sodium nitroprusside is frequently utilized for hypertensive urgency and emergency, acute congestive heart failure, and perioperative blood pressure (BP) control. Many providers prescribe this vasodilator in the perioperative management of coronary artery bypass grafting (CABG) surgery.

CABG surgery is an effective revascularization procedure for treatment of coronary artery disease. CABG is preferred to percutaneous coronary intervention in some settings, such as significant left main coronary artery stenosis and complex

3-vessel coronary artery disease.³ Among the Medicine, Angioplasty, or Surgery Study (MASS-II) registry of patients with proximal multivessel stenosis of >70% and documented ischemia, 85.4% attained event-free survival (absence of death, myocardial infarction, or refractory angina requiring revascularization) at 5 years, as compared with only 56.6% of medical therapy patients and 44.9% of patients managed with percutaneous coronary intervention ($P = .0026$).⁴ However, risks of CABG surgery include recurrent ischemia, stroke, bleeding, acute kidney injury (AKI), postoperative hypertension, infection, and death. Sodium nitroprusside may be beneficial in reducing the incidence of some complications of CABG.

Here, we review the literature on the use of perioperative sodium nitroprusside and examine potential alternative vasodilators.

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Materials and Methods

A literature search using the MEDLINE database was undertaken to identify published studies reporting on the use of sodium nitroprusside in the CABG setting. Keywords entered in the search were “sodium nitroprusside” or “nitroprusside” and “CABG” or “coronary artery bypass grafting.” Articles were limited to in vitro studies or studies of adult patients which were published in English. Manual review of the reference lists of the retrieved articles was performed to identify additional relevant studies. Studies were reviewed to determine the impact of vasodilator selection on CABG outcomes and complications.

Results

Several studies discussing the impact of sodium nitroprusside on postoperative hypertension, postoperative atrial fibrillation (AF), AKI, conduit vasospasm, and inflammation were identified.

Postoperative Hypertension

Postoperative hypertension during cardiac surgery affects 22% to 54% of patients.⁵ BP excursions in the perioperative period increase the risk of bleeding, myocardial ischemia and infarction, cardiac arrhythmia, heart failure, and stroke.⁶ Acute hypertension has also been reported to worsen reperfusion injury and the inflammatory response, indicating that adverse events resulting from postoperative hypertension are due to multiple mechanisms.⁷

In a prospective randomized trial, sodium nitroprusside 0.5 µg/kg/min titrated to response was compared with nicardipine 10 mg/h titrated to response after surgery. Nicardipine is a dihydropyridine calcium channel blocker commonly used for the treatment of hypertensive urgency and emergency that selectively dilates arteries with no effect on veins. Of the 139 patients enrolled in the trial, 43 underwent cardiac surgery. Both agents were equally effective at reducing BP in the postoperative cardiac patients (defined as >15% reduction from the pretreatment BP). However, nicardipine controlled BP more rapidly than sodium nitroprusside (14.0 ± 1 minutes vs 30.4 ± 3.5 minutes, respectively; $P = .0029$). Increased heart rate among cardiac surgery patients treated with sodium nitroprusside was observed from baseline to the end of titration (84 ± 3 to 95 ± 4 beats/min, $P < .05$); however, both arms had an increase in heart rate from baseline by the end of maintenance therapy. Similar rates of adverse effects were observed in both arms.⁸

One arm of the open-label ECLIPSE trials randomly assigned patients undergoing cardiac surgery (CABG alone in 70.6% or CABG plus valve surgery in 10.7%) in a 1:1 fashion to receive sodium nitroprusside or clevidipine. Clevidipine is a rapid-acting dihydropyridine calcium channel blocker which, like nicardipine, selectively vasodilates

arteries without impacting venous circulation. The majority of CABG procedures in the study were performed with cardiopulmonary bypass (CPB). Clevidipine was initiated at 0.4 µg/kg/min and titrated per algorithm to response. There was no protocol dictating dosing of sodium nitroprusside, and investigators were encouraged to administer the agent in accordance with their usual practice. The primary outcome, safety as assessed by the incidence of myocardial infarction, stroke, renal dysfunction, and all-cause mortality at 30 days, was similar between arms for all endpoints, except for an increased risk of mortality in the sodium nitroprusside arm (4.7% vs 1.7%, $P = .0445$). After multiple logistic regression adjusting for other risk factors, mortality was similar between arms. However, clevidipine was significantly more effective than sodium nitroprusside at keeping BP within prespecified target range, as measured by the median area under the curve analysis of BP excursions beyond predetermined limits. In addition, sodium nitroprusside patients had more systolic blood pressure (SBP)-time excursions both above and below the target BP range than clevidipine patients. The authors stipulate that difficulty maintaining goal BPs may be due to difficulty titrating the medication without “overshooting” and causing hypotension as well as unpredictable swings in BP that may occur in sodium nitroprusside-treated patients with diastolic dysfunction or hypovolemia due to the venodilatory effects of sodium nitroprusside.⁹

