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1. *Objective(s):* What scientific question was the study designed to answer?
2. *Methods and participants:* this section includes:
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 - b. *Setting:* Type of hospital or laboratory; university or community setting; single or multi-institutional.
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4. *Conclusions:* What conclusion(s) may be reasonably drawn from the results of the study?

No references or abbreviations should be used in the abstract. Do not include a summary at the end of an original research paper.

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2. Karpatkin S, Smith K, Charnatz A: Heterogeneity of human platelets. III. Glycogen metabolism in platelets of different sizes. *Br J Haematol* 19:135-137, 1970

Journal article, four or more authors

3. Golomb HM, Vardiman J, Sweet DL, et al: Hairy cell leukemia: Evidence for the existence of a spectrum of functional capabilities. *Br J Haematol* 38:161-162, 1968

Journal article in press

4. O'Malley JE, Eisenberg L: The hyperkinetic syndrome. *Semin Psychiatry* (in press)

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Complete book

5. Lillie RD: *Histopathologic Technic and Practical Histochemistry* (ed 4). New York, NY, Blakiston, 1965, pp 39-41

Chapter of book

6. Moore G, Minowada J: Human hemopoietic cell lines: A progress report, in Farnes P (ed): *Hemic Cells in Vitro*, vol 4. Baltimore, MD, Williams & Wilkins, 1969, pp 100-105

Chapter of book that is part of published meeting

7. Hatvåg JB, Kunkel HG, Gedde-Dahl T Jr: Genetic studies of the heavy chain sub-groups of gamma globulin, in Killander J (ed): *Gamma Globulins, Proceedings of the Third Nobel Symposium*. New York, NY, Wiley, 1967, pp 19-26

Chapter of book that is part of unpublished meeting

8. Polliak A: A morphologic study of the lymphoproliferative lesions induced by excess vitamin A. First Meeting, European Division, International Society of Hematology, Milan, Italy, 1971, p 181

Abstract

9. Curnutte JT, Karnovsky ML, Babior BM: Manganese-dependent NADPH oxidation by a particulate preparation from guinea pig granulocytes: An alternative interpretation. *Clin Res* 23:371A, 1975

Letter to Editor

10. Seeler RA: Sick cell anemia monthly variations. *Blood* 47: 879, 1976

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Recent innovations in myocardial protection strategies during cardiac surgeries

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Better understanding of the pathophysiology of myocardial injury has led to the development of multiple modifications and new strategies for myocardial protection. New drugs and techniques are always being investigated to add to the already proven techniques applied for myocardial protection.

Keyword:

conditioning and cardioplegia, ischemia-reperfusion injury, myocardial protection

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Learning objectives

The following were the objectives of the study:

- (1) To understand the pathophysiology of myocardial injury.
- (2) To report myocardial protection strategies.
- (3) To report the mechanisms of myocardial conditioning against ischemia-reperfusion injury.
- (4) To report the types of cardioplegia.

Pathophysiology of myocardial injury

Myocardial injury during cardiac surgery may result from the ischemia itself, the deleterious effects of cardiopulmonary bypass, and from restoration of blood flow during reperfusion.

Effects of ischemia

Short periods of ischemia lead to reversible changes in the myocytes which if prolonged will lead to necrosis and cell death. Changes include depletion of high-energy phosphate, intracellular acidosis, calcium overload inside the cells, cellular swelling, and loss of membrane integrity, with leaking of enzymes and metabolites [1].

Spectrums of ischemia are as follows:

- (1) Reversible:
 - (a) Stunning: it is defined as postischemic myocardial impairment after restoration of coronary blood flow. Proposed mechanisms are intracellular calcium overload and oxygen free radicals. It can be overcome by inotropes. Examples include unstable angina and after removal of aortic cross clamp.

- (b) Hibernation: it was first described by Rahimatoola (1989) and defined as a state of persistent impairment of myocardial function due to reduced coronary blood flow. It is reversed partially or completely if oxygen supply/demand balance is restored. It can be diagnosed by dobutamine stress echocardiography, positron emission tomography, and cardiac magnetic resonance. Recent theories consider hibernation is a repeated attack of ischemia, possibly silent, causing repeated stunning [2].

- (2) Irreversible: it includes apoptosis and cell death.

Effects of cardiopulmonary bypass

They include hemodilution, hemolysis, stress response with release of catecholamines, altered glucose metabolism, activation of complement and neutrophils, and fibrinolysis.

Reperfusion injury

It is defined as paradoxical myocardial injury after restoration of perfusion to the myocardium. Clinically, it may manifest by variable degree of dysfunction and/or arrhythmias. Causes include intracellular calcium overload, oxygen free radicals, neutrophil activation, and endovascular damage. Severity and duration depends on the extent of ischemia and the reperfusate composition [3].

Mediators of reperfusion injury include the following:

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- (1) Endothelial dysfunction: it leads to increased endothelin-1 and decreased nitric oxide production, which causes vasoconstriction and prothrombotic occlusion.
- (2) Oxygen free radicals: superoxide anions, hydroxyl radical, and nitrite are produced in radical oxygen scavenging pathway. Other enzymes released are xanthine oxidase, cytochrome oxidase, catecholamines, and cyclooxygenase. These enzymes also again reduce nitric oxide production and aggregate neutrophil and platelets.
- (3) Altered calcium metabolism: increased sarcolemmal calcium concentration by calcium influx is the main step of molecular myocardial injury. This calcium stimulates production of proteases such as Calpain-1 and myofibrils get degraded.
- (4) Altered myocardial metabolism: sudden changeover from aerobic to anaerobic glycolysis increases lactate and pyruvate production and reduces high-energy phosphates. Inhibition of mitochondrial pyruvate dehydrogenase activity increases pyruvate content. Reversibility of metabolism to aerobic is done by insulin and adenosine.

Endogenous protective mechanism include ATP production, nitric oxide release, K^+ ATP channel, and closure of mitochondrial permeability transitional pore (MPTP) [4].

Aim

The aim of cardioprotective strategies is as follows:

- (1) Prepare the heart to ischemia (preconditioning).
- (2) Minimize metabolic requirements during arrest (hypothermia and cardioplegia).
- (3) Provide favorable metabolic environment during arrest.
- (4) Ameliorate the reperfusion injury.

Now, it is established that optimal cardioprotection may require a combination of additive or synergistic multitarget therapies to cover the multifactorial myocardial injury and to overcome the comorbidities that may affect the protection provided by a single protection tool [5].

Preconditioning

'That which does not kill us makes us stronger' (Nietzsche, 1888).

It is an adaptive mechanism in which exposure to a physical or pharmacological stimulus may ameliorate the injury from subsequent ischemia [1].

The extent of myocardial protection may be recently measured by what is called critical time period (50) which is the duration of circulatory disruption compatible with 50% tissue survival [4].

Ischemic preconditioning

Repeated balloon inflation and deflation during angioplasty was proven to prepare the heart to reperfusion after angioplasty. Moreover, recurrent angina attacks were associated with reduced infarct size [6].

Ischemic preconditioning may occur in two phases

Early preconditioning: it starts within 15 min and last for several hours. It protects against myocardial infarction but not stunning. Adenosine activates protein kinase C leading to activation of mitochondrial ATP-sensitive potassium channels (K_{ATP}). It preserves cellular ATP molecules, inhibits neutrophil and mast cell activation, exerts antioxidant, and anti-free radicals, and inhibits 'No Reflow' mechanism by antiplatelet activity. Sulfonylureas drugs may inhibit preconditioning by blocking K_{ATP} channels [7].

Late preconditioning: this involves gene transcription and synthesis of stress proteins, so it starts from 12 to 24 h after ischemia. It protects against both infarction and stunning [4].

Pharmacologic preconditioning

Anesthetic preconditioning

Volatile anesthetics: they have direct effect by modulating action on K_{ATP} channels, interfering with neutrophils and platelets activation, gene transcription, and decrease calcium overload. As low as 0.25 minimum alveolar concentration may be protective but maximum protection is achieved at 1.5–2 minimum alveolar concentration. Halothane, isoflurane, sevoflurane, and desflurane have cardioprotective effects [8].

Opioids: opioid receptor agonist combines with G_i linked pathway and stimulates the protein kinases activity. Morphine, fentanyl, and remifentanyl have potent cardioprotective effects through mitochondrial K_{ATP} channel. Morphine has more potent cardioprotection than fentanyl through the delta receptor action and reduces infarct size [9]. Remifentanyl, an ultrashort-acting opioid, has cardioprotective effect similar to fentanyl [10].

Adenosine: it is a synthetic prototype of adenosine and has all protective activity of adenosine.

Nicorandil and pinacidil: they are calcium channel blockers with cardioprotective activity through activation of K_{ATP} . Nicorandil has special cardioprotective action in diabetic patients.

Propofol: it ameliorates lipid peroxidation and has cardioprotective effect.

