Original Article

Evaluation of Sodium Nitroprusside Efficacy in Decreasing the Incidence and Duration of Atrial Fibrillation After Coronary Artery Bypass Grafting

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ABSTRACT

Background: The incidence of atrial fibrillation (AF) after coronary artery bypass grafting (CABG) can leave irreparable sequelae; thus, the prevention of this common arrhythmia has particular importance. The aim of this prospective study was to evaluate the efficacy of sodium nitroprusside (SNP) in lessening the incidence and duration of AF after CABG.

Methods: This prospective double-blind randomized clinical trial compared the efficacy of SNP in reducing the incidence and duration of post-CABG AF between 2 groups of 30 patients each hospitalized in the Heart Surgery Department of Golestan Hospital, Ahvaz, Iran, between February 2017 and June 2017.

Results: Post-CABG AF occurred in 8 (26.7%) patients in the control group and 2 (6.7%) in the SNP group (P = 0.038). The average surgery time in the control and SNP groups was 189.93 ± 31.40 minutes and 167.47 ± 13.48 minutes, respectively, which was statistically significant (P = 0.001). The findings concerning preoperative treatment drugs showed that 52% (26/50) of the patients without AF had used clopidogrel, with 10% (1/10) of these patients suffering AF (P = 0.015). The consumption of another agent, either angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), was accompanied by AF in 3 (30%) patients, whereas the use of another agent was not accompanied by AF in 32 (64%) patients (P = 0.046).

Conclusions: This study demonstrated that the prophylactic administration of SNP during the rewarming period in CABG significantly reduced the incidence of postoperative AF and surgery time. Furthermore, preoperative treatment drugs, including clopidogrel and ACE inhibitors or ARBs played a significant role in reducing AF occurrence. ***(Iranian Heart Journal 2021; 22(1): 16-25)***

KEYWORDS: Coronary artery bypass grafting, Atrial fibrillation, Sodium nitroprusside

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The prevalence of cardiovascular diseases, especially coronary artery disease, is growing and despite efforts to treat these patients, the associated morbidity and mortality are still high.[1] Among the possible methods of treating coronary artery disease, coronary artery bypass grafting (CABG) is a method with high efficiency.[2] The outcome of this treatment modality hinges upon due attention and special management aimed at improving its performance,[3] and it is currently commonly practiced not only in both developed and developing countries.[4] Nonetheless, CABG is very risky and associated with high morbidity and mortality.[5] While some adverse effects such as bleeding and delirium are transient after CABG,[6] others such as stroke have long-term effects and impact the physical condition of the patient seriously. These effects include such cardiovascular complications as myocardial infarction, arrhythmias, infections, neurological problems, kidney failure, and digestive problems.[5-10] Among the mentioned effects, arrhythmias hold a special place, with atrial fibrillation (AF) having a high prevalence.[11] AF has a high prevalence of about 20% to 40% after CABG, and in fact, it is a supraventricular tachyarrhythmia that is determined with uncoordinated atrial activity.[12, 13] The cause of AF has yet to be fully elucidated, but research implies that the precipitating factors can be older age, male gender, AF history, unprotected ischemia, congestive heart failure, loss of electrolytes (lower potassium and magnesium), dysfunction of the left atrium, long-term aortic cross-clamping, low ejection fraction, treatment cessation with beta-blockers, underlying diseases such as chronic obstructive pulmonary disease, renal failure, and the number of diseased vessels.[14-16] In about 80% of cases, AF after CABG ultimately returns to sinus rhythm in the first 3 days with treatment.[15] Nevertheless, it should be noted that AF increases the risk of stroke, hypertension, and pulmonary edema, thereby requiring special attention. Research has shown that AF usually occurs on the second to fourth postoperative days.[11, 15] In addition to the mentioned effects, hemodynamic disorders, myocardial infarction, re-intubation, and thromboembolism after heart surgery, as well as long hospital lengths of stay and increased costs, are associated with AF treatment.[17, 18] For the treatment of this condition, many pharmacological agents such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), supplements such as vitamin C and vitamin E, thiazolidinediones, N-acetylcysteine, NADPH oxidase inhibitors, and xanthine inhibitors have been utilized. Still, researchers seek to find more efficient pharmacological interventions.[19, 20] Sodium nitroprusside (SNP) is the most commonly used vasodilator in cardiac surgery, mainly due to its efficacy, speed of onset, and short course of action.[21] Given the high incidence of AF following CABG and its associated morbidity, mortality, and costs, it is of vital importance to find reliable diagnostic measures to determine patients at risk of postoperative AF. Further, since the incidence of AF after CABG can leave irreparable sequelae, the prevention of this common arrhythmia is of particular importance. The present prospective study, designed as a randomized double-blind clinical trial, sought to evaluate the efficaciousness of SNP in the prevention of AF in patients undergoing elective CABG.

