Original Article

Combined Effect of Left Stellate Ganglion Blockade and Topical Administration of Papaverine on Left Internal Thoracic Artery Blood Flow in Patients Undergoing Coronary Revascularization

Abstract

Background: Left stellate ganglion blockade (LSGB) may have additive effect to topical administration of papaverine on prevention of vasospasm of left internal thoracic artery (LITA). **Aims:** This study aims to compare LITA blood flow with topical application of papaverine alone or in combination with LSGB. **Setting:** Tertiary care hospital. **Design:** Prospective randomized controlled study. **Materials and Methods:** A total of 100 patients operated for coronary revascularization were randomly and equally allocated into two groups. In control Group-C, papaverine was applied topically during the dissection of LITA. In Group-S, the additional LSGB was performed. Blood flow was measured from cut end of the LITA for 15 s. Primary objectives of the evaluation were to observe differences in the LITA blood flow. Observing incidence of radial-femoral arterial pressure difference after cardiopulmonary bypass (CPB) was secondary objective. **Statistical Analysis:** Student's unpaired *t*-test and Fisher's exact test to find out a significant difference between the groups. **Results:** LITA flow in Group-S was insignificantly more (49.28 ± 7.88 ml/min) than Group-C (47.12 ± 7.24 ml/min), ($P = 0.15$). Radio-femoral arterial pressure difference remained low for 40 min after termination of CPB in the Group-S compared to the Group-C (−0.99 ± 1.85 vs. −1.92 ± 2.26). **Conclusion:** Combining LSGB with papaverine does not increase the LITA blood flow compared to when the papaverine is used alone. However, ganglion blockade reduces radial-femoral arterial pressure difference after CPB. Blockade can be achieved successfully under the ultrasound guidance without any complications.

Keywords: *Cardiopulmonary bypass, coronary artery bypass grafting, femoral artery, internal thoracic artery, stellate ganglion block*

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Introduction

Left Internal thoracic artery (LITA) is routinely used during coronary artery bypass grafting (CABG) as a conduit for revascularization of the left anterior descending artery. One of the challenges confronted in the perioperative period is major vasoconstriction of the LITA pedicle graft occurring during the preparation of this graft. Walpoth *et al.*,[1] using intraoperative transit-time flow measurement demonstrated that the ITA undergoes major vasoconstriction and significant flow-reduction during the preparation of its pedicle. Severe coronary arterial and graft vasospasm has been reported to occur in the postoperative period in approximately 0.43% of patients.[2] The LITA-spasm produces severe hemodynamic disturbances, many times requiring intra-aortic balloon pump[3] to stabilize the circulation. A variety of drugs such as calcium channel blockers, nitroglycerine (NTG), papaverine, and sodium nitroprusside[4] have been tried to prevent LITA-vasospasm. Intraluminal injection of papaverine in the LITA[5] has been shown to be an effective way to prevent the vasospasm; however, hydrostatic dilation carries a potential risk of mechanical damage to media and dissection of intima caused by cannulation, overstretching, and acidity of the solution.[5,6] Topical papaverine solution also produces vasodilatory effects on LITA although it increases the flow[1] only by 30%. Vasodilatory effect of topical papaverine is much less than that produced by intraluminal injection. Catastrophic hemodynamic deterioration has been reported in the postoperative period due to LITA-spasm despite topical application of

How to cite this article: Chandran R, Sreedhar R, Gadhinglajkar S, Dash P, Karunakaran J, Pillai V. Combined effect of left stellate ganglion blockade and topical administration of papaverine on left internal thoracic artery blood flow in patients undergoing coronary revascularization. Ann Card Anaesth 2020;23:170-6.