Other pharmacological agents: xenon, norepinephrine, α -2 agonists, acetylcholine and carbachol have protective action [4].

Remote ischemic preconditioning

Remote ischemic preconditioning (RIPC) involves inducing multiple and short episodes of ischemia distant to the myocardium to obtain a myocardial protective effect after reperfusion of the remote tissue [11].

Two types are as follows:

- (1) Early RIPC – effect similarly decreases after a few hours. It is more effective than delayed when it is applied for cardioprotection. It is stronger and slows down the rate of ATP depletion [12].
- (2) Late RIPC – it starts after 12–24 h. It is more effective than early in preventing the kidney injury following cardiac surgery [13].

Method of stimulating RIPC consists of three cycles of sphygmomanometer blood pressure cuff inflation applied to upper or lower limbs for 5 min each and alternated rest time or deflation for 5 min. The blood pressure inflation is kept at 50 mmHg higher than systolic blood pressure. RIPC is supposed to protect myocardium primarily, but it protects other body organs such as kidney, liver, mesentery, brain, skeletal muscle, pancreas, and intestine [14].

The following theories are proposed [4]:

- (1) Systemic factor – systemic protective responses are stimulated such as anti-inflammatory and antiapoptotic.
- (2) Neural theory – RIPC generates endogenous substances such as adenosine, calcitonin gene-related peptide, and bradykinin which stimulate afferent neural pathway. Finally, these end up into heart and cardioprotection is achieved [15].
- (3) Humoral hypothesis – endogenous substances such as bradykinin, adenosine, angiotensin β 1, calcitonin gene-related peptide, and

endocannabinoids release into bloodstream, reach to the cellular membrane receptor of cardiomyocyte, and stimulate various intracellular signaling pathways [16].

- (4) Final common pathway involves induction of cascade of kinases and subsequent alteration of mitochondrial function.
- (5) Bradykinin has dual role as proinflammatory and anti-inflammatory. It gets released as a humoral and systemic factor as an endogenous substance in the circulation. It is a potent chemotactic for neutrophils and is involved directly in RIPC. However in a recent study published by Cho *et al.* [17], they found that the cardioprotective effect of limb RIPC were abolished under propofol, sevoflurane, and carvedilol therapy.

As an alternative to RIPC, an interesting study by Tuter *et al.* [18] used intermittent systemic hypoxic-hyperoxic training for myocardial protection. For 4 days before the cardiac surgery, patients received a hypoxic mixture with 12% oxygen content followed by hyperoxic mixture of 35–40% taking safety measure of lowest accepted SpO_2 82% and maximum accepted heart rate of +50% during the procedure. This procedure was compared against RIPC group and control group regarding postoperative troponin and serum lactate. There was significantly lower troponin and serum lactate in intermittent systemic hypoxic-hyperoxic training and RIPC compared with the control group [18].

Myocardial protection during cardiopulmonary bypass

- (1) Hypothermia.
- (2) Cardioplegia.
- (3) Decompression.

Hypothermia is known to decrease myocardial oxygen requirements during rest and also in the fibrillating and arrested heart. At 22°C, myocardial oxygen consumption is reduced from 80 to 0.3 ml/100 g/min. It also impedes the process resulting in apoptosis [1].

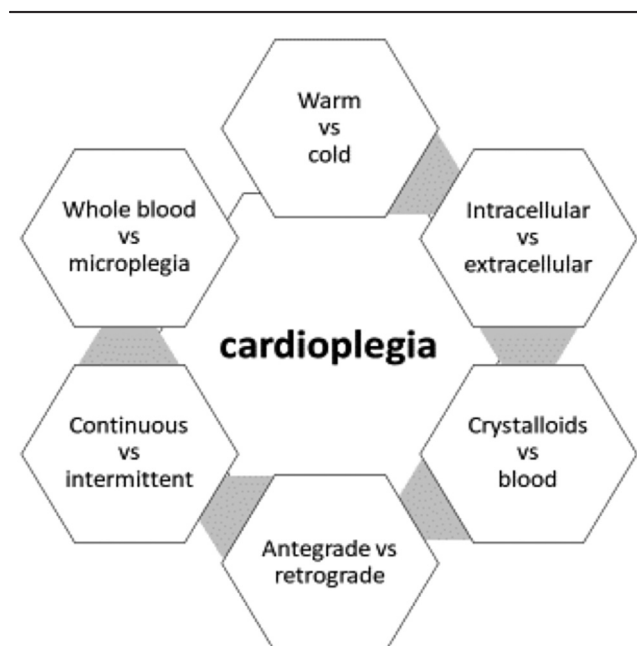
Hypothermia is applied locally by inserting ice directly on the myocardium or systemic hypothermia using the heat-cooler machine attached to the cardiopulmonary bypass. The deleterious effects of hypothermia include decreased production of ATP, paralysis of diaphragm by local ice affecting the phrenic nerve, oxygen delivery to tissues is decreased owing to an increase in

hemoglobin affinity for oxygen, metabolic acidosis, increased plasma viscosity, reduced erythrocyte deformability and subsequently lower flow through the microcapillaries, hypothermia-induced vascular spasm also impedes blood supply, platelet dysfunction, and coagulation defects [19].

Cardioplegia [20]

- (1) Cardioplegia is an integral and essential method for myocardial protection for patients of all ages requiring cardiac surgery. Since its initial discovery by Lamb in 1985, cardioplegia has gone in and out of favor. Its components have been manipulated, and a variety of techniques have been used. Cardioplegic solutions provide myocardium protection by reducing oxygen demand to below 10%. Therefore, a reliable cardioplegic solution is mandatory for achieving successful myocardial protection. Yet, to this day, there continues to be a debate over what the ideal cardioplegic solution should be like.
- (2) Cardioplegia solutions may be blood or crystalloids, warm or cold, continuous or intermittent (Fig. 1).
- (3) The advantage of blood cardioplegia over the crystalloid cardioplegia is that blood provides better oxygen delivery by its hemoglobin content, buffering, free-radical scavenger (red blood cells and platelets), provide nutrients (amino acids and fatty acids), reduces myocardial edema, and has less volume overload.

Figure 1



Types of cardioplegia.

A combined antegrade and retrograde delivery for cardioplegia ensures the adequate protection to areas of myocardium distal to totally occluded coronary arteries and overcomes the less effective protection of right ventricle provided by the retrograde alone technique.

- (1) Regarding the temperature of the cardioplegia, it may be cold (9°C), tepid (29°C), and warm (37°C). Early postoperative left ventricular function was best preserved after tepid cardioplegia with a decrease in ventricular rhythm disorders, need for postischemic DC shock, and blood loss [21].
- (2) The mechanism of action of all different types of cardioplegia solutions used is to ensure diastolic arrest of the heart to ensure decreased wall tension and decreased myocardial oxygen consumption during arrest. This was achieved by potassium (K⁺)-containing solutions, with potassium concentration range from 20 to 40 mEq/l. The high K⁺ extracellular levels block Na-K ATPase and maintain the cells in the depolarized state. Examples include St Thomas cardioplegia and Buckberg blood cardioplegia.
- (3) A recently introduced type of cardioplegia is the Del Nido cardioplegia. The single-dose, cold blood Del Nido cardioplegia, can be safely delivered antegrade or retrograde for longer redosing intervals. It is an acalcemic extracellular cardioplegia solution with the unique use of a sodium channel blocker causing polarization of the myocyte membrane. The unique formulation reduces energy consumption, blocks calcium entry into the intracellular environment, scavenges hydrogen ions, preserves high-energy phosphates, and promotes anaerobic glycolysis during myocardial arrest (Table 1).

Table 1 The Del Nido cardioplegia solution as described originally [22]

Ingredients	Volume (ml)	Role
Plasma-Lyte A	1000	Na 140 mmol/l; K 5 mmol/l; Mg 3 mmol/l; pH 7.4
Mannitol 20%	16.3	Osmotic pressure, free-radical scavenger
MgSO ₄ 50%	4	Calcium channel blocker, improved myocardial recovery
NaHCO ₃ 8.4%	13	pH buffer
KCl 2 mEq/l	13	Myocardial depolarization
Lidocaine 1%	13	Sodium channel blocker, hyperpolarizing agent

Table 2 Custodiol cardioplegia [23]

Ingredients	Concentration
Na	15 mmol/l
K	9 mmol/l
Mg	4 mmol/l
Ca	0.15 mmol/l
Histidine	198 mmol/l
Tryptophan	2 mmol/l
Ketoglutarate	1 mmol/l
Mannitol	30 mmol/l
pH	7.02–7.20

- (4) The other type of cardioplegia is the intracellular crystalloid cardioplegia (Custodiol). It is a nondepolarizing cardioplegia with very low sodium and calcium content. Sodium depletion of the extracellular space causes a hyperpolarization of the myocyte plasma membrane, inducing cardiac arrest in diastole. A high histidine content buffers the acidosis caused by the accumulation of anaerobic metabolites during the long ischemic period, ketoglutarate improves ATP production during reperfusion, tryptophan stabilizes the cell membrane, and mannitol decreases cellular edema and acts as a free-radical scavenger [23] (Table 2).

