Effect of stellate ganglion block versus intraluminal application of verapamil-nitroglycerine solution on internal mammary artery graft blood flow rate in patients undergoing on-pump coronary artery bypass grafting

Hoda Shokri^a, Ihab Ali^b

^aAnesthesiology, ^bCardiothoracic Surgery, Ain Shams University, Cairo, Egypt

Correspondence to Hoda Shokri, MD, PhD, Cardiothoracic Surgery, Ain Shams University, Cairo, 11772, Egypt. Tel: +20 121 117 9234; fax: +20 22439622; e-mail: drhoda10@yahoo.com

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Background

Left internal mammary artery (IMA) graft is the most promising arterial conduit for coronary artery bypass grafting. Stellate ganglion block (SGB) induces sympathetic blockade and is used to prevent or control spasm of the internal mammary artery. The purpose of this study was to investigate the effect of left SGB on left IMA blood flow rate.

Patients and methods

A total of 170 patients aged between 65 and 70 years, with American Association of Anesthesiologists physical status II and III, and scheduled for elective coronary artery bypass grafting, were randomly allocated to either a SGB group or a verapamil-nitroglycerine group. In the SGB group, the patients received SGB using 8 ml of bupivacaine 0.25%. In the verapamil-nitroglycerine group, the patients received intraluminal injection of the harvested IMA graft with a solution, containing verapamil 5 mg, nitroglycerine 2.5 mg, heparin 500 U, 8.4% NAHCO₃ 0.2 ml, and ringer solution 40 ml, throughout its whole length using a small syringe, and with a low dose of intravenous nicardipine infusion started after harvesting (5 mg nicardipine in 100 ml saline at a rate of 0.5 mg or 10 ml/h). IMA blood flow rate (primary outcome), abnormal ECG changes, ICU length of stay, intra-aortic balloon usage, pre–postoperative pulse rate and blood pressure, incidence of atrial fibrillation, radio-femoral arterial pressure difference, pre–postoperative ejection fraction, need for re-exploration, and mortality rate were observed.

Results

This prospective study showed a significant increase of IMA blood flow rate (P<0.001) and nonsignificant decrease in mortality rate in the SGB group compared with the verapamil-nifedipine group. There was no significant difference between the two groups regarding ICU length of stay, re-exploration, intra-aortic balloon usage, preoperative and postoperative mean pulse rate, preoperative and postoperative ejection fractions between study groups. The incidence of atrial fibrillation (P=0.030) and abnormal ECG changes (P=0.043) was significantly lower in SGB group. Radio-femoral pressure difference was significantly lower in SGB group at 20 and 40 min after cardiopulmonary bypass.

Conclusion

The results of this study showed that SGB prevents IMA spasm, increases its blood flow rate, and decreases incidence of atrial fibrillations compared with intraluminal injection of verapamil and nitroglycerine combined with intravenous nicardipine.

Keywords:

coronary artery bypass graft, internal mammary artery, nitroglycerine, stellate ganglion block, verapamil

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Introduction

Internal mammary artery (IMA) graft is a more popular arterial graft compared with saphenous vein graft for myocardial revascularization in coronary artery bypass. It is characterized by long-term patency, which results in lower mortality rates and excellent postoperative outcomes [1]. However, the arterial conduit spasm is always a frustrating complication in coronary artery bypass surgeries, as it can be lethal owing to its catastrophic hemodynamic consequences, with an incidence of 0.43% [2]. The mechanism of graft spasm is still unexplained [2]. The systemic or topical application of various

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pharmacological agents, such as calcium antagonists or nitroglycerine, has been proven to reverse or avoid spasm but is unfortunately associated with alarming adverse effects [3]. Stellate ganglion block (SGB) application using local anesthetics is effective in the pain management and treatment of vascular spastic conditions of the upper limb owing to its sympatholytic effect [4]. Regrettably, few studies have investigated the effect of SGB on the spasm of IMA grafts [5]. An earlier study by Koyama *et al.* [6] stated that SGB suppressed cardiac sympathetic function without any significant effect on blood pressure.

The aim of this prospective study was to evaluate the effect of left SGB compared with the intraluminal injection of verapamil combined with nitroglycerine on the left internal artery blood flow rate, the incidence of atrial fibrillations, ICU stay length, and incidence of postoperative adverse events.