Submitted: 20-Jul-2018
Revised: 28-Aug-2018
Accepted: 26-Oct-2018
Published: 07-Apr-2020

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Access this article online
Website: www.annals.in
DOI: 10.4103/aca.ACA_144_18
Quick Response Code:

papaverine.[7] Some of the studies demonstrated vasodilatory effects of sympatholysis through regional anesthesia techniques such as thoracic epidural anesthesia (TEA)[8] and left stellate ganglion blockade (LSGB) on LITA flow and diameter, respectively.[9,10] LSGB also has been shown to improve flow in free radial artery graft.[11] As various agents used for vasodilatation of arterial grafts differ in their actions, combination therapy has been advocated by some of the investigators to increase blood flow in the grafts. We conducted the present study with the primary objective of investigating whether combining topical application of papaverine with LSGB would increase the LITA blood flow compared to those receiving topical application of papaverine alone. A problem frequently encountered after cardiopulmonary bypass (CPB) is the development of blood pressure (BP) difference between the femoral artery and the radial artery,[12] which results in an underestimation of central aortic pressure when measured using cannula in the radial artery. LSGB by virtue of inducing vasodilatation in the left radial artery may abolish this pressure difference. The secondary objectives of our study included a comparison of radial and femoral arterial BP difference in the post-CPB period in the two groups.

Materials and Methods

This prospective, intervention-based, randomized controlled study was conducted in a university-level hospital after it was approved by the Institutional Ethics Committee. Written informed consent was obtained from all study participants. Hundred consecutive adult patients up to the age of 80 years, who were operated for elective CABG under CPB, were enrolled in the study. Exclusion criteria comprised of patients with left ventricular ejection fraction <45%; history of stroke, glaucoma, chronic obstructive pulmonary disease, renal dysfunction (serum creatinine >1.5 mg/dl), and allergy to local anesthetic drugs. Calcium channel blockers and angiotensin-converting enzyme inhibitors were discontinued 24 h before surgery, whereas beta blocker was included in the premedication if the patient had been on the drug.

After securing peripheral venous access and an invasive left radial artery cannula under local anesthesia, anesthesia was induced in all patients with intravenous injections of midazolam 0.1 mg/kg, fentanyl 10 mcg/kg, and sleep dose of propofol 0.5–2 mg/kg. Vecuronium 0.15 mg/kg was administered to facilitate endotracheal intubation. Anesthesia was maintained with isoflurane at 1–1.5 MAC, infusion of morphine 40 mcg/kg/h, and supplemental doses of midazolam, fentanyl, and muscle relaxants. Anesthetics were titrated to a BIS value of 40–50. A triple-lumen catheter was inserted in the right internal jugular vein, and a single-lumen catheter was inserted in one of the femoral arteries. Transesophageal echocardiography probe was inserted for monitoring cardiac function in all patients. Using a computer-generated randomization protocol, two groups were formed consisting of 50 patients each. The patients in Study group (S) were administered LSGB after induction of anesthesia, whereas, those in Control Group (C) did not receive the LSGB. In all patients, LITA was used as one of the conduits for CABG. Topical papaverine was applied during LITA dissection in all patients.

For the LSGB, patients were positioned supine, and the neck was extended slightly. After topical sterilization of the neck on the left side of mid-line, cricoid cartilage was palpated, and a 12-MHz linear ultrasound probe (Esaote MyLab One, Esaote Europe, Netherlands) was used to locate various structures. The internal jugular vein, carotid artery, thyroid gland and transverse process of the sixth cervical (C6) vertebra (characterized by its bright echo-luminance) were identified. Color Doppler imaging was used to confirm that there were no vascular structures along the intended track of the needle. A 22G, 10 cm long needle was inserted under ultrasound-guidance and directed toward the transverse process of C6 vertebra, with the needle passing between medial border of the carotid artery and lateral margin of the thyroid gland. After the needle tip made contact with the transverse process, it was withdrawn by 2 mm and 8 ml of 0.25% levobupivacaine solution was injected, visualizing the drug deposition into the longus colli muscle compartment [Figure 1]. Expansion