Additives to cardioplegia

- (1) Beta-blockers: the ultrashort-acting and cardioselective beta-blocker esmolol has a half-life of a few minutes, with rapid elimination after cessation of infusion. Clinical studies have shown that esmolol can be used to obtain minimal myocardial contraction during surgery while maintaining continuous normothermic coronary perfusion to avoid ischemia. The use of esmolol as a cardioplegic agent may be a beneficial alternative to standard techniques [24].
- (2) Glucose-insulin-potassium: these are used frequently to protect and provide nutrition to the myocardium. However, the recent insulin trial failed to document benefit of insulin-cardioplegic solution in coronary revascularization surgery for high-risk patients [25].
- (3) Antioxidants: these are used for protecting the heart from the oxygen free-radical generated during ischemia and to provide scavengers during the reperfusion phase. Reduced glutathione was shown to improve myocardial recovery. Moreover, iron-chelating agents such as deferoxamine have been used systemically and in cardioplegia to decrease lipid peroxidation and free-radical generation [20].

- (4) Nitric oxide/L-arginine: nitric oxide exerts a myocyte protective role as an antiapoptotic factor and as a mediator in ischemic preconditioning. L-arginine increases nitric oxide release and increases myocardial pH recovery [20].
- (5) Na^+/H^+ exchange inhibition: protons accumulating during ischemia are extruded at the time of reperfusion in exchange for sodium ions. The resulting sodium overload cannot be adequately handled by the sodium/potassium pump because it is inefficient owing to ischemia-induced shortage of energy. This excess of intracellular sodium is then extruded from cells through the sodium/calcium exchanger, which functions in a reverse mode. It brings calcium ions in the cells allowing a dangerous calcium overload, responsible for the ischemia/reperfusion tissue injury. GUARDIAN trial used cariporide, a Na^+/H^+ exchange inhibitor, at different dose but failed to demonstrate clinical benefit [26].

Ameliorating the reperfusion injury [1]

Ischemic postconditioning

Ischemic postconditioning is defined as interruption of reperfusion after completion of cardiac surgery. This may be applied by perfusion for 30 s followed by reocclusion for 30 s. This was found to decrease infarct size.

Volatile anesthetics have postconditioning effect that may be through inhibition of neutrophils-mediated reactive oxygen species generation.

Pharmacological postconditioning

- (1) Antioxidants: glutathione peroxidase, superoxide dismutase, and vitamin E.
- (2) Ionotropic stimulation: catecholamines.
- (3) Endogenous cardioprotectants: adenosine acts through A1 and A3 myocyte receptor. nitric oxide reverses endothelial dysfunction and improves coronary flow.
- (4) Metabolic stimulation by insulin and adenosine leads to rapid recovery of aerobic metabolism.
- (5) $\text{Na}^+/\text{H}_2\text{O}$ antiport inhibition: acidosis stimulates $\text{Na}^+/\text{H}_2\text{O}$ sarcolemmal antiport which removes intracellular H_2O for Na^+ . Intracellular hypernatremia activates $\text{Na}^+/\text{Ca}^{2+}$ exchanger system that extrudes Na^+ for intracellular Ca^{2+} .
- (6) Cyclosporine A was found to be a potent inhibitor of MPTP. This pore remains closed during ischemia; however, during the early minutes of reperfusion, calcium overload and excessive

production of reactive oxygen species prompt opening of the MPTP, precipitating the collapse of its membrane potential followed by irreversible damage and cell death. A single bolus dose of 2.5 mg/kg was used and demonstrated reduced extent of myocardial injury in patients with acute ST-elevation myocardial infarction [27].

- (7) Intralipid has recently been shown to be more effective than cyclosporine in an *in vivo* rat heart and isolated mouse heart experiment [28].

Markers of protection [29]

- (1) Two excellent markers for determining the adequacy of myocardial protection are cardiac enzyme levels (CPK-MB : creatine kinase or troponin) and postoperative septal motion, as both depict muscle injury and correlate with early and late mortality. In contrast, the markers frequently utilized in studies, such as hospital or ICU length of stay, arrhythmias, inotropes, IABP and in-hospital or 30-day mortality, are poor indicators of the adequacy of myocardial protection.
- (2) Cardiac enzyme release has been shown to directly correlate with muscle damage and outcomes. Even small elevations have been shown to be significant, and the higher the level, the more the deaths.
- (3) The septum is a subendocardial structure, so it is more vulnerable to inadequate myocardial protection. It is easily seen on an echocardiogram, and its dysfunction indicates muscle injury from inadequate myocardial protection.

Future recommendations [5]

Combinations of interventions with solid preclinical information on mechanism of action, efficacy, and safety, and that are easily applicable are good candidates to be moved to clinical trials. Some promising examples of approaches to multitargeted cardioprotection include the following:

- (1) A combination of RIC with a drug with a different mechanism of action – this is being tested in the COMBAT-MI trial (COMBin Ation Therapy in Myocardial Infarction) (NCT02404376).
- (2) A combination of a drug that activates endogenous cardioprotective pathways [RISK (Reperfusion-Induced Salvage Kinase), SAFE (Survivor Activating Factor Enhancement), cGMP (cyclic Guanine Mono Phosphate)/PKG (Protein Kinase G)] with a drug that inhibits cell death pathways.

- (3) A drug targeting vascular injury/inflammation with a drug targeting cardiomyocyte death.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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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

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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% NaHCO_3 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 mean blood pressure, and 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.

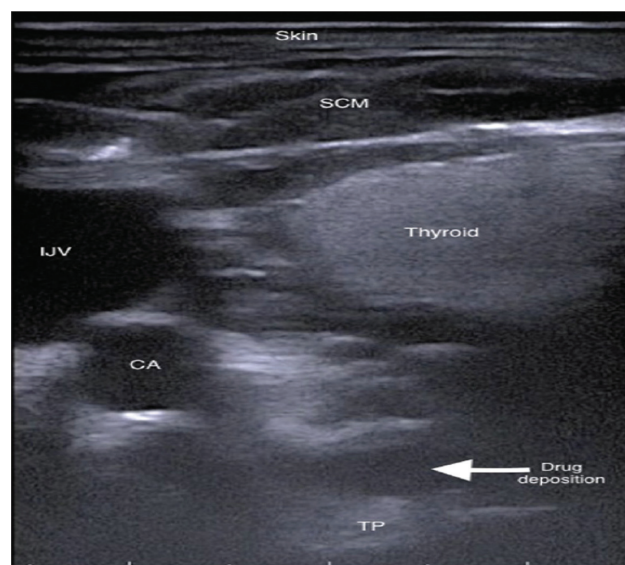
Patients and methods

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 µg/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 verapamil-nitroglycerine group ($n=85$) underwent intraluminal injection of the harvested IMA graft with the solution containing verapamil 5 mg, nitroglycerine 2.5 mg,

Figure 1



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% NaHCO_3 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 1 h 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/m^2 . 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 $36\text{--}37^\circ\text{C}$. 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 $60.5 \pm 5.2 \text{ ml/min}$ in the non-SGB and SGB groups, respectively.