Patients and methods

The study was approved by the ethics committee of Ain Shams University (reference no. FWASU R 27/ 2018), and written informed consent was obtained from each patient. This prospective, randomized, parallel-group study was conducted with 170 patients between 65 and 70 years old, with American Association of Anesthesiologists physical status II or III, scheduled for elective coronary artery bypass grafting (CABG) by the same surgical team. Operations were carried out in Ain Shams University Hospital cardiothoracic academy from November 2018 to November 2019. Patients with existing coagulopathy, recent myocardial infarction, pathological bradycardia (heart rate<60 beats/min), unstable angina, impaired ventricular function (ejection fraction <40%), emergency CABG, left main coronary artery disease, and contralateral phrenic nerve palsy were not eligible to participate in this study. The inclusion criteria were age between 65 and 70 years old; patients with ejection fraction more than 40%; absence of heart failure or chronic obstructive lung disease; and elective CABG.

Preanesthetic evaluation and routine investigations were carried out the night of surgery. In addition, all patients underwent elective left internal mammary artery (LIMA) angiography and echocardiography in conjugation with cardiac consultation. Patients fasted for 6–8 h. Intraoperative transesophageal Echo was performed by an experienced cardiac anesthesiologist throughout the whole surgery. All patients were administered standard general anesthesia. Midazolam premedication was limited to 0.05 mg/kg intravenous. Anesthesia was induced with $12 \mu g/kg$ fentanyl, 5–7 mg/kg sodium thiopental, and 0.15 mg/kg pancuronium and was maintained with isoflurane 1-2.0%. Heart rate and blood pressure were maintained within 20% of the baseline values. Patients were randomly allocated either to the SGB group or to the verapamil-nitroglycerine group according to a computerized randomization code, with allocation ratio 1 : 1. In the SGB group (n=85), patients were placed in the spine position, head to the right side with neck extension. First, the C6 vertebral body was spotted at the level of the cricoid cartilage, and next, the C6 anterior tubercle, named the carotid tubercle, was palpated. Later, pressure was applied to depress the lung dome to avoid pneumothorax. A 22 G needle was inserted toward the carotid tubercle and advanced inferomedially to the C6 body. Once it touched the body, it was withdrawn 1-2 mm, and 8 ml of bupivacaine 0.25% was injected (after negative aspiration for blood), as shown in Fig. 1. The correct placement of the needle and spread of bupivacaine were confirmed by rapid increase of the left index's skin temperature by 1.5°C compared with the baseline value; the block was performed by the same well-trained anesthesiologist. The verapamilnitroglycerine group (n=85) underwent intraluminal injection of the harvested IMA graft with the solution containing verapamil 5 mg, nitroglycerine 2.5 mg,





Ultrasound image of SGB. A 22 G needle was inserted toward the carotid tubercle and advanced inferomedially to the C6 body. Once it touched the body, it was withdrawn 1–2 mm and 8 ml of bupivacaine 0.25% was injected. CA, carotid artery; IJV, internal jugular vein; SCM, sternocleidomastoid; SGB, stellate ganglion block; TP, transverse process of C6 vertebra.

heparin 500 U, 8.4% NAHCO₃ 0.2 ml, and Ringer solution 40 ml throughout its whole length using a small syringe, followed by a low dose of intravenous nicardipine infusion (5 mg nicardipine in 100 ml saline at a rate of 0.5 mg or 10 ml/h) performed after initiation of harvesting. The IMA pedicle was also wrapped in the solution-soaked sponge. In case of the incidence of vasospasm, ITA flow volume was markedly reduced after mobilization from the chest wall. This vasospasm was caused by surgical dissection of the artery as well as physical factors such as diathermy or exposure to cold. The artery dilated, and its flow markedly improved following the intraluminal and topical administration of pharmacologic agents such as nitroglycerin-verapamil and was assessed by free flow measurement in this study.

After 1h of SGB performance, cardiopulmonary bypass (CPB) was established. All patients had median sternotomy. Anticoagulation was achieved with heparin 300 U/kg administered into the right atrium to maintain an activated clotting time above 480 s. CPB was conducted with nonocclusive roller pumps, membrane oxygenators, arterial line filtration, and cold blood-enriched hyperkalemic arrest. The CPB circuit was primed with 1.8 l lactated Ringer's solution and 50 ml of 20% mannitol. Management of CPB included systemic hypothermia (esophageal temperature 32°C) during aortic cross-clamping, targeted perfusion pressure between 60 and 80 mmHg, and pump flow rate of 2.2 l/min/m². Myocardial protection was achieved with antegrade cold blood cardioplegia. A 32-µm filter (Avecor Affinity, Minneapolis, Minnesota, USA) was used in the arterial perfusion line. Before separation from the CPB, patients were warmed to 36-37°C. After separation from the CPB, heparin was neutralized with protamine sulfate (1 mg/100 U heparin) to reach an activated clotting time within 10% of baseline. All patients were transferred to the ICU after surgery.