METHODS

Study Design and Patient Characteristics

The study protocol of the current prospective double-blind randomized clinical trial was approved by the university ethics committee. The aim of the study was to compare the efficacy of SNP in decreasing the incidence and duration of AF after CABG in 60 patients aged above 18 years hospitalized in the Heart Surgery Department of Golestan Hospital, Ahvaz, Iran, between February 2017 and June 2017.

Exclusion Criteria

The exclusion criteria consisted of a history of AF, previous CABG, severe valvular diseases, previous valvular repair or replacement surgery, candidacy for valvular repair or replacement surgery, atrial size greater than normal in preoperative echocardiography, anemia or severe electrolyte abnormalities before surgery, thyroid disease, sick sinus syndrome, bradycardia and significant changes in atrioventricular conduction, and a history of permanent pacemaker implantation.

Preoperative Assessments

Prior to surgery, changes in electrocardiograms; findings of echocardiographic examinations (eg, ejection fraction) and noninvasive tests (the exercise test or myocardial perfusion scanning); consumption of beta-blockers, calcium channel blockers, ACE inhibitors, ARBs, and nitric acid; frequencies of arrhythmias; presence of angina pectoris, hypertension, respiratory disease, kidney disease, diabetes, and hypercholesterolemia; and levels of hemoglobin, hematocrit, calcium, potassium, magnesium, and C-reactive protein were evaluated and recorded in the entire study population.

CABG

The patients underwent cardiopulmonary bypass via the standard method with myocardial perfusion protection through cardioplegia. After surgery, in the intensive care unit, changes in the electrocardiogram and hemodynamics, including arterial blood pressure, heart rate, and central venous pressure, were continuously monitored. After discharge from the intensive care unit and transfer to the ward, the patients were monitored for 5 days constantly.

Twelve-lead electrocardiography before surgery and thereafter daily until the fifth postoperative day was performed routinely for all the patients. The level of hemoglobin was checked routinely, and if anemia was detected, modifications were done. The serum magnesium concentration before surgery was maintained at more than 2 mEq/L. Also, potassium and calcium serum concentrations were kept at more than 4 mmol/L and 8 mg/dL, correspondingly.

Protocol Treatment With SNP

The patients in the control and treatment groups received 5% dextrose in water as a placebo and SNP at a dose of 0.5 to 2 µg/kg/min as an intravenous infusion during the rewarming period in CABG for 60 minutes, respectively. The mean arterial pressure in both groups of patients was kept at about 65 mm Hg.

The researchers in all stages, including drug preparation and the 1-hour drug infusion, monitored the patients at the bedside. The drug was infused at a minimum dose under continuous vital sign monitoring. When the mean arterial pressure reached 65 mm Hg, the infusion was discontinued.

AF Evaluation and Patient Follow-up

The primary endpoints of this study were the onset and duration of postoperative AF in both groups. The incidence of AF was considered for analysis if it occurred during a 5-day period after CABG. The instances of AF lasting more than 15 minutes were considered significant. The patients who developed AF, according to the protocol, were treated with intravenous amiodarone. Postoperatively, the levels of hemoglobin, hematocrit, calcium, potassium, magnesium, and C-reactive protein were checked as a routine and any disorder was listed and modified.

