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Original Article

Papaverine on Internal Mammary Artery Flow- Comparitive Study of Intraluminal versus Topical

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ABSTRACT

Background: Coronary artery bypass grafting (CABG) is the commonest method for surgical revascularisation and Left Internal Mammary artery (LIMA) is the conduit of choice. However it may develop vasospasm during harvesting. Vasodilators like Papaverine have been proposed to relieve vasospasm and hence increase blood flow. However the optimal method of papaverine application is not clear. In this study we have compared the effects of intraluminal versus topical application of papaverine on LIMA flow. **Methods:** This was prospective randomized controlled trial of 60 patients. They were divided into two groups: group 1 (n=30; intraluminal papaverine application) and group 2 (n=30; topical papaverine application). LIMA was harvested, divided and the blood flow from distal cut end was measured under controlled hemodynamics, before papaverine application and 5 min after papaverine application. **Results:** In group 1, the mean blood flow was 61.07±3.1 ml/min before papaverine application and 119.6±3.72 ml/min after intraluminal instillation (p value <0.0001). In group 2, it was 60.4±2.24 ml/min before and 72.13±2.56 ml/min after papaverine topical application. The increase in blood flow observed in group 1 was 95.84% versus 19.42% in group 2. **Conclusion:** In this trial, while papaverine increased blood flow with both methods, it caused a higher rate of increase of blood flow with intraluminal instillation than with topical application.

Key words: CABG, Intraluminal, Internal mammary, OPCAB, Papaverine.

INTRODUCTION

The Left internal mammary artery (LIMA) is the conduit of choice for patients undergoing coronary artery bypass grafting (CABG). This has been documented by various long term trials showing good outcome when LIMA is anastomosed with the left anterior descending artery.[1,2] However it is susceptible to vasospasm and the resulting decrease in blood flow can have a deleterious impact on outcome.[3] Vasospasm influences decisions for usage of LIMA conduit, makes anastomosis technically difficult and causes rise in morbidity and mortality. papaverine has been proven to be effective in preventing vasospasm by *in vitro*[4,5] and clinical studies. But there is still debate on which method to be used for papaverine application.[6]While topical application is commonly used, its effect on arterial blood flow has been found to be inconsistent.[7,8] Intra luminal usage is the other most commonly used method. With the rising usage of off pump CABG, where systemic heparinisation is done to a lesser degree, the effect on arterial blood flow needs to be seen. We aim in this study to compare effect of both topical and intraluminal instillation on palavering in preventing vasospasm and hence causing increase in internal mammary blood flow.

MATERIAL AND METHODS

A total of 60 patients undergoing coronary artery bypass grafting were divided into two groups, with group 1 receiving intraluminal papaverine and group 2 received topical papaverine.

- *Inclusion criteria*
  - Elective Off pump CABG
  - Mandatory LIMA coronary angiogram shoot
- *Exclusion criteria*
  - Emergency cases
  - On pump CABG
  - Other associated cardiac anomalies

Surgical technique:

- Routine median sternotomy was done & non skeletonised internal mammary artery pedicle harvested.
- Dissection was performed with low power electrocautery and major branches were controlled with hemoclips.
- Systemic heparinisation done and Internal mammary artery was transected after bifurcation.
- Internal mammary flow was measured by collecting blood for two minutes in bowl and measuring with the syringes (Mean Artery Pressure 70-80mm hg).
- Internal mammaryblood flow noted for two minutes immediately after distal transection.
- 30 mg of room temperature papaverine (3 mg/ml 0.9% saline) was used.
- in group 1, papaverine was delivered intraluminally with the 24G cannula after the internal mammary artery was transected distally and occluded with hemoclips after instillation
- in group 2, papaverine was applied locally with the help of sponge piece soaked in papaverine.
- Internal mammary flow was again measured for two minutes after 5 min of papaverine use
- Routine coronary artery bypass grafting was done off pump with the help of octopus and starfish stabilizer.

Statistical methods

- Student '*t*' test – Paired and unpaired
- Mean
- Standard deviation

RESULTS

A total of 34 men and 26 women were included in the study with mean age of 57.6 years. Both the groups were found to be comparable and

were randomised sequentially.All patients had multi vessel coronary artery disease and left main disease was found in 12 patients (20%). Diabetes mellitus was found in 42 patients (70%). 24 patients (40%) were hypertensive. Smoking was found in 12 patients (20%). None had peripheral vascular disease. Previous myocardial infarction was seen in 34 patients (57%). The distribution of NYHA class was as follows: class II in 10 patients (16.67%), class III in 48 patients (80%) and class IV in 2 patients (3.33%). The mean preoperative ejection fraction was 45+/-10.3% (range 30%-60%). The mean body surface area was 1.77 m^2 (range was 1.45 m^2-1.83 m^2). All patients received left internal mammary to left anterior descending artery anastomosis. There were no injuries to the internal mammary artery during harvesting. There were no mortalities in both the groups.