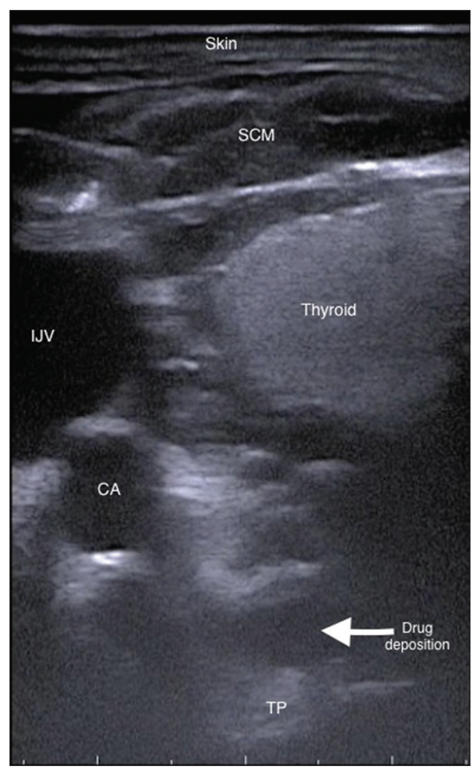

Figure 1: Figure demonstrates the ultrasonic image of stellate ganglion blockade. A 22G, 10 cm-long needle is directed towards the transverse process of the C6 vertebra, passing between the medial border of carotid artery and the lateral margins of the thyroid gland. The needle generates reverberation artefact during insertion. IJV: Internal jugular vein, CA: Carotid artery, TP: Transverse process of C6 vertebra, SCM: Sternocleidomastoid

of the longus colli compartment as seen on the ultrasound in short axis view marked the successful deposition of the drug. Expansion of the compartment was also confirmed in its long axis by rotating the probe by 90°. Block was considered a success if the skin temperature on the left index finger increased by more than 1.5°C as compared to the baseline value. At least 1 h interval was maintained between LSGB and establishment of CPB in all patients.

In both Group-S and Group-C, topical papaverine solution containing 20 mg papaverine in 20 ml saline was applied to the LITA pedicle graft during dissection of the vessel. In concordance to the Institutional protocol, papaverine was not injected in the peri-arterial sheath or into the lumen of ITA. Patients were maintained normothermic during the LITA dissection. After dissection of LITA pedicle, 300 IU/kg of heparin was administered to maintain ACT value of more than 400 s. The hematocrit was in the range of 44% ±5.4%. The LITA blood flow was measured when the mean arterial pressure (MAP) was maintained between 70 and 75 mmHg and $PaCO_2$ in the range of 35–45 mmHg. The MAP was maintained in the range of 70–75 mmHg primarily with the infusion of intravenous fluids. None of the patients received norepinephrine or phenylephrine infusion before the measurement of LITA flow. The LITA was cut to the appropriate length and allowed to bleed freely into a sterile bowl for 15 s, maintaining the mean BPs in the narrow range of 70–80 mmHg. The collected blood volume was measured with a syringe. The process was repeated twice and mean of the two values was used to calculate the LITA flow. A gauze piece soaked with papaverine solution was wrapped around the free end of the LITA pedicle after blood flow measurements. Patients, in whom no difference was observed in the skin temperature of the index fingers 20 min after the block, were treated as block-failure and were excluded from the study. Any complications occurring due to the administration of the block were recorded.