Statistical analysis

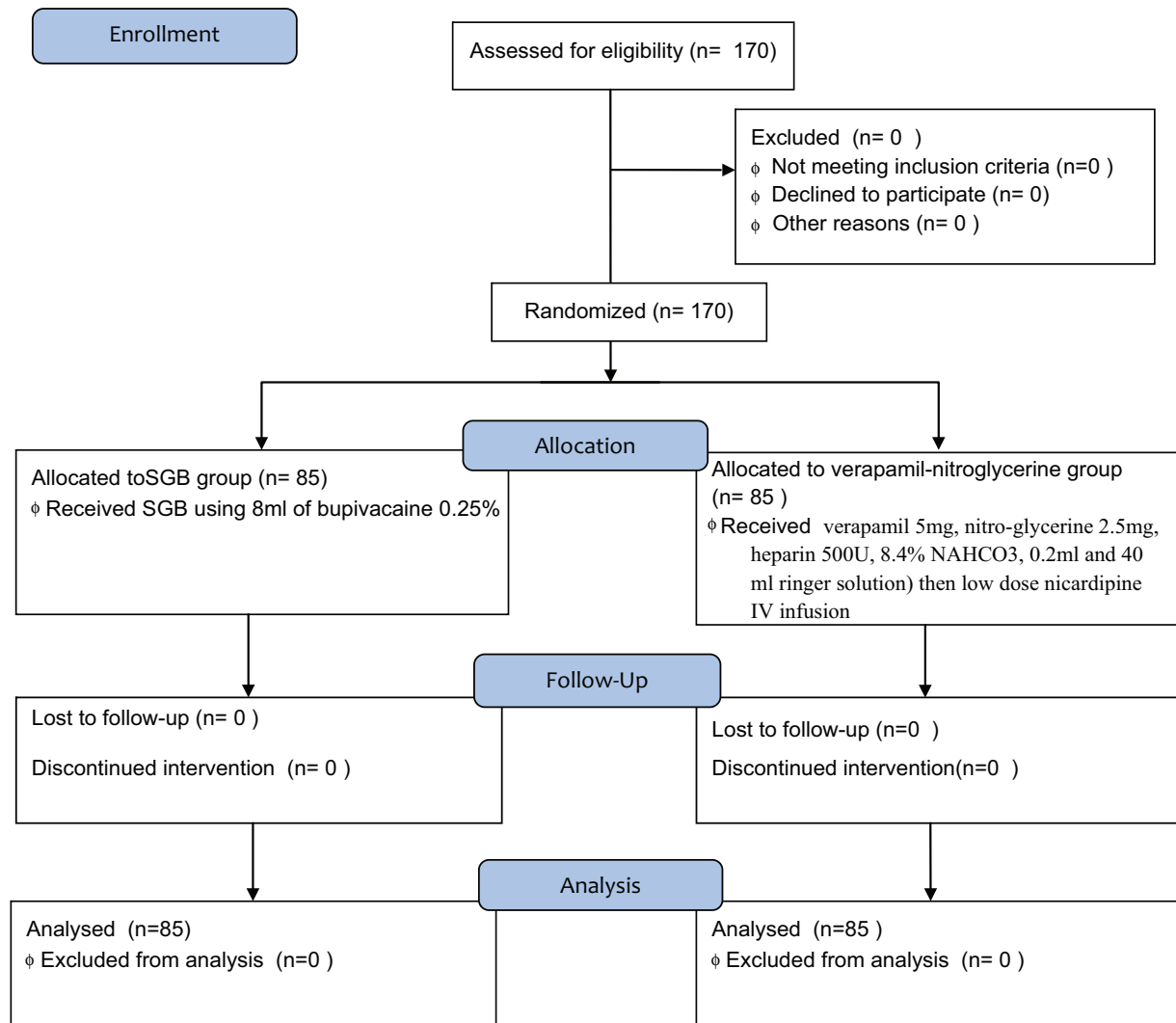
The collected data were coded and tabulated, and statistical analysis was performed using the SPSS software package, version 17.0 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics were carried out for numerical parametric data and presented as mean \pm SD, whereas categorical data are presented 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

Figure 2



Study flow chart.

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 ± 1.96 ml/min in SGB patients and 44.89 ± 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 0.112 , respectively) (Table 2). There was no significant difference between the groups regarding postoperative ejection fraction ($P=0.172$) (Table 2). The need for inotropic support and the ventilation 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

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
III	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, atrial 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.

Table 3 Mean radio-femoral arterial pressure difference: comparison between groups

	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 Yildirim *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 $\alpha 1$ -adrenoceptors; therefore, contractions are mediated by α -adrenoceptor agonists through activation of the $\alpha 1$ -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 verapamil-nitroglycerine combined with intravenous nicardipine.

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Conflicts of interest

There are no conflicts of interest.

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Perioperative hyperglycemia: a strong predictor for atrial fibrillation after coronary artery bypass grafting surgery

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Context

Atrial fibrillation is the most frequent arrhythmia following cardiac surgery. Many risk factors for this problem have been studied.

Aims

The objective was to investigate the relation between perioperative hyperglycemia and postoperative atrial fibrillation (POAF) after coronary artery bypass grafting. Settings and design The study was a retrospective observational study that took place at Benha University Hospital, which is a tertiary referral center.

Patients and methods

The study was conducted on 100 patients who were admitted for coronary artery bypass grafting. Patients were divided into two groups: group A included 50 patients who developed POAF and group B included 50 patients who did not.

Statistical analysis

Data were imported into Statistical Package for the Social Sciences (SPSS version 20.0) software for analysis. Qualitative data represented as number and percentage and tested by the χ^2 -test. Quantitative data were represented by mean \pm SD and tested by *t*-test or Mann–Whitney.

Results

The authors have found that a history of diabetes mellitus, mean postoperative blood sugar (BS), and maximum postoperative BS levels were more significant ($P<0.05$) in group A. The mean BS cutoff level that predicted the occurrence of POAF was 193.7 mg/dl. The authors also have found that postoperative drainage volume was higher in group A than group B, with *P* less than 0.001.

Conclusions

The authors believe that a history of diabetes mellitus, postoperative BS levels, and postoperative drainage volume were significant risk factors for the occurrence of POAF.

Keywords:

atrial fibrillation, coronary artery bypass grafting, postoperative arrhythmia

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Introduction

Postoperative atrial fibrillation (POAF) is defined as the development of new-onset atrial fibrillation (AF) early after surgery. It has an incidence of 20–40% of POAF after coronary artery bypass grafting (CABG) surgery. It causes many early adverse effects like increased ICU hospital stays. Furthermore, POAF was also linked to mid-term and long-term morbidity and mortality [1,2].

The pathophysiological mechanisms responsible for the occurrence of AF after cardiac surgery remain unclear. Recently, it was reported that metabolic diseases, including diabetes mellitus (DM), are related to AF occurrence [3,4].

Patients and methods

This retrospective observational study reviewed 100 patients who were admitted after CABG to the

cardiac surgery intensive care unit. Ethics approval of the study protocol was approved by the Ethical Committee of the Faculty of Medicine at Benha University. Patients were divided into two groups: group A included 50 patients who developed POAF and group B included 50 patients who did not. We included patients who underwent isolated elective CABG, and their rhythm was sinus before admission. We excluded any patients who had valvular or congenital heart diseases. We also excluded any patient who had a history of AF, cardiac surgery, and hepatics or renal impairment. Patients were observed postoperatively, and arrhythmia data were recorded using a 12-lead ECG

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during ventilation, after weaning, and after removing chest tubes until discharge from the ICU.

Serum blood sugar (BS) was recorded every hour in the first six hours after surgery and then every 6 h. This was continued until discharge from the ICU. The maximum postoperative BS was defined as the highest level recorded from day zero to discharge, and mean BS was defined as the mean value of the BS measurements.

Other postoperative routine morning laboratory parameters were recorded like glomerular filtration rate (GFR), complete blood count, maximum creatine kinase-MB level, maximum and minimum K⁺ and Na⁺ levels, aspartate aminotransferase, alanine aminotransferase, and lactate levels.

We have compared the two groups according to patients' preoperative data (medical history, GFR, preoperative fasting BS level, and preoperative heart rate and blood pressure, echo findings) and postoperative data (cross-clamping time, bypass time, ventilation time, ICU stay time, drainage volume, blood transfusion, routine laboratory examinations, mean BS, maximum BS, and GFR).

Sample size calculation and statistical analysis

MedCalc software version 16.1 (1993–2016, MedCalc Software, MedCalc Software Ltd., Acaciaaan, Ostend, Belgium) was used to calculate the required sample size using the percentage of AF (35%) according to Greenberg *et al.* [1]. The following variables were entered: level of significance (type I error)=0.05, type II error (1-level of power)=0.2, and prevalence of AF=35%. Null hypothesis

percentage was 50%. So, the least sample size required was 85 patients undergoing CABG. It was increased to 100 for more accuracy and divided into two groups (with AF and without AF, 50 patients each).

Data were imported into Statistical Package for the Social Sciences version 20.0 software (International Business Machines Corporation (IBM), Armonk, New York, USA) for analysis. Qualitative data were represented as number and percentage and quantitative continuous group was represented by mean±SD. The difference and association of the qualitative variables were tested by the χ^2 test. Differences between quantitative independent groups were tested by *t*-test or Mann–Whitney and paired by significance level. The *P* value was set at less than 0.05 for significant results and less than 0.001 for highly significant results.

Results

There were no significant differences ($P>0.05$) between both groups regarding age, sex, preoperative heart rate, and blood pressure (systolic and diastolic), and medical history regarding smoking and hypertension, but the history of DM was significant in group A ($P<0.001$), as shown in Table 1.