Atrial Fibrillation

Postoperative AF is another potential consequence of CABG surgery impacting about one-third of patients, and is associated with substantial morbidity and mortality.¹⁰ To determine whether sodium nitroprusside prevents postoperative AF, a blinded pilot study enrolled 100 patients undergoing elective on-pump CABG. Fifty patients received a 60-minute infusion of sodium nitroprusside 0.5 to 1 µg/kg/min titrated to maintain a mean arterial pressure (MAP) near 65 mmHg, and 50 patients received a placebo infusion with the same MAP goal. All patients received left internal mammary artery grafts. After discontinuation of the aortic cross-clamp, 9 patients in the sodium nitroprusside and 24 patients in the placebo group required cardiac defibrillation ($P = .001$). Postoperative AF developed in 12% of sodium nitroprusside patients versus 36% of control patients ($P = .005$), and the duration of AF was shorter in the sodium nitroprusside group (5.33 ± 1.86 vs 7.55 ± 1.94 hours, $P = .023$). The length of intensive care unit (ICU) stay was similar between groups, but the total duration of hospitalization was shorter in the sodium nitroprusside group (7.34 ± 0.72 vs 9.10 ± 1.22 days). After multivariate analysis, sodium nitroprusside use was found to be an independent protective factor against development of postoperative AF (odds ratio: 4.282, 95% confidence interval [CI]: 1.495-12.267).¹¹

The causes of postoperative AF are multifactorial, and include alterations in electrical conduction, operative trauma,

perioperative medications, rapid rewarming after cardioplegic arrest, and reflex sympathetic tone.⁵ Nitric oxide (NO) may be disrupted during reperfusion injury after CABG. Sodium nitroprusside may be protective against postoperative AF due to replacement of NO. NO-induced reduction of calcium release in myocytes may protect cardiomyocytes from AF-induced calcium overload and/or attenuation of the inflammatory process after surgery.⁵ The postoperative AF study previously described also found that C-reactive protein levels were lower in the sodium nitroprusside group than placebo, supporting the hypothesis that inflammation plays a role in postoperative complications.¹¹

Acute Kidney Injury

Another potential consequence of CABG surgery is AKI. A meta-analysis of 33 randomized controlled trials revealed incidences of AKI after off-pump and on-pump CABG of 19.1% and 22.2%, respectively.¹² AKI after cardiac surgery is caused by decreased renal perfusion, enhanced vasoconstriction due to sympathetic nervous system activation, the inflammatory response, and reperfusion injury.¹³ Avoiding AKI in CABG patients receiving sodium nitroprusside is crucial, as use of sodium nitroprusside in kidney impairment may result in accumulation of toxic metabolites. A randomized, blinded study investigated the impact of sodium nitroprusside versus placebo on renal function in 240 elective on-pump CABG patients with a left ventricular ejection fraction (LVEF) $\leq 50\%$ and an estimated glomerular filtration rate (eGFR) >30 mL/min. Sodium nitroprusside was infused at a starting dose of 0.1 mg/kg/h (equivalent to 1.66 $\mu\text{g/kg/min}$) at the initiation of the rewarming period and titrated to maintain a MAP of 50 to 70 mmHg. Placebo patients received routine medical management to maintain MAPs at goal. Sodium nitroprusside patients excreted more urine during the surgery than placebo ($P < .05$); however, this effect attenuated during the first 24 hours after surgery. Postoperative serum creatinine peaks were significantly higher, and eGFR was significantly lower on postoperative days 1 to 5 in the placebo group, but the clinical significance of these findings is small, as serum creatinine differences between groups ranged from 0.05 to 0.14 mg/dL and eGFR differences ranged from 3 to 6 mL/min at each time point. However, despite similar renal function at baseline, the percent of patients with a new baseline creatinine clearance <50 mL/min was 14.7% in the sodium nitroprusside group versus 38.3% in the placebo arm ($P < .001$). In addition, the percent creatinine increase from baseline was 50% to 99% in 28.5% of placebo and 12.1% in sodium nitroprusside patients, and $>100\%$ in 6.9% of placebo and 1.6% of sodium nitroprusside patients ($P < .001$). Overall, the study suggests that sodium nitroprusside administration during the rewarming period of on-pump CABG surgery is associated with improved renal function compared with conventional management.¹⁴