The following parameters were observed in all patients:

1. Pulse rate, systolic BP, diastolic BP, and mean BP were noted before the block (baseline), every 5 min after the block for 20 min, and just before measuring the ITA blood flow. The heart rate and mean BP were recorded at every 10-min interval after the patient was weaned from CPB until the time of transportation to the intensive care units (ICU)
2. The LITA blood flow was measured when the MAP was maintained between 70 and 75 mmHg
3. The success rate of LSGB was ascertained
4. The occurrence of any complications such as hematoma formation at the site of the block on inspection, severe hypotension requiring inotropes or vasopressor infusions in the intraoperative period, postoperative difficulty in swallowing possibly due to esophageal injury or hoarseness of voice attributed to airway injury were documented
5. The data obtained was subjected to statistical analysis using Student's Unpaired *t*-test and Fisher's exact test to find out a significant difference between the groups. For statistical comparison, the difference was considered statistically significant when the $P < 0.05$. Statistical analysis was performed using SPSS statistical software for Macintosh (Version 16, SPSS Inc. Chicago, Illinois).

Results

The patients in both Group-S and Group-C had a similar demography pertaining to age, weight and body surface area [Table 1]. About 82% of patients in the stellate ganglion group and 84% of patients in the control group were males. The LVEF was in the mean range of 58.6%–60.18% in all patients. There was no difference in the average number of bypass grafts received by patients in the two groups. Comorbidities such as hypertension, diabetes mellitus, smoking, and dyslipidemia were found to be distributed equally in patients of the two groups. The LSGB did not have a significant impact on the pulse rate.

The success rate of SGB was 100% without exception as assessed by the expansion of the longus colli compartment under ultrasound imaging and the rise in skin temperature of the left index finger by more than 1.5°C from the baseline value. The LITA flow in the stellate ganglion group was marginally more (49.28 ± 7.88 ml/min) than in the control arm of the study (47.12 ± 7.24 ml/min), although, the difference was statistically insignificant ($P = 0.15$). It suggested that the LSGB did not have any added advantage over the topical application of papaverine in increasing the LITA blood flow.

The mean pulse rate in both the groups was not different (except at 30 min) [Figure 2]. Some of the patients required temporary pacing in post-CPB period;

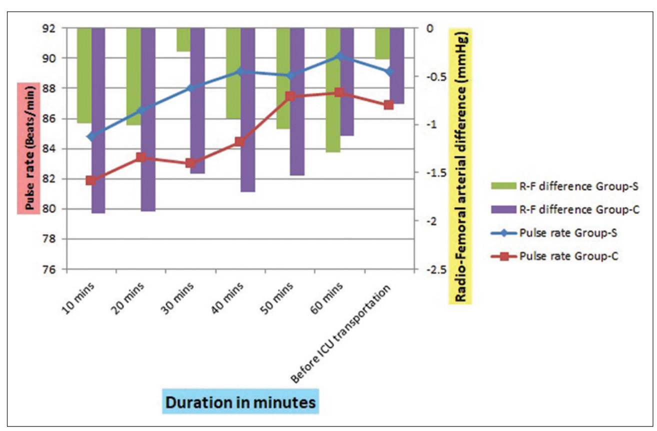

Figure 2: Figure depicts pulse rate and radial-femoral arterial pressure difference against every 10 min time interval in the postcardiopulmonary bypass period. The mean pulse rate in both the groups is without any difference except at 30 min. The mean pressure difference between the left radial artery and femoral artery was negative in the postcardiopulmonary bypass period. The radio-femoral arterial pressure difference remained lower in the Group-S compared with Group-C, which remained statistically significant for first 40 min after weaning from cardiopulmonary bypass