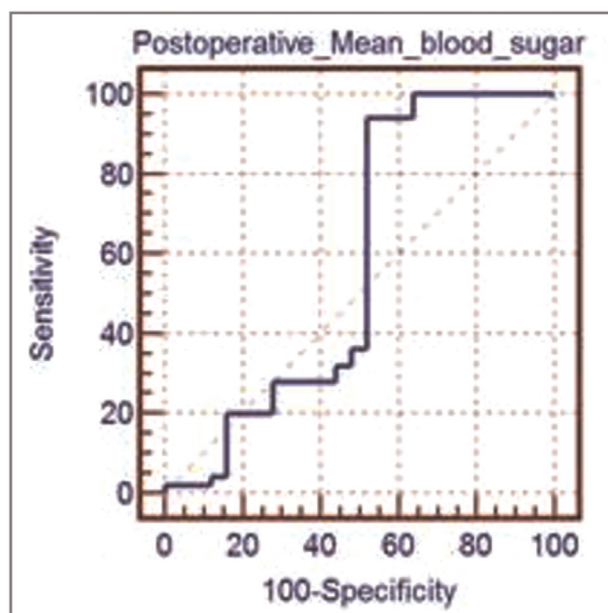
The preoperative echo findings were not statistically significant ($P=0.563$). The left atrium (LA) was dilated in 15 (30%) patients in group A versus 11 (22%) in group B, and the left ventricle (LV) was dilated with low EF in nine (18%) patients in group A in contrast to six (12%) patients in group B. The postoperative ejection fraction in group A was normal ($>50\%$) in 26 (52%) patients and impaired

Table 1 Comparison between the two groups' demographics and clinical parameters

	Group A (n=50)	Group B (n=50)	<i>t</i> or χ^2	<i>P</i> value
Age				
Range	31–70	44–69	0.599	0.551
Mean±SD	58.36±10.33	59.44±7.47		
Sex [n (%)]				
Female	8 (16)	12 (24)	1.000	0.317
Male	42 (84)	38 (76)		
Medical history [n (%)]				
Smoking	41 (82)	45 (90)	1.329	0.249
Diabetes mellitus	36 (72)	15 (30)	17.647	<0.001
Hypertension	27 (54)	20 (40)	1.967	0.161
Preoperative heart rate (beats/min)				
Mean±SD	85.60±9.62	84.48±8.99	0.602	0.549
Diastolic blood pressure (mmHg)				
Mean±SD	86.60±14.23	87.20±14.00	0.213	0.832
Systolic blood pressure (mmHg)				
Mean±SD	131.80±20.77	133.40±20.06	0.392	0.696

Table 2 Comparison between the two groups' pre and postoperative blood sugar levels

Blood sugar level (mg/dl)	Mean±SD		t	P value
	Group A (n=50)	Group B (n=50)		
Preoperative fasting blood sugar	135.12±18.8	122.16±20.49	1.790	0.077
Postoperative mean blood sugar	206.68±53.65	187.88±27.81	2.200	0.030
Postoperative maximum blood sugar	277.37±58.91	255.00±47.01	2.098	0.038

Figure 1

Receiver operating characteristic curve between group A and group B regarding postoperative mean blood sugar (mg/dl).

(<50%) in 24 (48%) patients, whereas in group B, 22 (44%) patients had normal EF and 28 (56%) had impaired EF, with P value 0.702 between both groups.

There was no statistically significant difference ($P>0.05$) between the two groups regarding the preoperative fasting BS level. Postoperative mean and maximum BS level showed a statistically significant difference between the two groups ($P<0.05$), which was higher in group A, as shown in Table 2.

The receiver operating characteristic curve showed the best cutoff point is less than or equal to 193.7 mg/dl, with a sensitivity of 94%, a specificity of 48%, a positive predictive value of 64.4%, and a negative predictive value of 88.9%. We have assumed that patient with a mean BS more than 193.7 mg/dl is considered a positive risk factor for AF occurrence, as shown in Fig. 1.

There was no statistically significant difference ($P>0.05$) between the two groups regarding bypass

time, cross-clamp time, ventilation time, ICU stay time, blood product transfusion, postoperative fluid balance, and presence of intra-aortic balloon. There was a statistically significant difference between the two groups regarding postoperative drainage volume ($P<0.001$), which was higher in group A than group B, as shown in Table 3.

There was no statistically significant difference ($P>0.05$) between the two groups regarding minimal and maximum hemoglobin levels, total leukocytic count, platelet count, maximum creatine kinase-MB level, minimal and maximum K^+ and Na^+ , lactate, alanine aminotransferase, and aspartate aminotransferase levels, as shown in Table 4.

Discussion

In this study, a postoperative BS of less than 193.7 mg/dl was independently associated with lower incidence of POAF. Although the best cutoff remains controversial, Tatsuishi *et al.* [5], reported BS cutoff of less than 180 mg/dl predicts POAF. Others have reported that controlling BS to less than 200 mg/dl is beneficial. Furthermore, using tight glycemic control, such as reducing BS to less than 140 mg/dl, improves the early morbidity and mortality, especially those related to infections and ischemic events [6]. However, owing to the risk of hypoglycemia with such tight control [7], the guidelines from the Society of Thoracic Surgeons recommend mean BS of less than or equal to 180 mg/dl [8].

According to Tatsuishi *et al.* [5] and Ismail *et al.* [9], age was identified as an independent risk factor for POAF, which could be attributed to age-related comorbidities. This has been explained by Amar *et al.* [10], who believed that degenerative changes occurring in the atrium by aging are sufficient to cause this type of arrhythmia.

We have found that the percentage of patients having a history of DM was 72% in group A compared with 30% in group B ($P<0.001$). This highly significant difference was similar to findings of Ismail *et al.* and Omer *et al.* [9,11].

Table 3 Comparison between the two groups regarding operative and postoperative data

	Group A (n=50)	Group B (n=50)	<i>t</i> or χ^2	<i>P</i> value
Bypass time (min)				
Range	60–140	60–140	0.117	0.907
Mean±SD	90±25.39	89.4±25.75		
Cross-clamping time (min)				
Range	30–110	30–105	1.318	0.191
Mean±SD	48.1±24.01	54.4±23.79		
Ventilation time (h)				
Range	6–35	6–47	0.926	0.357
Mean±SD	12±6.66	13.56±9.88		
ICU stay time (days)				
Range	2–6	2–6	1.523	0.131
Mean±SD	3.1±1.45	2.72±1.01		
Blood product transfusion [<i>n</i> (%)]				
Fresh blood	32 (64)	36 (72)	0.735	0.391
Packed RBCs	36 (72)	40 (80)	0.877	0.349
Plasma	37 (74)	41 (82)	0.932	0.334
Postoperative volume balance [<i>n</i> (%)]				
Positive	5 (10)	4 (8)	0.122	0.727
Negative	45 (90)	46 (92)		
Postoperative drainage volume (ml) [<i>n</i> (%)]				
Range	500–1800	400–1200	6.118	<0.001
Mean±SD	1164±401.91	768±218.94		
Intra-aortic balloon pump [<i>n</i> (%)]				
Yes	9 (18)	5 (10)	1.329	0.249
No	41 (82)	45 (90)		

RBCs, red blood cells.

Table 4 Comparison between the two groups' routine postoperative laboratory parameters

	Mean±SD		<i>t</i>	<i>P</i> value
	Group A (n=50)	Group B (n=50)		
Minimal hemoglobin (g/dl)	9.44±0.66	9.51±0.80	0.531	0.597
Maximum hemoglobin (g/dl)	12.55±1.15	12.12±1.57	1.582	0.117
TLC count (×10 ⁹ /l)	19.10±5.52	19.08±4.89	0.019	0.985
Platelet count (×10 ⁹ /l)	149.96±47.22	143.44±44.85	0.708	0.481
Max CKMB	38.18±47.28	39.34±60.41	0.107	0.915
Minimal k level (mEq/l)	3.85±0.29	3.85±0.27	0.036	0.972
Maximum k level (mEq/l)	5.07±0.40	5.02±0.44	0.645	0.521
Minimal Na level (mEq/l)	140.50±3.19	141.04±2.40	0.957	0.341
Maximum Na level (mEq/l)	144.20±2.02	143.84±1.75	0.951	0.344
Minimal lactate level (mmol/l)	1.72±0.58	1.56±0.41	1.557	0.123
Maximum lactate level (mmol/l)	6.64±1.62	7.12±2.03	1.289	0.201
ALT (μl/l)	19.40±10.11	19.24±8.46	0.086	0.932
AST (μl/l)	19.52±7.07	18.76±4.77	0.630	0.530
GFR (ml/min)	77.30±14.46	77.64±14.54	0.117	0.907

ALT, alanine aminotransferase; AST, aspartate aminotransferase; KMB, creatine kinase-MB; GFR, glomerular filtration rate; TLC, total leukocytic count.

In the Framingham heart study, DM was identified as an independent risk factor for AF on the long-term follow-up. This was explained by different mechanisms, which included DM-related atrial fibrosis owing to exaggerated systemic and tissue level oxidative stress and dysfunction in the autonomic innervation of the cardiovascular system [12]. Furthermore, according to Erickson *et al.* [13], Ca²⁺/calmodulin-dependent protein kinase II

(CaMKII) is increased in the heart and brain of diabetic patients. In cardiac cells, increased glucose level significantly stimulates Ca²⁺ release by CaMKII-dependent activation of sarcoplasmic reticulum, which contributes to myocardial dysfunction and arrhythmia [14,15].