The primary end point

Mean blood flow measurement

Five minutes after systemic heparinization, the free flow from the distal cut end of the IMA was determined by allowing the IMA to bleed into an open beaker for 1 min and measuring the volume per min. The IMA was then occluded gently with a bulldog clamp (flow 1), known as timed volumetric collections of the cut end of the IMA. Before the start of CPB, the flow of the IMA was repeated (flow 2). Before measurement of IMA blood flow, none of the patients received phenylephrine or norepinephrine infusion. IMA blood flow was measured while mean arterial blood pressure was maintained between 70 and 75 mmHg.

Secondary endpoints

Evidence of postoperative electrocardiogram changes such as postoperative cardiac arrhythmia as ventricular fibrillations, ventricular tachycardia, and S-T segment elevation (time frame: up to 7 days); ICU stay length; need for intra-aortic balloon pumping; need for inotropic drugs postoperatively; postoperative atrial fibrillation; pre–postoperative pulse rate and blood pressure; radio-femoral arterial pressure difference; pre–postoperative ejection fraction; and 30-day postoperative mortality rate were the secondary endpoints. All cardiac parameters were measured by the same expert cardiologist.

Sample size calculation

Power Calculations and Sample Size software (PASS; NCSS, LLC, East Kaysville, Utah, USA) revealed that 170 patients, 85 per arm, were needed after considering a 5% dropout (power of 80%, alpha error at 5%). These calculations were based on a previous study [5], which showed that the mean blood flow was 47.3±3.4 and 60.5±5.2 ml/min in the non-SGB and SGB groups, respectively.

Statistical analysis

The collected data were coded and tabulated, and statistical analysis was performed using the SPSS software package, version 17.0 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics were carried out for numerical parametric data and presented as mean \pm SD, whereas categorical data are presented as number and percentage. Variables such as demographic data and comorbidities were compared using the χ^2 test. A *P* value less than 0.05 was considered statistically significant.

Results

A total of 170 patients were assessed for eligibility and were all enrolled in our study with no single case of protocol violation as shown in the consort flow diagram (Fig. 2). They were randomized, and their data were analyzed. The research team decided to exclude patients according to their clinical condition or in cases of violation of the protocol.

The demographic and surgical data in addition to comorbidities were comparable between the study groups (Table 1). There was no significant





difference regarding preoperative mean blood pressure, pulse rate, preoperative ejection fraction, and need for re-exploration between the study groups (Table 1).

The intention-to-treat analysis of the primary outcome revealed that the IMA blood flow rate was 57.33 \pm 1.96 ml/min in SGB patients and 44.89 \pm 1.9 ml/min in verapamil-nifedipine patients; the IMA blood flow rate was significantly higher in the SGB group than in the verapamil-nifedipine group (Table 2). The incidence of abnormal ECG changes was significantly higher in the verapamil-nifedipine group compared with SGB group (*P*=0.043) (Table 2).

There was no significant difference between the groups regarding the length of ICU stay and intra-aortic balloon usage (P=0.281 and 0.650, respectively) (Table 2). The mortality rate was comparable between the study groups (P=0.560) (Table 2). The

incidence of atrial fibrillations was significantly higher in verapamil-nifedipine group compared with SGB group (P=0.030) (Table 2).

Postoperative mean blood pressure and pulse rate values were comparable between the study groups (P=0.080 and 0112, respectively) (Table 2). There was no significant difference between the groups regarding postoperative ejection fraction (P=0.172) (Table 2). The need for inotropic and ventilation support the time were comparable between the study groups (P=0.119 and 0.203, respectively) (Table 2).

There was no significant difference between the groups regarding radio-femoral arterial pressure difference at baseline, 60 min after CPB, on admission to ICU, and 10 min after admission (P=0.166, 0.294, 174, and 0.408, respectively) (Table 3).

	Table 1	Demographic,	surgical data,	and	comorbidities
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Demographic data	SGB group (N=85)	Verapamil-nifedipine group (N=85)	P value
Sex			
Female	38 (44.7)	42 (49.4)	0.539
Male	47 (55.3)	43 (50.6)	
Age (years)	68.32±2.09	67.76±2.22	0.097
ASA			
II	51 (60.0)	57 (67.1)	0.339
111	34 (40.0)	28 (32.9)	
Procedure duration (min)	456.86±4.98	455.46±6.21	0.107
Cross-clamp time (min)	65.98±10.73	68.94±11.55	0.085
CPB time (min)	141.14±1.19	141.15±1.18	0.948
Hypertension	33 (38.8)	28 (32.9)	0.424
Diabetes mellitus	17 (20.0)	22 (25.9)	0.362
Number of grafts			
Single graft	10 (11.8)	9 (10.6)	0.896
2 grafts	29 (34.1)	27 (31.8)	
3 grafts	46 (54.1)	49 (57.6)	
Preoperative EF (%)	53.96±2.74	54.64±2.57	0.102
Preoperative mean blood pressure	68.07±1.46	67.71±1.54	0.115
Preoperative mean pulse rate	72.53±3.52	73.07±3.53	0.318
Re-exploration	2 (2.4)	3 (3.5)	0.650