Table 1: Comparison of demographic data and co-morbidities between the groups

Parameter	Group-S	Group-C	Test applied	*P*	Significance
Age (years)					
Mean±SD	60.42±8.09	56.7±8.57	Unpaired *t*-est	0.27	NS
Range	42-76	40-78			
Weight (kg)					
Mean±SD	64.75±8.38	64.5±7.3	Unpaired *t*-test	0.87	NS
Range	45-89.8	50.1-83.3			
Sex (%)					
Male	41	42	Fisher's exact test	0.69	NS
Female	9	8			
BSA					
Mean±SD	1.7±0.14	1.7±0.12	Unpaired *t*-test	0.79	NS
Range	1.36-2.07	1.43-2.06			
LVEF (%)					
Mean±SD	58.6±6.08	60.18±6.68	Unpaired *t*-test	0.22	NS
Range	45-70	45-72			
Number of grafts					
Mean±SD	4.26±0.75	4.44±0.58	Unpaired *t*-test	0.18	NS
Range	2-5	3-5			
Hypertension					
Positive	41	40	Fisher's exact test	0.72	NS
Negative	9	10			
Diabetes mellitus					
Positive	26	30	Fisher's exact test	0.24	NS
Negative	24	20			
COPD					
Positive	2	3	Fisher's exact test	0.55	NS
Negative	48	47			
Smoking					
Positive	24	22	Fisher's exact test	0.56	NS
Negative	26	28			
Dyslipidemia					
Positive	46	44	Fisher'sexact test	0.38	NS
Negative	4	6			

SD: Standard deviation, BSA: Body surface area, LVEF: Left ventricular ejection fraction, COPD: Chronic obstructive pulmonary diseases, NS: Not significant

however, there was no difference in the incidence of pacing requirement in patients of either group. After the patients were weaned from CPB, the mean radial arterial pressures were consistently lower than the mean femoral arterial pressures in both groups. The radio-femoral arterial pressure difference was lower in the Group-S compared with Group-C, which remained statistically significant for 40 min after weaning from CPB. After 40 min, the pressure difference diminished and became statistically insignificant [Table 2]. Transesophageal echocardiography did not reveal fresh regional wall motion abnormalities in any of the patients. After transfer to the postoperative ICU, none of the patients developed hemodynamic instability and/or ST-T changes on electrocardiography attributable to vasospasm of the grafted LITA.

Patients were monitored for any complications of the SGB for 24 h after the surgery. None of the patients had hematoma formation at the site of block. None of the patients developed severe hypotension after the SGB requiring inotropes or vasopressor infusions in the intraoperative period. Accidental arterial injection and cardiac toxicity of levobupivacaine did not occur in any of the patients as suggested by the absence of blood aspiration before drug injection or development of cardiac arrhythmias after the injection. No patient complained of postoperative difficulty in swallowing attributable to esophageal injury or hoarseness of voice due to the airway injury.

Discussion

Coronary arterial and graft vasospasm has been reported to occur in 0.43% of patients, although this incidence may be underestimated.[1,2] Smooth muscle fibers in tunica media of the arterial grafts are prone for vasospasm during surgical handling.[13] Preparation of LITA pedicle and adequate

Table 2: Mean pulse rate and mean radial-femoral arterial pressure difference after the cardiopulmonary bypass in Group-S and Group-C

Duration (min)	Mean pulse rate (beats/min)			Mean radio-femoral arterial pressure difference (mmHg)		
	Group-S	Group-C	*P*	Group-S	Group-C	*P*
Pre-CPB						
Baseline	67.3±10.6	66.5±12.9	0.93	1.51±2.25	1.91±2.15	0.37
Before LITA flow measurement	63.5±9.6	64.3±8.9	0.65	0.61±1.73	1.00±2.3	0.34
Post-CPB (min)						
10	84.84±12.77	81.86±11.45	0.22	−0.99±1.85	−1.92±2.26	0.03*
20	86.52±10.31	83.38±12.01	0.16	−1.01±1.68	−1.90±1.93	0.02*
30	88.04±12.8	82.98±12.24	0.04*	−0.24±2.3	−1.51±1.84	0.0003*
40	89.14±11.96	84.40±12.98	0.06	−0.94±1.83	−1.70±2.0	0.05*
50	88.88±11.93	87.48±13.23	0.57	−1.05±2.34	−1.53±1.86	0.25
60	90.16±12.18	87.72±11.86	0.31	−1.29±1.4	−1.12±1.68	0.58
Before ICU transportation	89.12±9.82	86.86±10.47	0.26	−0.32±1.54	−0.79±1.56	0.13