Furthermore, the postoperative mean BS showed statistical significance (*P*=0.030) between the two

groups, and maximum BS also showed statistical significance between the two groups ($P=0.038$). These results were supported by Tatsuishi *et al.* [5]. Moreover, they found a strong positive correlation between the maximum postoperative BS level and the timing of postoperative AF. This was explained by various studies that tried to detect the effect of hyperglycemia on different stages of the cardiac cycle. Hyperglycemia prolongs both the P-wave dispersion and corrected QT duration, which are considered risk factors for AF. These effects were referred to the dysfunction of human ether-a-go-go-related gene K⁺-channel [16–18].

The preoperative and postoperative GFR showed no statistically significant difference between the two groups ($P=0.493$ and 0.907 , respectively). According to Tatsuishi *et al.* [5], the postoperative GFR was significantly different between the AF and the non-AF groups, with P value 0.032 , but in multivariate analysis, risk factors for POAF showed no significant difference.

In contrast to these results, Abdel-Salam and Nammas [19] and Gorczyca *et al.* [20], have shown that impaired renal function is related to the development of AF after cardiac surgery. This could be explained by activation of the sympathetic nervous system owing to stimulation of intrarenal chemoreceptors and mechanoreceptors, which leads to increased sympathetic nerve activity to the heart [21].

There was a statistically significant difference between the two groups regarding postoperative drainage volume ($P<0.001$), which was higher in group A than group B. According to many authors, hypovolemia and low cardiac output were related to POAF. Moreover, the use of β -blockers in such patients to prevent or treat AF is usually postponed owing to their hemodynamic instability [5,9]. The postoperative levels of K and Na showed no significant difference ($P>0.05$) between the two groups. This can be explained by the tendency to rapidly correct any electrolyte disturbance postoperatively. However, it is well established that electrolyte imbalance in the form of hypokalemia or hypomagnesemia is associated with an increased risk of POAF [5].

In our study, there was no significant difference between both groups regarding ventilation time and ICU stays ($P>0.05$). In contrast, results from other studies have shown a significant difference in ventilation time and ICU stay, which was explained

as a result of arrhythmia, which necessitates more time for treatment and patient stabilization [9,19].

Although we did not find a significant difference between both groups regarding preoperative and postoperative LA dimensions and EF ($P>0.05$), the influence of depressed preoperative EF and enlarged left atrium on POAF has been demonstrated in several studies [9,22].

Study limitations

The study was retrospective with its drawbacks of patient selection and investigation biases. Another limitation is the short-term follow-up.

Conclusion

We advocate to intensively control BS before and after surgery to less than 193.7 mg/dl and also to prevent and manage any postoperative bleeding to make drainage volume as less as possible to reduce the risk of developing post-POAF.

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Conflicts of interest

There are no conflicts of interest.

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Effect of the fresh whole blood transfusion on perioperative bleeding in adult patients undergoing emergency coronary artery bypass grafting surgery: a randomized study

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Objective

The present study aimed to assess the hemostatic effects of fresh whole blood (FWB) transfusion on bleeding and blood product transfusion in patients on clopidogrel undergoing emergency coronary artery bypass grafting surgery (CABG).

Design

A randomized study was conducted.

Setting

The study was conducted at a cardiac center.

Patients and methods

The study included 124 patients undergoing CABG surgery. The patients were divided into two groups: FWB group patients received two to six units of FWB after weaning off cardiopulmonary bypass and in the cardiac surgery ICU. Control group patients received blood products (packed red blood cells, platelets, fresh frozen plasma, or cryoprecipitate) after weaning off cardiopulmonary bypass and after surgery in cardiac surgery ICU. Total number of the transfused FWB, platelets, packed red blood cell, fresh frozen plasma, and cryoprecipitate (intraoperative and postoperative transfusion), bleeding time, and platelet aggregation function were measured. Moreover, the thorax closure time and amount of blood losses, re-exploration, pulmonary edema, and postoperative mechanical ventilation were monitored.

Results

FWB significantly decreased the blood loss and blood product transfusion compared with the control group ($P=0.001$ and 0.001 , respectively). The bleeding time and platelet aggregation function were better in the FWB group compared with the control group ($P=0.020$ and 0.034 , respectively). Moreover, the thorax closure time, cardiac tamponade, re-exploration, pulmonary edema, and postoperative mechanical ventilation decreased significantly in the FWB group compared with the control group ($P<0.05$).

Conclusion

FWB decreased the blood loss, blood product transfusion, cardiac tamponade, and re-exploration in patients on preoperative clopidogrel undergoing emergency CABG.

Keywords:

bleeding time, blood loss, blood product transfusion, Clopidogrel, fresh whole blood, platelet aggregation, re-exploration, thorax closure time

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Introduction

The antiplatelet combination of clopidogrel and aspirin is the most common medication used in patients with acute coronary syndrome and to reduce the in-stent thrombosis after the percutaneous coronary intervention [1,2].

Clopidogrel reduces the risk of incidence of myocardial ischemia and infarction, strokes, and mortality. Clopidogrel inhibits adenosine 5'-diphosphate-induced platelet aggregation, whereas aspirin inhibits cyclooxygenase and reduces thromboxane A₂ [3–5].

The clopidogrel inhibits platelet aggregation irreversibly [6], and AHA/ACC guidelines recommend that clopidogrel must be discontinued for at least 5 days and preferably for 7 days before coronary artery bypass grafting (CABG) [7]; however, in the case of urgent CABG, it impossible to wait for 5 days, being sufficient for generation of new young platelets that would be adequate to maintain firm

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hemostasis, and therefore, it might expose the patient to severe and sometimes refractory perioperative bleeding, cardiac tamponade, complications of massive blood products transfusion, surgical re-exploration, prolonged length of hospital stay, and mortality that impair the outcome after cardiac surgery [8–11].

Fresh whole blood (FWB) transfusion is defined as the transfusion of the whole blood through 48 h from donation [12]. FWB transfusion results in a combination of fresh red blood cells, increased function and number of platelets, along with increased coagulation factor levels, contributing to improved hemostasis and lower donor exposure rates [13,14].

We hypothesize that the FWB transfusion is associated with a decrease in perioperative bleeding than the platelet transfusion during cardiac surgery. The present study aimed to assess the hemostatic effects of FWB transfusion on perioperative bleeding and blood product transfusion in adult patients on preoperative clopidogrel undergoing emergency CABG surgery.

Patients and methods

Outcomes

The primary outcomes were blood loss and requirements for blood product transfusion. The secondary outcome was the safety of FWB and blood product transfusion which was assessed by the occurrence of complications.

Sample size calculation

Power analysis was performed using the χ^2 -test for independent samples on the frequency of patients experiencing perioperative bleeding and requiring blood transfusion, because it was the main outcome variable in the present study. A pilot study was done before starting this study to assess the frequency of patients with decreased perioperative bleeding and blood transfusion in patients undergoing urgent cardiac surgery. The results of the pilot study (eight cases in each group) showed that the incidence of severe perioperative bleeding was 37.5% in the fresh blood group, and 62.5% in the control group. Taking power 0.8, α error 0.05, and β 0.2, a minimum sample size of 62 patients was calculated for each group.

Patients

The study was carried out as a prospective randomized during the period from December 2016 to November

2019. After local Ethics Committee approval, all patients scheduled for urgent CABG plus or minus valve surgery and on preoperative clopidogrel (discontinuation of administration <24 h) and platelet aggregation inhibition >40% (mean of clopidogrel platelet aggregation inhibition therapy $64 \pm 25\%$) [15], and ventricular function (ejection fraction >40%) were screened for eligibility enrollment. The exclusion criteria included patients who had aneurysmal aortic surgery, thrombolytic therapy less than 24 h preoperatively, or severe liver disease. The study included 124 cases, and the patients were assessed using the New York Heart Association, American Society of Anesthesiologists Physical Status Score, and Euroscore. Included patients were those who still had refractory bleeding either intraoperatively (there were excessive generalized oozing and unable to close the chest) or postoperatively (if the chest loss >3 ml/kg/h). This was defined by persisting bleeding despite accurate surgical hemostasis and reversal of heparin by protamine guided by activated clotting time (ACT). The surgical bleeding source was excluded by surgical re-exploration. For these patients, FWB or blood products were administered when the blood loss amount evoked a significant compromise in systemic hemodynamics (severe bleeding that decreases hemoglobin <9 g/dl and associated with a decrease in MAP <70 mmHg). The patients were randomly allocated to one of the two groups (62 patients in each group). FWB group patients received two to six units of FWB (donated <24 h before surgery) after weaning off cardiopulmonary bypass (CPB) in addition to other blood products if needed (platelets, fresh frozen plasma, or cryoprecipitate) and postoperatively in the cardiac surgery ICU (CSICU) to maintain the hemoglobin greater than 9 g/dl. Control group patients did not receive FWB and received only other blood products (packed red blood cells, platelets, fresh frozen plasma, or cryoprecipitate) after weaning off CPB and postoperatively in the CSICU.