Inflammation

CPB is known to trigger an acute inflammatory response as a result of blood contact with artificial surfaces in the pump, the use of priming solutions, and reperfusion injury.¹⁵ Increases in leukocytes, platelets, C-reactive protein, and inflammatory mediators including tumor necrosis factor α (TNF- α), interleukin 6 (IL-6), and IL-8 have been documented after CABG.^{15,16} Sodium nitroprusside, which functions as an NO donor, has been shown to attenuate the inflammatory response after surgery.¹⁷

Massoudy and colleagues conducted a prospective, randomized trial comparing administration of sodium nitroprusside 0.5 $\mu\text{g/kg/min}$ or placebo for 20 minutes immediately after release of the aortic cross-clamp during elective CABG surgery in 22 patients with an LVEF of $\geq 55\%$. In patients who received sodium nitroprusside, circulating IL-6 levels were reduced within a minute of sodium nitroprusside infusion, and IL-8 levels were reduced 15 minutes after the cessation of the sodium nitroprusside infusion. No differences in clinical outcomes such as need for dopamine or duration of ICU stay were observed.¹⁷ Later, Massoudy and colleagues conducted a similar prospective, double-blind study comparing sodium nitroprusside 0.5 $\mu\text{g/kg/min}$ with placebo, this time enrolling 30 elective CABG patients with an LVEF $\leq 40\%$ and increasing the duration of infusion to 60 minutes after cross-clamp removal. In this study, arterial levels of IL-6 and IL-8 were similar between groups. However, there was a trend toward lower concentrations of IL-6 and TNF- α in the coronary sinus in the sodium nitroprusside group, with decreases in the sodium nitroprusside arm reaching statistical significance for IL-6 at the 5-minute and for TNF- α at the 75-minute postperfusion time point. The study showed that sodium nitroprusside reduces the transcardiac release of some inflammatory mediators. Again, no clinical differences were observed between the groups.¹⁸ The sodium nitroprusside-mediated reductions in IL-6 and IL-8 levels may improve myocardial function.

Because cytokines are known to exert negative inotropic effects,¹⁹ Freyholdt and colleagues later conducted a prospective, double-blind study comparing the impact of sodium nitroprusside 0.5 $\mu\text{g/kg/min}$ or placebo infused for 60 minutes after aortic cross-clamp removal on myocardial performance in 30 patients with LVEF $\leq 40\%$ undergoing elective CABG.²⁰ Cardiac index (CI) was significantly higher in the sodium nitroprusside group at the 35th minute of reperfusion (immediately after termination of CPB: 4.4 ± 0.3 L/min/m² vs 3.7 ± 0.7 L/min/m², respectively) and the 75th minute of reperfusion (after operation complete: 3.8 ± 0.3 L/min/m² vs 3.0 ± 0.2 L/min/m², respectively). MAP was significantly lower in the sodium nitroprusside group at the same time points (67.7 ± 2.6 vs 77.1 ± 3.1 mmHg and 77.9 ± 3.7 vs 75.5 ± 3.5 mmHg, respectively), and mean pulmonary capillary wedge pressure was significantly higher in the sodium nitroprusside group at the same time points (13.9 ± 1.1 vs 11.5 ± 0.7 mmHg and 13.4 ± 0.9 vs 11.1 ± 0.7 mmHg, respectively),

suggesting that the improved CI in the sodium nitroprusside may be due to enhanced preload. The need for dopamine 24 hours after the operation was significantly lower in the sodium nitroprusside arm. One common concern related to the use of sodium nitroprusside is tachycardia, but in this study, the mean heart rate was lower in the sodium nitroprusside arm than placebo at the end of operation (97.6 ± 4.1 beats/min vs 109.6 ± 4.0 beats/min). The same study also measured concentrations of proinflammatory mediators in the radial artery and coronary sinus, and found a weak to moderate negative correlation between CI at the end of surgery and concentrations of proinflammatory mediators (correlation between CI and TNF- α levels at 5 minutes: $r = 0.398$; $P < 0.05$; IL-8 at 35 minutes: $r = 0.394$, $P < 0.05$; and IL-6 at 75 minutes: $r = 0.421$; $P < 0.025$).²⁰ The study supports the hypothesis that circulating cytokines reduce CI and that sodium nitroprusside may mitigate this response.⁵