In case of group 1, (as shown in Figure 1) mean blood flow in the LIMA before papaverine administration was 61.07 ± 3.1 mL/min. After intraluminal administration, it increased to 119.6 ± 3.72 mL/min (p <0.0001).

While in group 2, the mean blood flow in the LIMA before papaverine administration was 60.4 ± 2.24 mL/min which increased to 72.13 ± 2.56 mL/min (p <0.0001) after topical application.

Using delta flow, the difference between pre and post papaverine instillation was found to be 58.53 for group 1 and 11.93 for group 2. On calculation of confidence interval, the mean of group one minus group two was 47.47. The 95% confidence interval of this difference was calculated to be from 45.85 to 49.09. The percentage increase in blood flow observed in group 1 (intraluminal) v/s in group 2 (topical) was found to be statistically significant.

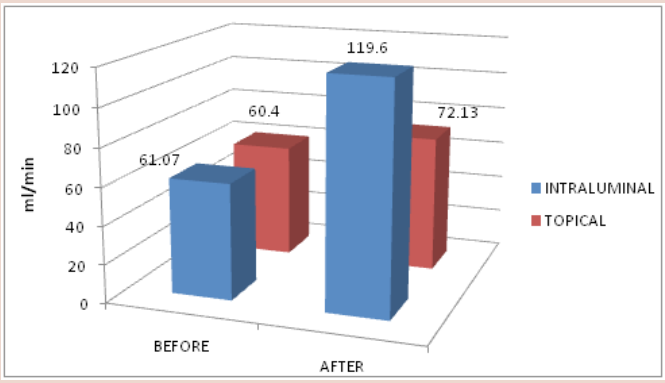

Figure 1: Internal mammary blood flow after Papaverine instillation in ml/min.

DISCUSSION

The usage of arterial grafts for performing coronary artery bypass grafting is becoming ubiquitous with long term advantages being proven by various long term studies.[1,2] The internal mammary artery is now the conduit of choice to achieve good outcome. But it is prone to vasospasm which when occurs can influence choice of conduit, make technically challenging and have a deleterious effect on mortality and morbidity.[3]This phenomenon of vasospasm has been found to be universal immediately after LIMA harvest and was relieved only after pharmacological intervention.[4] Various agents have been tried to prevent vasospasm of the internal mammary artery.[5] with papaverine now being the most preferred agent. Papaverine is an opioid derivative but differs from other opioids in both structure and function. Its mechanism of action is not clear but is thought to act by inhibiting enzyme phosphodiesterase causing rise in cyclic AMP and direct inhibition of calcium channels resulting in a spasmolytic action on smooth muscle cells. It has been proven to effectively treat vasospasm by various studies.[5,6]The most effective method to administer papaverine is controversial.[7-9] The method used to measure internal mammary blood flow used in our study is similar to that other studies[7-10] but we have measured the flow only at a fixed mean arterial pressure range of 70 to 80 mm of Hg to overcome variation due to different filling pressures. We believe this way we were able to avoid confounding factors which could have influenced other studies. Additionally by using fixed times for measuring internal mammary blood flow, sufficient time had been given to allow papaverine to act. Cooper *et al*[4] compared topical application of various pharmacological agents and concluded that sodium nitroprusside was the best vasodilator. Hillier *et al*[6] have disproven endothelial damage caused due to papaverine and have shown comparable effect to sodium nitroprusside. Studies by Sasson *et al*[8] and Dregelid[9]*et al* have concluded lack of efficacy with topical application. In our study, we did find that topical papaverine application caused increase in internal mammary flow but was significantly lesser compared to intraluminal application. Dregelid[9]*et al* also showed while intraluminal application was more efficacious, they also documented cases of mechanical injury secondary to intraluminal instillation. We had no such issues in our study as we did not depend on hydrostatic mechanical distension but after instillation of papaverine, the distal cut end was clipped and we waited for five minutes to allow arterial pressure itself to cause mechanical distension. Our observation correlates with Mills[10] *et al* who also concluded that intraluminal instillation of papaverine caused maximal increase in internal mammary blood flow and thereby increases safety and efficacy of coronary artery bypass grafting and that this holds good even for off pump surgery.

CONCLUSION

In this trial, both intra luminal and topical methods of papaverine application were effective in preventing vasospasm and causing an increase in internal mammary artery blood flow. However, the rate of increase in internal mammary blood flow was significantly higher with intraluminal method compared to topical method of papaverine application and should be used as the method to prevent vasospasm even in off pump coronary artery bypass grafting.

CONFLICT OF INTEREST

All authors declared no conflict of interest.

ABBREVIATION USED

LIMA: Left Internal Mammary Artery; **CABG:** Cornary Artery Bypass Graft; **NYHA:** New York Heart Association.

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