Anesthetic technique

Anesthetic technique: for all patients and under local anesthesia, the radial arterial cannula and central venous line were inserted before induction to enable continuous hemodynamic monitoring. Induction was done by intravenous fentanyl (3–5 $\mu\text{g/kg}$), etomidate (0.3 mg/kg), rocuronium (0.8 mg/kg). The anesthesia was maintained with oxygen/air (50%), sevoflurane (1–3%), fentanyl infusion (1–3 $\mu\text{g/kg/h}$), and cisatracurium (1–2 $\mu\text{g/kg/min}$). The patients received tranexamic acid as 20 mg/kg as a bolus dose over 10 min,

then infusion 5 mg/kg/h after induction and continuously throughout the operation until skin closure. All patients received 4 mg/kg of heparin before bypass, aiming to provide an ACT greater than 480 s. After bypass, heparin was reversed with protamine which was titrated to achieve an ACT less than 140 s. CPB used centrifugal pumps with 1–1.5 l prime of ringer lactate, in addition to antibiotics, solu-medrol, and mannitol. Both antegrade blood cardioplegia and retrograde blood cardioplegia were used. Cooling was passive to around 34°C or active to 22°C. FWB, platelets, packed red blood cells, fresh frozen plasma, and cryoprecipitate were administered according to the study protocol (to control the bleeding and to maintain hemoglobin >9 g/dl). The transfusion was done either intraoperatively (if there was excessive generalized oozing with the inability to close the chest) and/or postoperatively if the chest drains' loss was more than 3 ml/kg/h. At the end of surgical intervention, the patients were prepared for weaning off CBP. If there was difficulty to wean off CPB, pharmacological support (dopamine, epinephrine, norepinephrine, or nitroglycerine) or mechanical support (IABP) was started. At the end of surgery, the patients were transferred to cardiac surgery ICU with full monitoring.

Patients monitoring

For all patients, the following laboratory investigations were closely monitored: bleeding time (BT), platelet aggregation inhibition, prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), ACT platelets, fibrinogen, D-dimer, hemoglobin, total number of the transfused FWB, platelets, packed red blood cell, fresh frozen plasma, and cryoprecipitate (intraoperative and postoperative transfusion). Moreover, the thorax closure time and amount of blood losses through the postoperative 24 h were monitored. Chest radiography was done on admission to CSICU, and as indicated to rule out widened mediastinum.

Statistical analysis

Data were statistically described in terms of mean \pm SD, or frequencies (number of cases) and percentages when appropriate. A comparison of numerical variables between the study groups was done using the Student *t*-test for independent samples. For comparing categorical data, a χ^2 test was performed. The exact test was used instead when the expected frequency is less than 5. *P* values less than 0.05 were considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, Illinois, USA) version 15 for Microsoft Windows.

Results

Table 1 shows no significant differences in the demographic data, co-morbidities, preoperative medications, New York Heart Association class, American Society of Anesthesiologists Physical Status Score physical status score, and the Euroscore ($P>0.05$).

Table 2 shows the coagulation profiles of patients. The preoperative BT and platelet aggregation inhibition were significantly higher than the normal level in patients of the two groups, but the difference between the two groups was insignificant ($P=0.830$ and 0.310 , respectively). There was no significant difference in the preoperative PT, INR, aPTT, ACT, platelets number, fibrinogen, and D-dimer between the two groups ($P>0.05$). The postoperative BT significantly decreased in patients of the two groups compared with the preoperative values, but the decrease was significantly lower in the FWB group compared with the control group ($P=0.020$). The postoperative platelet aggregation inhibition significantly decreased in patients of the two groups compared with the preoperative values, but the decrease was significantly lower in the FWB group than the control group ($P=0.034$). There was no significant difference in the postoperative PT, INR, aPTT, ACT, platelets number, and fibrinogen between the two groups ($P>0.05$). Postoperatively, the D-dimer increased mildly in patients of both groups, but the difference between the two groups was insignificant ($P=0.403$).

Table 3 shows the blood losses and blood products transfusion. The mean blood loss during the first 24 postoperative hours was lower in the FWB group than the control group ($P=0.001$). The number of transfused platelets was significantly lower in the FWB group compared with the control group ($P=0.001$). Patients of FWB group received fresh frozen plasma less than the control group patients ($P=0.001$). Moreover, the number of transfused cryoprecipitate units was significantly lower in the FWB group compared with the control group ($P=0.001$). There was no significant difference in the postoperative hemoglobin level between the two groups ($P=0.150$).

Table 4 shows the surgical data of patients. There was no significant difference in the types and number of surgical procedures (CABG or mitral valve repair) between the two groups ($P>0.05$). There was no significant difference in the postoperative mean

Table 1 Preoperative data of patients (data are presented as mean±SD, number, %)

Variable	FWB group (n=62)	Control group (n=62)	P value
Age (years)	56.70±10.20	53.22±11.50	0.077
Weight (kg)	86.40±13.78	88.15±14.50	0.492
Sex			
Male : female	46 : 16	40 : 22	0.330
Diabetes mellitus	62 (100)	62 (100)	1.000
Hypertension	52 (83.87)	45 (72.58)	0.191
Ischemic heart diseases	62 (100)	62 (100)	1.000
Atrial fibrillation	36 (58.06)	42 (67.74)	0.352
Mitral valve regurgitation	19 (30.64)	13 (20.96)	0.304
Pulmonary hypertension	12 (19.35)	7 (11.29)	0.318
Ejection fraction	47.40±5.30	48.15±5.80	0.453
Angiotensin-converting-enzyme inhibitors	39 (62.90)	43 (69.35)	0.569
β-Blockers	48 (77.41)	56 (90.32)	0.087
Calcium channels-blockers	25 (40.32)	32 (51.61)	0.279
Aspirin	62 (100)	62 (100)	1.000
Clopidogrel	62 (100)	62 (100)	1.000
Statins	57 (91.93)	52 (83.87)	0.270
Chronic renal impairment	9 (14.51)	13 (20.96)	0.369
Carotid stenosis			
<50%	18 (29.03)	24 (38.70)	0.342
Unilateral	11 (17.74)	16 (25.80)	0.384
Bilateral	5 (8.06)	8 (12.90)	0.557
Smoking			
Current smokers	35 (56.45)	28 (45.16)	0.281
Ex-smokers	13 (20.96)	19 (30.64)	0.304
NYHA			
III : IV	25 : 37	29 : 33	0.586
ASA			
III : IV	18 : 44	23 : 39	0.445
Euroscore (%)	16.63±5.30	15.87±5.13	0.418
Blood sugar (mmol/l)	7.25±1.17	7.44±1.30	0.394
Body surface area (m ²)	1.74±0.15	1.78±0.17	0.167
Hemoglobin (g/dl)	13.70±1.17	14.02±1.46	0.180

ASA, American Society of Anesthesiologists Physical Status Score; FWB group, fresh whole blood group; NYHA, New York Heart Association.

heparin dose and ACT, protamine dose, CPB duration, aortic cross-clamping time, and temperature between the two groups ($P>0.05$). The mean thorax closure time was significantly lower in the FWB group compared with the control group ($P=0.001$).

Table 5 shows the postoperative outcomes of patients. The dose of pharmacological support after weaning off CPB was lower in FWB group than in the control group ($P<0.05$). The incidence of postoperative cardiac tamponade was two patients in FWB group and seven patients in the control group ($P=0.166$). Surgical re-exploration (because of postoperative bleeding or cardiac tamponade) was needed in four patients in FWB group and 13 patients in the control group ($P=0.034$), and in all cases, the bleeding was owing to generalized oozing. The number of patients who experienced pulmonary edema and required postoperative mechanical ventilation was significantly lower in FWB group than the control group

($P=0.028$). The incidence of allergic reactions was significantly lower in the FWB group than the control group ($P=0.047$). The incidence of renal failure was insignificant between the two groups ($P=0.241$). The ICU and hospital length of stay were shorter in the FWB group compared with the control group ($P=0.002$ and 0.016 , respectively). There was no incidence in the anaphylactic reaction, disseminated intravascular coagulopathy, postoperative graft occlusion and acute myocardial infarction, thromboembolism, neurological complications, or mortality in the two groups.