Conduit Vasospasm

The use of arterial grafts during CABG surgery has increased in recent years due to increased duration of graft patency compared with venous grafts. However, graft vasospasm and inadequate blood flow through arterial grafts may cause a hypoperfusion syndrome.^{21,22} Circulating vasoconstrictors such as angiotensin II (Ang II) and endothelin 1 (ET-1) are elevated after CABG and enhance this effect. An in vitro study of internal mammary artery grafts treated with Ang II, ET-1, sodium nitroprusside, and nitroglycerin found that both vasodilators induced near-maximal conduit relaxation after Ang II- or ET-1-mediated contraction, but when applied to conduits prior to vasoconstrictor treatment, sodium nitroprusside outperformed nitroglycerin in preventing Ang II- or ET-1-mediated contraction.²¹ The same group later conducted a similar in vitro study of radial artery conduits and found that both sodium nitroprusside and nitroglycerin were effective at inducing relaxation. In addition, conduits which became tolerant to nitroglycerin are only weakly cross-tolerant to sodium nitroprusside, and the potency of sodium nitroprusside was maintained.²³ The potential clinical implications of these studies are that sodium nitroprusside may be effective at preventing Ang II- and ET-1-mediated graft contraction, treating said vasoconstriction, and may likely maintain its effect even in patients pretreated with nitroglycerin as low levels of cross-tolerance were reported. Additional clinical studies are required to confirm these findings in vivo.

Discussion

Currently available literature describes the impact of sodium nitroprusside on important postoperative complications including hypertension, AF, AKI, inflammation, and conduit vasospasm. Clinicians must practice evidence-based, pharmacoeconomically sound medicine when selecting vasodilators for CABG patients to mitigate these complications.

Several limitations to assessing the effectiveness of sodium nitroprusside in CABG patients exist. First, with the exception of trials examining postoperative hypertension, the majority of literature available compares sodium nitroprusside with placebo rather than another vasodilator. All of the studies identified enrolled only patients undergoing elective CABG, and the majority of surgeries were conducted on-pump. Studies enrolling emergent CABG patients and patients undergoing off-pump CABG procedures are needed. Because the potential risks of CABG-induced inflammation, postoperative AF, postoperative hypertension, AKI, and conduit vasospasm are well described, sodium nitroprusside should be compared with other agents hypothesized to reduce the incidence of these adverse events, rather than placebo. In addition, when available direct comparisons of intravenous vasodilators in CABG should be considered to aid in selection of the most appropriate agent.

As described above, clevidipine and nicardipine both reduced the rate of postoperative hypertension at least as well as sodium nitroprusside in randomized trials. These results confirm the findings of previous, smaller studies of sodium nitroprusside.²⁴ Sodium nitroprusside was associated with slower attainment of target BP, more excursions outside of BP goal, and more early heart rate increases than the intravenous calcium channel blockers. This data lend support to selecting an alternative vasodilator in preference to sodium nitroprusside for the management of postoperative hypertension in CABG patients. However, there is a paucity of head-to-head comparisons of other vasodilators in the setting of postoperative hypertension.

In one small randomized trial, 20 patients undergoing on-pump CABG surgery were randomized to receive nicardipine or nitroglycerin toward the end of surgery and continuing upon arrival to the ICU. Sodium nitroprusside could be added if the study drug did not adequately reduce SBP. Mean SBP was significantly lower in the nicardipine group at the time of arrival to the ICU; other SBP readings were similar between groups. Five nitroglycerin patients (50%) did not achieve the SBP goal, and 3 patients (30%) required the addition of sodium nitroprusside. In contrast, all nicardipine patients achieved the target SBP. In addition, the mean infusion duration required for nitroglycerin was 11.9 hours compared with 7.7 hours in the nicardipine group ($P < .025$).²⁵ This study suggests that nicardipine is a reasonable alternative to sodium nitroprusside for reducing postoperative hypertension; however, the sample size was small and requires further validation.

Another arm of the ECLIPSE trials described above included a comparison of nicardipine with clevidipine for management of postoperative hypertension after cardiac surgery. There was no difference in the primary endpoint of death, stroke, myocardial infarction, or renal dysfunction. Both agents performed similarly at maintaining BP within the target range. However, when BP targets were narrowed, patients treated with clevidipine experienced smaller excursions outside of range compared with nicardipine ($P = .0231$).