All data were presented as *n* (%)except age, procedural duration, cross-clamp, and cardiopulmonary bypass time that were presented as mean±SD. ASA, American Association of Anesthesiologists; CPB, cardiopulmonary bypass; EF, ejection fraction; SGB, stellate ganglion block.

Table 2 Internal mammary artery blood flow rate, S-T segment depression, ICU length	of stay,	intra-aortic balloon	usage, at	rial
fibrillation, and mortality rate: comparison between the study groups				

	SGB group (N=85)	Verapamil-nifedipine group (N=85)	P value
IMA blood flow rate (ml/min)	57.33±1.96	44.89±1.9	<0.001**
Abnormal postoperative ECG changes	0	4 (4.7)	0.043*
ICU stay length (days)	2.47±0.5	2.39±0.49	0.281
	2–3	2–3	
Intra-aortic balloon usage	2 (2.4)	3 (3.5)	0.650
Incidence of AF	1 (1.2)	7 (8.2)	0.030*
30-day postoperative mortality rate	1 (1.2)	2 (2.4)	0.560
Postoperative EF (%)	59.99±0.76	59.74±1.47	0.172
Postoperative mean blood pressure	78.82±1.22	79.29±2.14	0.080
Postoperative mean pulse rate (beats/min)	93.25±4.41	94.2±3.28	0.112
Need for inotropic support	3 (3.5)	8 (9.4)	0.119
Ventilation time (h)	10.06±0.9	10.24±0.9	0.203

All data were presented as *n* (%)except IMA blood flow rate, mean blood pressure, mean pulse rate, ventilation time and length of ICU stay that were presented as mean±SD. AF, atrial fibrillations; EF, ejection fraction; IMA, internal mammary artery; SGB, stellate ganglion block. **Highly significant. *Significant.

Fable 3 Mean radio-femoral arteria	pressure difference: cor	nparison between groups
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	SGB group (N=85)	Verapamil-nifedipine group (N=85)	P value
Duration (min): baseline	2.73±0.65	2.87±0.61	0.166
Post-CPB (min)			
Post-CPB 20	-1.05±1.18	-1.86±1.15	< 0.001**
Post-CPB 40	-0.97±1.16	-1.44±1.05	0.005*
Post-CPB 60	-1.36±0.93	-1.2±1.08	0.294
Post-CPB On ICU admission	-0.32±0.92	-0.50±0.86	0.174
Post-CPB 10 min after admission	-0.31±0.74	-0.41±0.79	0.408

All data were presented as mean±SD. CPB, cardiopulmonary bypass; SGB, stellate ganglion block. *Significant. **Highly significant.

Radio-femoral arterial pressure difference was significantly lower in SGB group at 20 and 40 min

after CPB (P<0.001 and P=0.005, respectively) (Table 3).

Discussion

Arterial grafts are the most popular conduits for myocardial revascularization in CABG [1]. The strength of this study is derived from being one of the first trials discussing the efficacy of SGB in improving IMA blood flow rate and reducing abnormal ECG changes after CABG.

The results of this prospective study showed that SGB is a feasible option for prevention of IMA spasm in elderly patients undergoing CABG. This was shown by a significant increase in IMA blood flow rate in addition to a significant reduction in the incidence of atrial fibrillations or ECG changes in the SGB group. There were no significant differences between the study groups regarding the incidence of the length of ICU stay and intra-aortic balloon usage.

The most aggravating adverse event following arterial conduit harvesting was the perioperative graft spasm caused by increased α -adrenergic activity or increase in blood pH, systemic hypothermia, local manipulation of the artery, endothelial dysfunction, enhanced platelet activity, release of vasoconstrictor substances, elevation of histamine and vasopressin levels, and elevation of potassium levels [7].

Following the isolation of the vessel, vasospasm occasionally occurs leading to reduced early graft blood flow and resulting in perioperative morbidity and mortality [8]. This annoying problem can be either reversed or prevented by various intraluminal or topical vasodilators [8].

