DOI- https://doi.org/10.3329/cardio.v17i1.79948

Original Article

Effects of Glyceryl Trinitrate-Verapamil Solution in Comparison with Papaverine Solution by Organ Bath Technique in Preparation of Left Internal Mammary Artery for Off Pump Coronary Artery Bypass Surgery

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Keywords: *Glyceryl Trinitrate, Verapamil, Papaverine, Left internal mammary artery, CABG, IHD*

Abstract:

Background: *Papaverine has been the conventional vasodilator used to combat vasospasm at the time of left internal mammary artery (LIMA) preparation. Recent evidence associating Papaverine with vascular wall damage in bypass conduits has prompted the search for safe and effective alternative vasodilators. A buffered vasodilator solution containing glyceryl trinitrate and verapamil solution (GV solution) made a promising vasodilator for preparation of vascular conduits.*

Methods: *The study compared the effects and safety of GV solution to Papaverine solution on 60 patients. Group A (30 patients) received GV solution, while Group B (30 patients) received conventional Papaverine solution. The study analyzed LIMA flow before (Flow 1) and after (Flow 2) the organ bath, ICU stay, ECG, Echocardiography, mortality, morbidity, and other important parameters.*

Results: *The administration of a vasodilator agent using the organ bath technique resulted in a significant increase in free flow (Flow 2) in both group A and group B compared to Flow 1 ($p < 0.0001$). However, Flow 2 was significantly higher in group A than in group B ($p < 0.0001$). There were no deaths in group A, but two deaths occurred in group B, indicating that the GV solution was safe solution. While there were lower rates of morbidity and ICU stay in group A compared to group B, these differences were not statistically significant ($p > 0.05$).*

Conclusion: *The GV solution was found to be a safe and effective substitute for Papaverine, preventing or rapidly reversing LIMA spasms during preparation for OPCAB surgery.*

(Cardiovasc j 2024; 17(1): 18-23)

Introduction:

Ischemic heart disease (IHD) is the most common form of heart disease and incidence is increasing rapidly in developing countries, including Bangladesh.[1-3] Coronary artery bypass graft (CABG) surgery remains one of the standard modes of revascularization in ischemic heart disease. OPCAB is done to avoid cardiopulmonary bypass (CPB) related complications like pulmonary dysfunction, increased bleeding tendency & renal failure.[4] Left internal mammary artery (LIMA), is the most widely used graft for anastomosis to left anterior descending artery (LAD), which is considered as gold standard in coronary artery surgery due to its high long-term patency rates.[5] LIMA has anatomical features of an elastic artery and capable of undergoing severe spasm. Intractable spasm of LIMA lead to

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transmural myocardial infarction and death.[6,7] Green introduced papaverine to cardiac surgery in 1971. Since then, many cardiac surgeons have used this drug to treat the spasm of both LIMA and vein grafts. Most surgeons use this agent topically due to known adverse effects of papaverine on endothelium because of acidic pH.[8,9]

Recent evidence associating papaverine with vascular wall damage in bypass conduits has prompted the search for safe and effective alternative vasodilators. On the basis of previous laboratory studies, a buffered vasodilator solution containing glyceryl trinitrate and verapamil (GV) solution (pH 7.4) made a promising vasodilator for preparation of vascular conduits.[10,11] While nitrates are effective in treating existing vascular spasms, they are not as powerful in preventing vasospasms and exhibit slightly better efficacy in blocking receptor-operated channels than depolarizing agent-induced contraction.[12,13] Verapamil is a papaverine derivative, highly effective in preventing or treating K+ induced contraction in the IMA or RA by blocking L-type calcium channels and reducing Ca2+ influx.[14] In addition, GV solution is useful in preventing spasm of veins during harvesting of saphenous vein grafts. Because most patients need saphenous vein grafts in addition to IMA grafts. It is convenient to have one solution that can be used for both the IMA and the saphenous vein.[14,15]

This study was designed to compare the effects of GV solution with papaverine by organ bath technique on the free blood flow of LIMA and to determine whether this solution could be an appropriate substitute for papaverine solution for the preparation of LIMA during OPCABG surgery or not.