Clevidipine was also compared with nitroglycerin in the same study and was found to be more effective at keeping BP within goal range than nitroglycerin ($P = .0006$). Adverse events including postoperative AF were similar between all treatment arms.¹³

Based on the ECLIPSE trials, clevidipine and nicardipine may be preferred over sodium nitroprusside and nitroglycerin for managing postoperative hypertension. When selecting the most appropriate agent, clinicians should also consider pharmacokinetic differences between the 2 calcium channel blockers. Nicardipine plasma concentrations decline triexponentially with alpha, beta, and terminal half-lives of 3 minutes, 45 minutes, and 14 hours, consecutively. In contrast, clevidipine displays biphasic elimination with an initial half-life of 1 minute (predominant) and a terminal half-life of about 15 minutes. The longer half-life of nicardipine compared with clevidipine may interfere with rapid titration and increase the risk of hypotension. The Efficacy Study of Clevidipine Assessing Its Postoperative Antihypertensive Effect in Cardiac Surgery 2 (ESCAPE-2) trial provides additional evidence supporting the use of clevidipine in the setting of cardiac surgery. This placebo controlled, double blind trial which randomized 110 patients with a post-operative SBP ≥ 140 mm Hg warranting at least a 15% reduction after cardiac surgery to receive either clevidipine ($n = 61$) or placebo ($n = 49$). The treatment failure rate was lower in the clevidipine group versus placebo (8.2% vs. 79.6% respectively, $p < 0.0001$). The median time to target SBP with clevidipine was 5.3 minutes. The clevidipine group showed a significantly greater decrease in MAP than placebo. There were no differences between the clevidipine and placebo groups in rates of reflex tachycardia or other adverse events.²⁶

Literature supporting the use of sodium nitroprusside in CABG patients is largely based on placebo-controlled rather than head-to-head trials. Indeed, both the studies demonstrating a reduction in AKI and post-operative atrial fibrillation with use of sodium nitroprusside utilized a placebo comparator arm. To our knowledge, there are no head-to-head studies designed to compare rates of postoperative atrial fibrillation based on vasodilator selection. However in the ECLIPSE trial, rates of atrial fibrillation were similar between all treatment arms (clevidipine, nicardipine, nitroglycerin, and sodium nitroprusside).¹³ In addition, a recent meta-analysis confirms that there is no difference in rates of atrial fibrillation between clevidipine and comparator arms in published studies.²⁷

While sodium nitroprusside improves rates of renal dysfunction after CABG compared to placebo, the rates of renal dysfunction were also similar between all treatment arms in the ECLIPSE trial.¹³ Little data is available about the best vasodilator for reducing the risk of AKI after CABG. However, it is known that increased magnitude and/or duration of SBP excursions outside the target range are independent predictors of postoperative AKI (OR 1.8, $p = 0.0119$).²⁸ Since clevidipine seems to mitigate BP excursions compared to nitroglycerin,

nicardipine, and sodium nitroprusside, it may be the most effective agent at reducing rates of postoperative AKI.

Additional purported benefits of sodium nitroprusside include reductions in inflammation after surgery. While sodium nitroprusside has been shown to reduce the hospital length of stay compared to placebo, head to head trials are needed to determine if this is a vasodilator class effect or a specific property of the drug. Little is known about other vasodilators in this setting.

Conclusions

In summary, sodium nitroprusside is an intravenous vasodilator which is frequently utilized in the perioperative CABG setting. It effectively attenuates the inflammatory response caused by surgery, reduces the risk of postoperative AF, and improves kidney function compared with placebo. However, it performs similarly to nicardipine and is less effective than clevidipine at maintaining perioperative BP within target range.

In contrast to the increase in AWP for sodium nitroprusside, a 50-mL vial of clevidipine 25 mg/50 mL was \$79.62 at the time of this publication.²⁹ In response to rising drug costs and an evidence-based class review of vasodilators, one hospital has described a therapeutic interchange program substituting clevidipine for sodium nitroprusside in cardiac surgery patients. The program is projected to result in a net cost avoidance of about \$300 000 over 1 year at a 520-bed institution which performs more than 300 cardiac surgeries annually.³⁰

Clevidipine is generally well-tolerated, quickly titratable, and has no clinically relevant metabolic drug interactions. It can be administered through peripheral or central lines. Clevidipine formulations contain soya bean oil and egg phospholipids, so use is contraindicated in patients with egg or soy allergy. Potential adverse events are hypotension and nausea. Increased serum triglycerides or acute pancreatitis are possible with prolonged infusions.

For patients undergoing cardiac surgery, clevidipine is more effective than sodium nitroprusside, nicardipine, and nitroglycerin at reducing BP excursions, which may also be protective against AKI. Current data suggest similar rates of postoperative AF compared with other agents. This evidence compounded by the high costs of sodium nitroprusside lends support to utilizing clevidipine as an alternative to sodium nitroprusside after CABG surgery.

Declaration of Conflicting Interests

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