Statistical Analysis

SPSS software, version 25, was used to analyze the data. Numbers and mean±SD were employed to express the descriptive statistics. For the determination of statistically significant differences in the mean values between the characteristics of the control and SNP groups, the χ^2 test and the *t*-test with 95% confidence intervals were conducted for the nominal and scale variables, respectively. Once again, the χ^2 test and the independent samples *t*-test were applied to compare the mean values between the patients with AF and those without AF. Asymptotic significance (2-sided) and 2-tailed significant differences were reported from the results of the descriptive statistics.

RESULTS

The study population was comprised of 60 patients, divided into 2 equal groups of control and SNP. As is seen in Table 1, both SNP and control groups consisted of 20 male and 10 female patients; the difference between the 2 groups was, therefore, nonsignificant (P = 1.000). The 2 groups of control and SNP were also not statistically significantly different in terms of the prevalence of risk factors, including myocardial infarction, angina, dyslipidemia, diabetes mellitus, hypertension, cerebrovascular accident, and family history of coronary artery disease (P > 0.05). The only significant difference was seen as regards current smoking in the history of the patients.

According to Table 1 during the study period, 8 (26.7%) patients in the control group and 2 (6.7%) in the SNP group developed AF following CABG (P = 0.038). Postoperatively, 1 patient in the SNP group and 2 patients in the control group used inotropes, but the difference between the 2 groups was nonsignificant (P = 0.083). Intraoperatively, 5 patients in the control group and 10 patients in the SNP group consumed inotropes; however, the difference between the 2 groups failed to constitute statistical significance (P = 0.136). The use of intraoperative defibrillation for the SNP group was 4 times that of the control group, but the difference was nonsignificant (P = 0.161). Consequently, the data on preoperative treatments and operative characteristics showed no statistically significant differences between the control and SNP groups. Furthermore, no death occurred in the 2 study groups during the study period.

The data analysis on the quantitative variables, presented in Table 2, showed that the mean age of the patients was 62.23 ± 10.80 years in the control group and 63.23 ± 9.82 years in the SNP group, denoting no significant difference between the 2 groups (P = 0.709). Also, no significant differences were observed between the SNP and control groups vis-à-vis the mean base value of the body mass index, the glomerular filtration rate, the ejection fraction, and the erythrocyte sedimentation rate (P > 0.05).

As is depicted in Table 2, the average surgery time was 189.93 ± 31.40 minutes in the control group and 167.47 ± 13.48 minutes in the SNP group; the difference between the groups was, thus, statistically significant (P = 0.001). The mean cross-clamp time was 44.67 ± 12.25 minutes in the control group and 42.17 ± 11.08 minutes in the SNP group, with the difference between the groups failing to constitute statistical significance (P = 0.410). The mean cardiopulmonary bypass time was 69.6 ± 20.28 minutes in the control group and 71.2 ± 16.59 minutes in the SNP group; the difference was nonsignificant (P = 0.739). The mean rewarming time was 35.40 ± 7.97

minutes in the control group and 32.47 ± 7.29 minutes in the SNP group, and the difference was not statistically significant (*P* = 0.142). Furthermore, the mean±SD of variables such as heart rate, mean blood pressure, hemoglobin, and temperature in both groups before AF is presented in Table 2. The test results showed no significant differences with respect to these variables between the 2 groups. AF in the control group occurred 2.00 ± 0.58 days after surgery, while it occurred 2.33 ± 0.58 days following surgery in the experimental group (SNP). The nonparametric Mann–Whitney test results showed no significant difference apropos the onset AF between the control and SNP groups (*P* = 0.427). Similarly, the mean duration of AF was 27.43 ± 23.96 minutes in the control group and 30.00 ± 25.46 minutes in the SNP group; the difference was not statistically significant (*P* = 0.898).

Apart from a statistically significant difference in surgery time between the control and SNP groups, more saphenous vein grafts were used for the SNP group, and the difference in this regard between the groups was statistically significant (*P* = 0.046).