Methods:

This was a prospective observational study conducted at the Department of Cardiac Surgery, National Institute of Cardiovascular Diseases (NICVD), Bangladesh from January 2018 to December 2018 and included patients who underwent off-pump coronary artery bypass surgery and were selected through purposive sampling. The patients were divided into two groups: Group A consisted of 30 patients who underwent OPCABG using glyceryl trinitrate-verapamil solution during LIMA preparation, and Group B consisted of 30 patients who underwent OPCABG using papaverine solution during LIMA preparation.

Patients with impaired left ventricular function (E<35%), conventional or on-pump CABG, redo CABG surgery, recent myocardial infarction, associated valvular heart disease or other congenital heart diseases. Or subclavian artery stenosis was excluded from the study.

Anesthesia was given following a standard protocol, and vital signs were monitored continuously. LIMA was harvested using low-power electrocautery, and major branches were ligated with hemo-clips. LIMA dissection time was recorded, and heparin was administered before dividing the artery distally. Free flow from the distal end of the LIMA was measured for 15 seconds in a heparin-tinged open beaker under controlled hemodynamic conditions, and the flow was calculated (Flow 1). Before the anastomosis, the LIMA was allowed to dilate in a solution bath, and its flow was measured again (Flow 2). Two solutions were used in the study: GV solution, which consisted of nitroglycerin 2.5 mg, verapamil 5 mg, 7.5% NaHCO3 0.25 ml, heparin 500 units, and Ringer's lactate solution 300 ml; Papaverine solution consisted of 1 mg /ml 0.9% normal saline. The method was used in this study:

Organ Bath Technique: Following the graft harvesting, it was kept in a solution soaked gauze repeatedly flushing with either GV or papaverine solution to facilitate the dilatation of the graft in the solution bath. Just before the anastomosis the conduit was removed from the gauze immediately prior to using it for anastomosis.

The flow from LIMA was measured twice during the procedure - immediately after the graft harvest (Flow 1) and just before the anastomosis (Flow 2), both for a duration of 15 seconds. Throughout the procedure, systolic blood pressure was maintained within the normal limit. Patients were closely monitored for any potential adverse events until discharge.

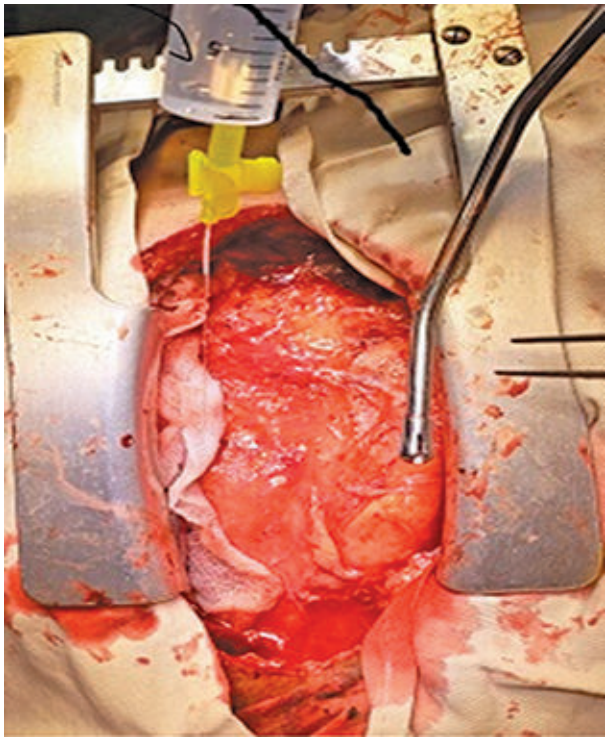

Figure 1: *organ bath technique with either GV or papaverine solution.*

Statistical Methods:
The data was analyzed manually and using SPSS Version 22.0. Quantitative data was expressed as mean and standard deviation and compared using a "t" test. Qualitative data was expressed as frequency and percentage and compared using Chi-square or Fisher's exact test. A p-value of <0.05 was considered significant for all analyses.

Results:
The age ranged from 32 to 72 years with (mean ± SD) 50.11± 11.11 years. In group A, male 28 (93.3%) and female 2(6.6%) and in group B; male 27(90%) and female were 3(10%). There were no significant difference between age and sex of two groups (Chi square test); p= 0.64.

Table I includes risk factors that were taken into account for both Group A and Group B patients, such as hypertension, diabetes mellitus, smoking, and hypercholesterolemia. The Chi-square test did not show any significant difference between Group A and Group B (p>0.05).