The *P* value less than 0.05 is considered statistically significant. CPB: Cardiopulmonary bypass, LITA: Left internal thoracic artery, ICU: Intensive care unit

flow in the vessel immediately after grafting is critical to the success of the operation.[14] Spasm of LITA is of multifactorial origin. Various drugs tried for the prevention and treatment of LITA-spasm include papaverine, calcium channel blockers, sodium nitroprusside, organic nitrates and phosphodiesterase inhibitors.[4] Spasm of LITA can be prevented using nonpharmacological modalities[2] such as skeletonization of the vessel, carbon dioxide insufflation and normothermic graft harvesting. There are reports on successful LITA-dilatation achieved through sympatholysis induced by TEA.[8] LSGB also has been shown to cause vasodilatation of LITA.[9,10] Majority of the vasodilatory effects on LITA are attained through endothelial expression of nitric oxide and blockade of alpha-receptors or receptors of vasoactive agents such as thromboxane-A2, endothelin-1, prostaglandin-II, adenosine, and angiotensin II. Which pathway among them provides maximum vasodilatory effect still remains controversial. All vasodilating techniques have their own limitations in preventing LITA-spasm, and every individual technique acts through a specific mechanism. None of the pharmacological or nonpharmacological methods achieve desirable effects through all mechanisms. Hence, the combination of vasodilatory methods is believed to offer better results than any individual treatment modality.[4,15] Some of the drug combinations such as intraluminal or topical administration of calcium antagonists or milrinone with NTG have demonstrated synergistic effects on vasodilation.[15,16] Papaverine produces vascular relaxation through several mechanisms, including inhibition of phosphodiesterase and release of intracellularly stored calcium resulting in decreased calcium influx.[17] Intraluminal and periarterial injections have been shown to induce more vasodilatation than the topical application of papaverine.[5,18] However, which route of application of papaverine yields a better effect is still a matter for investigations. Being an acidic drug, its intraluminal delivery is associated with intimal damage. Microscopic analysis by Dregelid *et al*.[6] showed that intraluminal instillation causes mechanical injury to the lumen of the ITA in the form of dissections, disruption, or invaginations into the lumen of the vessel. Topical application of papaverine has been shown to cause significant LITA dilatation, although it is less than that produced by intraluminal injection. The vasodilatory effect of papaverine is slower in onset when compared to other vasodilators. The sympathetic nervous system plays a role in regulating tone of the arterial grafts through alpha-1 adrenoceptors.[19] Intrinsic as well as extrinsically-infused catecholamines can increase arterial tone through alpha-1 agonistic mechanisms. The density of beta-2 receptors, which have vasodilating property, remains sparse in the LITA.[20] Hence, the vasodilatation of LITA can be achieved primarily through alpha-adrenoceptor blockade. Sympatholysis produced by TEA is mediated through enhanced expression of the endothelial nitric oxide. As LSGB also causes sympatholysis, we hypothesized that blocking the LSG would have synergistic effects on the papaverine-induced vasodilatation of LITA. We noticed that LITA flow was marginally higher in patients of Group-S compared to those of Group-C although this difference was not statistically significant. There may be more than one reason for the fact that the vasodilatory effects of LSGB are nonadditive to that of the papaverine. First, papaverine alone was probably adequate enough to prevent LITA vasoconstriction because it is a potent vasodilator. Endogenous catecholamines acting through alpha-adrenoceptors have been implicated as mediators for LITA vasospasm. Papaverine is known to completely inhibit noradrenaline-induced contraction of the LITA.[21] As LSGB also acts predominantly through blockade of alpha-adrenoceptors, it does not contribute to any additional vasodilation.