Table 3 shows the comparison of operative variables between patients with AF and those without AF. Except for smoking history (*P* = 0.046), the other history variables were not statistically significantly different between the control and SNP groups (*P* > 0.05). In regard to the preoperative treatment drugs, the results showed that 52% (26/50) of the patients without AF had used clopidogrel, with 10% (1/10) of these patients developing AF (*P* = 0.015). The consumption of another agent, either ACE inhibitors or ARBs, was accompanied by AF in 3 (30%) patients, whereas the use of another agent in 32 (64%) patients was not accompanied by AF (*P* = 0.046). There were no significant differences between the groups as regards the comparison of the other variables.

According to Table 4, the mean surgery time was 192.80 ± 26.78 minutes in the patients who developed AF and 175.88 ± 25.79 minutes in those who did not develop this arrhythmia; nonetheless, this difference between the 2 groups was not statistically significant (*P* = 0.065). The other variables, including the mean cross-clamp time, the mean cardiopulmonary bypass time, and the mean rewarming time, were not statistically significantly different between the SNP and control groups (*P* > 0.05). The mean ejection fraction before surgery was 47.50 ± 7.91 in the AF group and 40.00 ± 11.25 in the group without AF; the difference was statistically meaningful (*P* = 0.05). The mean ejection fraction after surgery was 46.00 ± 7.75 in the AF group and 38.06 ± 10.96 in the group without AF, and the difference was statistically significant (*P* = 0.033).

The results of our multinomial logistic regression analysis to identify the predictors of AF in the control and SNP groups showed that age, gender, and ejection fraction exerted no significant effect on the incidence of AF (Table 5).

Table 1: Pre- and postoperative characteristics of the patients

Variables	SNP Group (n=30)	Control Group (n=30)	*P* value
Gender: Male	20(66.7%)	20(66.7%)	1
History			
MI within the preceding 2 weeks	7(23.3%)	4(13.3%)	0.317
Angina	28(93.3%)	26(86.7%)	0.612
DLP	20(66.7%)	19(63.3%)	0.787
DM	13(43.3%)	8(26.7%)	0.176
Hypertension	21(70.0%)	23(76.7%)	0.559
CVA	4(13.3%)	2(6.7%)	0.389
FH of CAD	3(10.0%)	1(3.3%)	0.284
MI	7(23.3%)	7(23.3%)	0.942
Current smoker	11(36.7%)	4(13.3%)	**0.037**
Preoperative Treatment			
Beta-blockers	27(90.0%)	25(83.3%)	0.448
Statin	29(96.7%)	27(90.0%)	0.301
Calcium channel blockers	1(3.3%)	4(13.3%)	0.161
ASA	27(90.0%)	30(100.0%)	0.076
Clopidogrel	13(43.3%)	14(46.7%)	0.795
ACE inhibitors / ARB	16(53.3%)	19(63.3%)	0.432
CAD			
2VD	2(6.7%)	8(26.7%)	0.128
3VD	21(70.0%)	15(50.0%)	
2VD+LM	0(0.0%)	1(3.3%)	
3VD+LM	7(23.3%)	6(20.0%)	
Operative Characteristics			
Incidence of AF	2(6.7%)	8(26.7%)	**0.038**
LIMA use	28(93.3%)	24(80.0%)	0.129
Intraoperative defibrillation	4(13.3%)	1(3.3%)	0.161
Intraoperative inotrope consumption	10(33.3%)	5(16.7%)	0.136
Special situation	2(6.7%)	1(3.3%)	0.389
Postoperative Inotrope Consumption	1(3.3%)	2(6.7%)	0.083
Operative Mortality	0(0.0%)	0(0.0%)	1

SNP, Sodium nitroprusside; MI, Myocardial Infarction; DLP, Dyslipidemia; DM, Diabetes mellitus; CVA, Cerebrovascular accident; FH, Familial history; CAD, Coronary artery disease; ASA, Aspirin; ACE, Angiotensin-converting enzyme; ARB, Angiotensin receptor blockers; VD, Vessel disease; LM, Left main; AF, Atrial fibrillation; LIMA, Left internal mammary Artery
Values are shown as n (%).