SGB is a safe, feasible, and effective procedure with minimal complications reported at ~0.17% [4]. The stellate ganglion innervates the nerve bundles that extend along the IMA [9]. The site of these nerve fibers plays a vital role in the surgical management of myocardial ischemia [10]. SGB is important for the prevention and control of perioperative hypertension induced by sympathetic activity [11]. Importantly, SGB has been shown to alleviate refractory angina pain unresponsive to medical treatment or revascularization [12].

The SGB technique is effective for treatment of spastic vascular disorders because it induces vasodilatation, thus increasing blood flow [13].

Dihydropyridine derivatives are the most effective spasmolytic drug so they are preferred for use in CABG particularly if radial artery graft is harvested. Recently, nicardipine, one of dihydropyridine derivatives, replaced verapamil for intravenous use in CABG [14].

Calcium antagonists such as nicardipine effectively prevent potassium-mediated spasm in both IMA [15] and radial artery [3].

After reviewing the literature, few studies seem to support the findings of the present study and confirm the efficacy and safety of this blockage. In a study by Yildrim *et al.* [5], SGB prevents IMA spasm which was evidenced by significantly lower incidence of S-T segment depression and postoperative atrial fibrillation. The use of inotropic agents was significantly restricted in the SGB group. It was emphasized that preemptive SGB reversed right atrial spasm, which increased right atrial blood flow leading to better surgical outcomes in patients undergoing CABG [5]. These findings support the findings of the current study.

A study by Sasson et al. [16] showed that vasodilators such as nifedipine, verapamil, and glyceryl trinitrate had no remarkable effect on IMA blood flow rate. A prospective study by Gopal et al. [17] found that SGB significantly increased LIMA graft diameter (*P*<0.0001) without causing any remarkable hemodynamic complications. For this reason, it could be used as a suitable alternative to vasodilating agents. These findings agreed with the findings of the present study.

Various pharmacological agents such as nitrates and calcium channel blockers are commonly used for the prevention of LIMA spasm, but their use is associated with several limitations as shown by a few studies [18]. The preemptive administration of verapamil is associated with minor effects on the induced right atrial contraction. In contrast, nitroglycerine was found effective for the reversal of the established right atrial contractions [19].

Several studies have revealed that human IMA mainly incorporates α 1-adrenoceptors; therefore, contractions are mediated by α -adrenoceptor agonists through activation of the α 1-adrenoceptors [20].

An earlier study showed that SGB prevents the incidence and stops the maintenance of atrial fibrillation, through the control of the immune and autonomic systems [21]. SGB stops the stress response through decreasing inflammatory mediators' production, which prevent the electrical and structural remodeling of cardiac muscle cells, thus

decreasing the incidence of atrial fibrillation [21]. Application of the ultrasound-guided SGB facilitates the block, increasing its efficacy and reducing the volume of injection and the risk of esophageal, neuronal, or vascular injury by direct visualization of the site of injection [22].

He *et al.* [23] reported that IMA spasm results from some metabolic abnormalities such as hypercalcemia, hypomagnesemia, hypokalemia, and increased serum lactates.

The manipulation of coronary arteries during cardiac surgery initiates postganglionic sympathetic fiber stimulation, which resembles stellate ganglion stimulation. For this reason, SGB can stop this reflex by reducing the efferent cervical sympathetic discharge and causes vasodilatation of IMA [24].

The theory behind the occurrence of radio-femoral pressure difference is questionable. Pauca *et al.* [25] assumed that this pressure difference is caused by a decrease in vascular resistance of upper extremity vessels, whereas other studies proposed that peripheral vasoconstriction may be the underlying cause [26]. In the current study, SGB usage causes radial artery vasodilatation, thus decreasing this pressure difference, particularly at the end of CPB.

Limitations

This study had the following limitations. First, insufficient studies comparing the efficacy of SGB with pharmacological agents such as nitrates and calcium channel blockers in IMA diameter are available; second, placebo was not considered as a third arm in this study because during recruitment many patients were not eligible to participate in the study due to their critical medical condition or violation of the protocol; third, none of the patients were followed up using angiographic imaging after discharge home; fourth, the sample size was relatively small to provide definitive results, and also comparison with other sympathetic block techniques could be more beneficial; and finally, intraoperative flow devices such as pencil Doppler probe were not used to quantify the intraoperative flow, and it was assumed that the blood flow collected from cut end of IMA equalizes its blood flow when used as a conduit following the anastomosis.

Conclusion

The results of this study showed that SGB prevents the IMA spasm, increases IMA blood flow rate, and

decreases the incidence of atrial fibrillations compared with intraluminal injection of verapamilnitroglycerine combined with intravenous nicardipine.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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