In both Group A and Group B patients, pre-operative ECG showed old myocardial infarction in a proportion of patients, as well as ST-T abnormalities, left ventricular hypertrophy, and right bundle branch block. However, there was no significant difference between the two groups in terms of ECG findings (p > 0.05). Pre-operative echocardiography revealed similar results for both groups in terms of left ventricular internal dimensions and ejection fraction. Coronary angiogram showed that the majority of patients had significant stenosis of triple vessels, with a small proportion of patients having significant stenosis of single or double vessels, or significant left main coronary artery lesion. However, there was no significant difference between the two groups in terms of coronary angiogram findings (p > 0.05) were shown.

There was no significant difference between two groups regarding number of grafts, LIMA harvesting time and total surgical time (Table-II).

Table-I
Showing risk factors of group-A and group-B patients with CAD.

Risk factors	Group A, n=30	Group B, n=30	P value
Hypertension	12 (40%)	18 (60%)	0.1213^{NS}
Diabetes mellitus	9 (30%)	11 (36%)	0.5839^{NS}
Smoking	27 (90%)	22 (73%)	0.0953^{NS}
Dyslipidemia	4 (13%)	7 (23%)	0.3169^{NS}

Table-II
Showing surgical data analysis in group A & group B.

Variables	Group-A n = 30 (Mean±SD)	Group-B n = 30 (Mean±SD)	P value
No. of grafts	2.8±0.78	2.87±0.71	0.7176^{NS}
LIMA harvesting time (minute)	21.80±3.89	21.77±3.45	0.9749^{NS}
Total surgical time (hour)	5.88± 0.92	5.95± 1.08	0.7879^{NS}

Table-III

Showing LIMA Flow before & after organ bath in group A & group B.

LIMA flow measurement (ml/min)	Group-A, n-30 (Mean±SD)	Group B, n=30 (Mean±SD)	p value
Flow-1 (ml/min)	43.83±6.46		
	41.97 ± 6.23	0.2610	
Flow-2 (ml/min	94.93±10.43		
	80.73±10.96	< .0001	

The study showed, LIMA flow measurement before and after organ bath in two groups (n=30), with Group A having a mean LIMA flow of 43.83±6.46 ml/min for Flow-1 and 94.93±10.43 ml/min for Flow-2, and Group B having a mean LIMA flow of 41.97±6.23 ml/min for Flow-1 and 80.73±10.96 ml/min for Flow-2. An unpaired t-test was used to compare the groups, with a P value of 0.2610 for Flow-1 indicating no significant difference and a P value of <0.0001 for Flow-2 indicating a significant difference (Table-III).

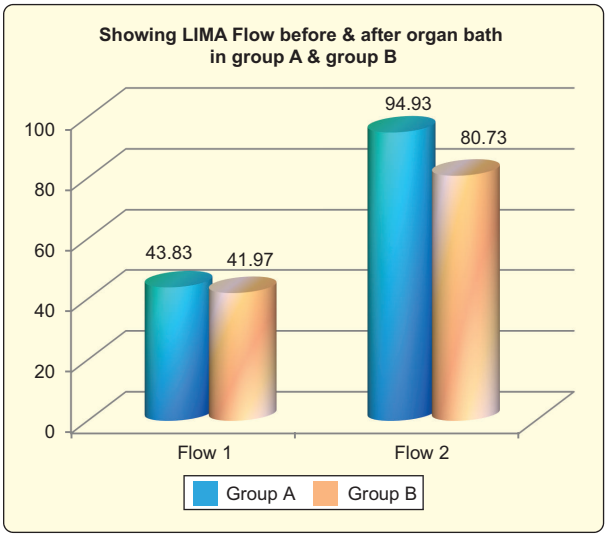

Figure 2: *Bar diagram Showing LIMA flow before & after organ bath in group A & group B*

Post-Operative Variables: During the early post-operative period, one patient (3.33%) from group-B developed myocardial infarction and died, while 4 patients (6.67%) developed low output syndrome (LOS), with 1 patient from group-A recovering and 3 patients from group-B, of which 1 died and 2 recovered. Two patients in group-A developed supraventricular tachycardia and 3 patients in group-B developed premature ventricular contraction, but all patients recovered well. These findings were not significantly different between the two groups.