Table 2: Comparisons of the operative characteristics between the SNP and control groups

Variables	**SNP Group (n=30)**	**Control Group (n=30)**	***P* value**
Age, y	63.23±9.82	62.23±10.80	0.709
BMI, kg/m^2	24.86±2.17	24.32±1.35	0.252
GFR, mL/min per 1.73 m^2	72.20±23.65	73.46±9.59	0.787
Preoperative EF	41.83±11.41	40.67±10.89	0.687
ESR, mm/h	25.17±16.50	18.67±10.28	0.072
Surgery time, min	167.47±13.48	189.93±31.41	**0.001**
Cross-clamp time, min	42.17±11.08	44.67±12.25	0.410
Bypass time, min	71.20±16.59	69.60±20.28	0.739
Rewarming time, min	32.47±7.29	35.40±7.97	0.142
Mechanical ventilation, min	28.00±11.07	26.40±7.32	0.512
Heart rate before AF, bpm	105.67±20.60	103.71±11.00	0.845
Temperature before AF, °C	36.87±0.15	36.97±0.20	0.441
Mean blood pressure before AF, mm Hg	75.00±13.08	76.00±8.79	0.889
Hb before AF, mg/DL	10.57±1.10	10.49±0.83	0.900
AF duration, min	30.00±25.46	27.43±23.96	0.898
Time of AF onset of day	2.33±0.58	2.00±0.58	0.427
Postoperative EF, %	39.00±11.17	39.77±10.70	0.787
SVG	2.50±0.68	2.07±0.94	**0.046**

SNP, Sodium nitroprusside; BMI, Body mass index; GFR, Glomerular filtration rate; ESR, Erythrocyte sedimentation rate; EF, Ejection fraction; AF, Atrial fibrillation; Hb, Hemoglobin; SVG, saphenous vein graft use
Values are shown as mean±SD.

Table 3: Pre- and postoperative characteristics of the patients with AF and those without AF

Variables		With AF (n=10)	Without AF (n=50)	*P value*
Gender: Male		7(70%)	33(66%)	0.806
History				
	MI within the preceding 2 weeks	0(0%)	11(22%)	0.101
	Angina	8(80%)	46(92%)	0.758
	DLP	5(50%)	34(68%)	0.276
	DM	3(30%)	18(36%)	0.717
	Hypertension	6(60%)	38(76%)	0.296
	CVA	0(0%)	6(12%)	0.248
	FH of CAD	1(10%)	3(6%)	0.657
	MI	2(20%)	12(24%)	0.761
	Current smoker	0(0%)	15(30%)	**0.046**
Preoperative Treatment				
	Beta-blockers	10(100%)	42(84%)	0.174
	Statin	9(90%)	47(94%)	0.643
	Calcium channel blockers	2(20%)	3(6%)	0.144
	ASA	9(90%)	48(96%)	0.427
	Clopidogrel	1(10%)	26(52%)	**0.015**
	ACE inhibitors / ARB	3(30%)	32(64%)	**0.046**
CAD				
	2VD	3(30%)	7(14%)	0.525
	3VD	6(60%)	30(60%)	
	2VD+LM	0(0%)	1(2%)	
	3VD+LM	1(10%)	12(24%)	
Operative Characteristics				
	LIMA use	9(90%)	43(86%)	0.734
	Intraoperative defibrillation	2(20%)	3(6%)	0.144
	Intraoperative inotrope use	4(40%)	11(22%)	0.23
Operative Mortality		0(0%)	0(0%)	1

BMI, Body mass index; GFR, Glomerular filtration rate; ESR, Erythrocyte sedimentation rate; EF, Ejection fraction; AF, Atrial fibrillation; Hb, Hemoglobin; SVG, saphenous vein graft use
Values are shown as mean±SD.