Our study demonstrated that the use of ultrasound provides 100% success for LSG blockade. The principle advantage of ultrasound technique is accurate delivery of the drug and low drug volume requirement.[22] A small volume of the local anesthetic drug could be precisely deposited into the longus colli compartment without producing any complications, although all the patients subsequently received large doses of heparin before the institution of cardiopulmonary bypass. The ganglion blockade could be completed within 5–6 min in all patients. The assessment of the success of SGB under anesthesia is difficult compared to when the patient is in the awake-state as many indicators are masked by the effects of general anesthesia. High-dose opioid-based anesthesia produces miosis, which interferes with the assessment of Horner's syndrome. Ptosis and enophthalmos which are other signs of Horner's syndrome cannot be demonstrated after administration of muscle relaxants. Malmqvist *et al*.[23] reported that rise in skin temperature after SGB may be considered as a sign of successful blockade. Other methods proposed by them to detect signs of SGB such as monitoring the blood flow in the limb or checking the sympathogalvanic response were not feasible for our patients in the intraoperative setting. Hence, in our opinion, the ultrasonic imaging of expansion of the longus colli compartment during injection of the local anesthetic drug, succeeded by the rise in skin temperature of the index finger should be regarded as indicators of successful SGB under general anesthesia.

We observed that SGB did not cause significant bradycardia or fall in the systemic mean and diastolic arterial pressures. This finding favors the maintenance of coronary perfusion in a patient with triple vessel disease. The radiofemoral arterial pressure difference became less in the SGB group than in the control group for 40 min after the patients were weaned from CPB, which is the most crucial period when maximum pressure differences are observed. Although the femoral arterial pressures remained higher than those measured from radial artery, a significant (>5 mmHg) difference between pressures measured at the two sites was seen in 28% of the study subjects and the majority of them belonged to the control group. Femoral arterial pressure exceeding the radial arterial pressures during rewarming and post-CPB period is a frequent observation.[24] This pressure difference gets abolished within an hour after weaning patients from CPB. Hence, some of the investigators advocate the routine insertion of femoral arterial cannula in patients undergoing CPB. Our results corroborate with the previously reported literature on this issue. In addition, we noted that the magnitude of radio-femoral arterial pressure difference is lesser in the group receiving SGB as compared to controls. However, this magnitude in the pressure difference with or without SGB was relatively small to exert any significant clinical impact. The mechanism behind the development of this pressure difference is still a matter of controversy as multiple studies have suggested contradictory theories about its mechanism. Pauca *et al*.[25] proposed a decrease in vascular resistance of the upper extremity or the hand as the mechanism, whereas others.[26,27] reported that peripheral vasoconstriction or vasospasm was responsible for the development of the pressure gradient. Abolition of the radio-femoral arterial pressure difference through vasodilation of the radial artery by the LSGB signifies that radial artery vasoconstriction may be the underlying mechanism behind the generation of this pressure difference after the CPB. As the radial artery pressure equaled femoral arterial pressure in the majority of patients who received SGB, there may not be a need for additional femoral artery cannulation in those who receive the SGB.

We acknowledge certain limitations to our study. We presumed that flow of blood collected from the open end of LITA would be the same as the flow through the vessel when it would function as a conduit after the anastomosis. The LITA flow after anastomosis depends on factors including distal coronary vascular resistance, duration of diastole and left ventricular end-diastolic pressure and it may be different from the flow through the open end of the artery. We did not use intraoperative flow quantifying devices such as pencil Doppler probe or transit-time flow measurement. We did not compare the effect of only LSGB with only topical administration of papaverine on LITA blood flow in patients undergoing coronary revascularization.

Conclusion

Combined treatment modalities have been advocated for the prevention of LITA vasospasm during CABG. We compared LITA blood flow in two groups of patients in whom the papaverine was applied topically in combination with LSGB or without the ganglion blockade. We found that combining the LSGB with papaverine does not increase LITA blood flow compared to when the papaverine is used alone. However, LSGB reduces the incidence of radial-femoral arterial pressure difference. Before coronary revascularization, LSGB can be given successfully under ultrasound guidance without any complications.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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