Within 48 hours, 12 patients (20%) left the ICU, while most of the patients (43.33%) stayed for 72 hours, 16 patients (26.67%) stayed for 96 hours, and only 6 patients (10%) stayed for more than 96 hours. The average ICU stay was 68.33±17.31 hours in group-A and 73.43±22.67 hours in group-B, and the difference was not statistically significant (P=0.3315).

The follow-up 12-lead ECG showed no significant changes from the pre-operative findings, except for one patient in group-B who died on the first post-operative day with ST elevation. Post-operative echocardiography at discharge showed improvements in LVEF, LVIDd, and LVIDs in both groups, but the differences in improvement were not statistically significant (p>0.05).

Discussion:

Coronary artery disease is the most common form of heart disease and single most important cause of premature death in developed countries. OPCAB surgery has recently became widespread internationally and has produced good clinical outcome. LIMA is a gold standard conduit for LAD. At the time of LIMA preparation vasospasm is a common problem. Papaverine has been the conventional vasodilator used in this regard in many cardiac surgery centers. Papaverine solution is highly acidic (pH 4.8). Acidic solutions have been shown to damage the endothelium. Recent evidence associating papaverine with vascular wall damage in bypass conduits has prompted the search for safe and effective alternative vasodilators. A buffered vasodilator solution containing glyceryl trinitrate and verapamil (GV)

solution (pH 7.4) made a promising vasodilator for preparation of vascular conduits. Since its introduction GV solution has received attention from investigators as a potential substitute for papaverine.[7,16] The technique of harvesting the LIMA has a great influence on the fate of the CABG surgery. This study was based on a novel harvesting technique of LIMA for CABG, whereby the arterial endothelium was well preserved by GV solution that protected the LIMA from spasm and ischemia. This compromises endothelial and medial integrity and influences the short-term and long-term success of LIMA graft in CABG. The purpose of this study is to analyze the effects and safety of GV solution compared to papaverine solution on this regard. The results of this study showed the difference of two vasodilators in terms of type of solution. Nitroglycerin has a more rapid onset and verapamil has a longer action than papaverine, encouraged to continue to use the GV solution. The blood vessel resistance after organ bath technique had a significant reduction in the groups treated with the antispasmodic agents. We routinely harvest skeletonized LIMA in our institution and we had never tried to compare the flow with pedicled LIMA. Using organ bath technique, LIMA is uniformly exposed to the vasodilator solution throughout the exposure time. When the vasodilator agent was administered by organ bath technique, a dramatic increase of free flow i.e. Flow-2 in both the group A and the group B than Flow 1 (P< 0 .0001). However, Flow 2 was significantly more in group A than group B (P< 0 .0001). Another study found that the GV solution was effective in quickly relieving perioperative spasm of the LIMA and SV during cardiac surgery. Additionally, using GV solution during conduit preparation could eliminate the need for systemic vasodilators postoperatively, especially in the case of the LIMA which has a higher tendency for spasm. Overall, GV solution can be considered a safe and efficient alternative to papaverine for preparation of both arterial and venous coronary conduits. [17] According to Mohapatro et al. (2017), the use of GV solution as an organ bath technique during LIMA preparation may result in improved flow compared to the use of papaverine solution.[18]

Although there were no deaths in group A, two deaths occurred in group B, one due to myocardial infarction and the other due to low output syndrome. This finding indicates that the use of GV solution may be safer than the use of papaverine solution. Furthermore, although group A had less morbidity and shorter ICU stays than group B, this difference was not statistically significant (P>0.05).

Based on the study results, it is recommended that GV solution could be considered as an alternative to papaverine solution for LIMA preparation during off-pump CABG surgery using the organ bath technique. However, to further validate these findings, it is recommended to conduct a prospective large-scale multi-center study.

Study Limitations: This study has several limitations including a small sample size, being conducted in a single center, involving multiple surgical teams, using a less sophisticated system for measuring blood flow, and not comparing LIMA flow to post-operative patency using coronary angiogram.

Conclusion:

In conclusion, this study suggests that the use of GV solution in the organ bath technique during LIMA preparation for off-pump CABG surgery leads to significantly better LIMA outflow, lower post-operative morbidity, and no mortality when compared to the use of papaverine solution. These findings indicate that GV solution can be a viable alternative to papaverine solution for LIMA preparation in off-pump CABG surgery.

Conflict of Interest - None.

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