Table 4: Operative characteristics of the patients with AF and those without AF

Variables	With AF (n=10)	Without AF (n=50)	*P value*
BMI, kg/m^2	24.83± 1.80	24.53± 1.82	0.639
GFR, mL/min per 1.73 m^2	73.40± 11.70	72.71± 18.99	0.913
ESR, mm/h	21.30± 10.23	22.04± 14.74	0.880
Preoperative EF, %	47.50± 7.91	40.00± 11.25	**0.050**
Surgery time, min	192.80± 26.78	175.88± 25.79	0.065
Cross-clamp time, min	45.20± 13.77	43.06± 11.30	0.600
Bypass time, min	77.90± 22.38	68.90± 17.36	0.159
Rewarming time, min	36.00± 8.93	33.52± 7.48	0.358
Postoperative EF, %	46.00± 7.75	38.06± 10.96	**0.033**

BMI, Body mass index; GFR, Glomerular filtration rate; ESR, Erythrocyte sedimentation rate; EF, Ejection fraction; AF, Atrial fibrillation; Hb, Hemoglobin; SVG, saphenous vein graft use
Values are shown as mean±SD.

Table 5: Multinomial logistic regression analysis to determine predictors

Effect	χ2	*P value*
Age	1.733	0.188
Preoperative EF	0.002	0.964
Postoperative EF	0.467	0.495
Gender	0.097	0.755

EF, Ejection fraction
The χ2 statistic is the difference in -2 log-likelihoods between the final model and a reduced model.

DISCUSSION

The results of the present study showed that 8 (26.7%) patients in the control group and 2 (6.7 %) patients in the experimental group during the study period developed AF after CABG, and the prevalence of AF in the SNP group was significantly lower (*P* = 0.038). The differences between our 2 study groups concerning the other variables evaluated were not statistically significant. Some of the changes in the variables were similar between the control and SNP groups due to the detailed design of the inclusion and exclusion criteria. Be that as it may, the only difference with statistical significance between the groups was the number of current smokers: 4 in the control group and 11 in the SNP group (*P* = 0.037).

Our analysis of operative characteristics showed that the patients in the SNP group had a shorter surgery time than the control group; the difference was statistically meaningful. Therefore, SNP curtailed surgery time significantly. More saphenous vein grafts were also used in the SNP group than in the control group, and the difference between the groups in this regard was statistically significant.

The mean surgery time in the patients who developed AF was less than that in those who did not develop AF; the difference was, however, nonsignificant (*P* = 0.065). We observed a statistically significant difference with regard to the pre- and postoperative ejection fraction between the patients with AF and those without AF. Additionally, the results of our multinomial logistic regression revealed that age, gender, and pre- and postoperative ejection fraction were not related to the incidence of AF. There was also no statistically meaningful difference in terms of AF onset between the control and SNP groups.

Cavolli et al[22] showed the effectiveness of SNP in the prevention of AF in patients undergoing CABG. They found AF in 12% of their SNP group and 27% of their control group. The occurrence of AF in the SNP group was significantly less than that in the control group (*P* = 0.005). In their study, in line with our investigation, SNP reduced the rate of AF. In this regard, we also found that surgery time in the SNP group was significantly shorter than that in the control group.

In the United States, Bolesta et al[23] conducted a study to determine the relationship between the intraoperative consumption of SNP and postoperative AF. The incidence of postoperative AF was 25.4% in the SNP group and 27.9% in the control group. Their study showed no relationship between the intake of SNP during cardiac surgery and AF after surgery.

Unlike the studies by Cavolli et al[22] and Bolesta et al,[23] our results showed that preoperative treatment drugs, including clopidogrel and ACE inhibitors or ARBs, played a significant role in reducing AF occurrence. Some previous investigations have also reported that preoperative drugs such as beta-blockers affect the prevalence of postoperative AF.[13]

A previous study on SNP indicated that not only could the drug prevent heart arrhythmias but also it was useful with respect to other negative consequences and complications of cardiac surgery. For instance, it was shown that the infusion of SNP through the use of cardiopulmonary bypass lessened renal effects after surgery.[24]

CONCLUSIONS

Overall, the results of the current study demonstrated that the prophylactic administration of SNP during the rewarming period in CABG significantly reduced the incidence of postoperative AF and surgery time. Preoperative treatment drugs also played a significant role in lessening the incidence of postoperative AF. However, further studies with larger sample sizes and more cardiac-related variables are required to show other preventive benefits of SNP use in patients undergoing CABG.

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