Discussion

The present study showed that the FWB is effective to decrease the perioperative blood loss and blood product transfusion in patients on preoperative clopidogrel undergoing emergency CABG surgery. The BT and platelet aggregation inhibition significantly decreased in patients of the two groups, but the decrease was

Table 2 Coagulation profiles of patients (data are presented as mean±SD, number, %)

Variables	FWB group (n=62)	Control group (n=62)	P value
Preoperative coagulation profiles			
BT (min)	17.24±7.55	16.96±6.93	0.830
Platelet aggregation inhibition (%)	57.36±8.46	55.90±7.48	0.310
PT (s)	10.08±1.09	10.15±1.10	0.722
INR	1.04±0.13	1.07±0.17	0.271
aPTT (s)	40.96±6.30	41.20±7.15	0.843
ACT (s)	131.35±11.65	129.80±12.70	0.480
Platelets (×10 ³ /μl)	265.83±67.30	272.40±70.50	0.596
Fibrinogen (g/l)	3.31±0.47	3.44±0.43	0.110
D-dimer (μg/ml)	0.24±0.16	0.21±0.15	0.283
Postoperative coagulation profiles			
BT (min)	9.42±1.78†	10.25±2.15†	0.020*
Platelet aggregation inhibition (%)	33.03±4.93†	35.11±5.85†	0.034*
PT (s)	11.15±1.24	10.92±1.16	0.288
INR	1.24±0.19	1.21±0.23	0.430
aPTT (s)	42.47±6.15	41.35±5.26	0.278
ACT (s)	133.2±5.58	132.50±5.25	0.433
Platelets (×10 ³ /μl)	245.48±47.80	249.00±51.40	0.693
Fibrinogen (g/l)	3.22±0.42	3.31±0.48	0.268
D-dimer (μg/ml)	1.18±0.45	1.12±0.34	0.403

ACT, activated clotting time; aPTT, activated thromboplastin time; BT, Bleeding time; FWB group, Fresh whole blood group; INR, international normalized ratio; PT, prothrombin time. * $P<0.05$ significant comparison between the two groups. † $P<0.05$ significant within the same group compared with the preoperative value.

Table 3 Blood losses and blood products transfusion (Data are presented as mean±SD)

Variables	FWB group (n=62)	Control group (n=62)	P value
Blood loss (ml/24 h)	815.55 ±126.40	1183.90 ±150.10	0.001*
Fresh whole blood	4.60±1.56	–	0.001*
Packed red blood cells (unit)	–	9.58±2.80	0.001*
Platelets (unit)	3.75±2.15	13.40±4.70	0.001*
Fresh frozen plasma (unit)	3.15±2.86	14.80±3.40	0.001*
Cryoprecipitate (unit)	3.20±1.50	9.70±3.35	0.001*
Hemoglobin (g/dl)	11.55±1.30	11.23±1.16	0.150

Group FWB, fresh whole blood group. * $P<0.05$ significant comparison between the two groups.

significantly more in the FWB group compared with the control group, and this means that FWB improved the platelet function than the transfused platelets, in spite there being no difference in the postoperative number of platelets. Mohr *et al.* [16] found that fresh blood improved the platelet function as shown by the improvement of the platelet aggregation and BT with the fresh blood than the transfused platelet after cardiac surgery. Moreover, they found that the hemostatic effect of one-unit FWB after CPB is at least equal, if not superior, to the effect of 10 units of platelets. Another study showed improved hemostasis in cardiac surgery after FWB administration compared with the transfused platelets, as the FWB contains large and potent platelets than the transfused platelet concentrate

[17]. The large platelets in the FWB resist inhibition, aggregate better, and induce a superior hemostatic effect than the transfused platelets [18–20].

The fresh blood has preserved clotting factors and full platelet activity [16,21], and many studies showed the use of FWB improves hemostasis, reduces exposures to cytokines and inflammatory mediators with the stored packed red blood cells, and also reduces the overall blood product exposures [22–25].

One study showed that the mixture of one unit of RBC has a hematocrit of 55%, one unit of platelet concentrate has platelets level 5.5×10^{10} , and one unit of FFP has 80% coagulation factors activity. In contrast, one unit of FWB has a hematocrit of 33–43%, 130 000–350 000 platelets per microliter, and 86% activity of coagulation factors [21,26]. Moreover, unlike the use of the stored blood products, FWB is anticipated to have full platelet activity [16,21,27–30]. Lavee *et al.* [28] showed a similar effect of whole blood on the preservation of platelet function by showing that platelet aggregation as assessed by electron microscopy after CPB in adult patients was restored by one unit of whole blood to a level equivalent to 8–10 platelet units.

Whole fresh blood is the product of choice if massive bleeding is expected, as it provides volume

Table 4 Surgical data of patients (data are presented as mean±SD, number, %)

Variables	FWB group (n=62)	Control group (n=62)	P value
Emergency surgery	62 (100)	62 (100)	1.000
Coronary artery bypass grafting	62 (100)	62 (100)	1.000
Number of coronary grafts			
2	8 (12.90)	5 (8.06)	0.559
3	26 (41.93)	30 (48.38)	0.863
4	18 (29.03)	21 (33.87)	0.698
5	10 (16.12)	6 (9.67)	0.421
Mitral valve repair	12 (19.35)	7 (11.29)	0.318
CPB time (min)	118.30±25.45	125.16±27.80	0.154
Cross-clamping time (min)	92.40±20.35	95.10±23.00	0.230
Temperature (°C)	29.48±3.15	28.86±4.03	0.341
Total heparin dose (mg)	318.60±66.83	311.55±62.79	0.546
Post heparin ACT (s)	584.74±115.60	610.15±123.30	0.238
Total protamine dose (mg)	345.25±63.50	337.90±60.85	0.511
Postprotamine ACT (s)	134.07±12.46	135.20±15.90	0.959
Thorax closure time (min)	72.50±15.35	84.00±17.70	0.001*

ACT, activated clotting time; CPB, cardiopulmonary bypass; FWB group, fresh whole blood group. * $P<0.05$ significant comparison between the two groups.

Table 5 Intraoperative data and outcome of patients (data are presented as mean±SD, number, %)

Variables	FWB group (n=62)	Control group (n=62)	P value
Dopamine(μg/kg/min)	6.50±2.80	8.18±3.40	0.003*
Norepinephrine (μg/kg/min)	0.06±0.03	0.08±0.04	0.002*
Nitroglycerine (μg/kg/min)	1.37±0.29	1.50±0.39	0.037*
Postoperative cardiac tamponade	2 (6.45)	7 (11.29)	0.166
Surgical re-exploration	4 (3.22)	13 (20.96)	0.034*
Postoperative graft occlusion and acute MI	—	—	
Pulmonary edema	5 (8.06)	15 (24.19)	0.028*
Postoperative mechanical ventilation	5 (8.06)	15 (24.19)	0.028*
Allergic reaction	3 (4.83)	11 (17.74)	0.047*
Renal failure	5 (8.06)	9 (14.51)	0.241
Neurological complication (stroke)	—	—	
ICU length of stay (days)	5.10±1.30	6.03±1.45	0.002*
Hospital length of stay (days)	10.75±2.65	12.10±3.50	0.016*
Anaphylactic reaction	—	—	
Disseminated intravascular coagulopathy	—	—	
Thromboembolism	—	—	
Mortality	—	—	

Acute MI, acute myocardial infarction; FWB group, fresh whole blood group; MI, myocardial infarction. * $P<0.05$ significant comparison between the two groups.

replacement, higher oxygen-carrying capacity, and coagulation factor replacement [31]. Jobes *et al.* [12] found that the FWB is associated with an improvement of hemostasis and decreased blood product transfusion as a result of preserved platelet function in the FWB in cardiac operations in children younger than 2 years old. Moreover, the FWB reduced the donor exposures compared with other blood products of multiple donors, and similar results were shown by other studies [13,14]. Another study showed that the reversal of the antiplatelet effect required 12 units of platelets that were 48 h after extraction, compared with four units of fresh platelets [32].

In the present study, the transfusion of FWB decreased the transfusion of other blood products such as platelets, fresh frozen plasma, and cryoprecipitate in patients on preoperative clopidogrel undergoing emergency CABG. Therefore, FWB group is associated with a lower dose of pharmacological support, decreased incidence of postoperative cardiac tamponade, allergic reaction, pulmonary edema, postoperative mechanical ventilation, and renal failure. Moreover, the ICU and hospital length of stay were shorter with FWB than the control group. Some studies showed that FWB in pediatric cardiac surgery significantly improved the clinical outcomes, reduced the postoperative chest tube volume loss

during the first 24 h, and significantly decreased the required inotropic support, ventilation time, and hospital length of stay [25,33,34].

Contrary to the results of the present study, McLean *et al.* [35] showed that there was no significant increase in bleeding in the patients receiving clopidogrel undergoing urgent CABG, and Karabulut *et al.* [36] suggest that preoperative use of clopidogrel does not increase perioperative bleeding, surgical exploration, or blood product transfusion after CABG.

There is limitation to the present study as thromboelastography was not used to assess the efficiency of blood coagulation, as it was not available.

Conclusion

FWB decreased the blood loss, blood product transfusion, cardiac tamponade, and re-exploration in patients on preoperative clopidogrel undergoing emergency CABG.

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Conflicts of interest

There are no conflicts of interest.

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