EFFECTS OF PAPAVERINE AND SODIUM NITROPRUSSIDE SOLUTION AS TOPICAL VASODILATORS FOR INTERNAL MAMMARY ARTERY

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ABSTRACT

Objective: To compare the effects of topical sodium nitroprusside (SNP) and papaverine solutions to treat left internal mammary artery spasm.

Study Design: Randomized Control Trial (RCT).

Place and duration of Study: AFIC / NIHD Rawalpindi from Jan 2009 to March 2009.

Patients and Methods: Fifty consecutive patients undergoing elective coronary artery bypass graft surgery (CABG) were randomly assigned to two groups: group N (n=25, Sodium Nitroprusside solution), and group P (n=25, Papaverine). In each patient, pedicled left internal mammary artery was harvested, five minutes after heparin administration, left internal mammary artery was divided distally; flow per minute was calculated after measuring the free flow for over 15 seconds; this is named "Flow 1." Then, the pedicled left internal mammary artery was sprayed with the randomized solution, and covered with the test solution soaked sponge. The second flow measurement "Flow 2" was done before commencing cardiopulmonary bypass. A third flow measurement "Flow 3" was recorded just before left internal mammary artery to left anterior descending coronary artery anastomosis, while the patient was on cardio pulmonary bypass.

Results: Analysis of variance was applied to detect differences among groups; paired-sample t test was used for left internal mammary artery topical free flow in both groups. Mean left internal mammary artery free flows were as follows: group N, flow1=32.72±27.67 ml/min, versus group P flow1=23.44±15.16 ml/min ($p<0.148$), group N flow2=63.92±33.40 ml/min versus group P flow2=38.88±24.54 ml/min ($p<0.004$), and group N flow3=62.44±38.38 ml/min versus group P flow3=49.52±30.29 ml/min ($p<.170$). Topical free flow difference amongst the two groups was statistically significant in the flow2 ($p< 0.004$); whereas topical mean free flow difference was statistically significant when the groups were individually compared group N flow1:flow2, flow 1: flow 3and flow 2: flow 3 group N (p<.000, .000, .846) and group P (p<.001, .000, .001) respectively.

Conclusion: Sodium nitroprusside (SNP) and papaverine solutions are able to treat vascular spasm and increase the flow of left internal mammary artery, when they are used topically. However sodium nitroprusside allows early and better relief of vascular spasm.

Keywords: Coronary artery bypass graft, Internal mammary artery, Papaverine, Nitroprusside.

INTRODUCTION

The internal mammary artery (IMA) is the conduit of choice for myocardial revascularization because of its proven long term patency rate and survival benefit[1,2]. Nevertheless, perioperative spasm of IMA, with consequent low free flow, has been described[3, 4] and held responsible for perioperative and postoperative morbidity. It is reported that surgical harvesting of the IMA leads to arterial spasm[5,6]; therefore, several antispasmodic agents, such as papaverine[7-9], calcium-channel blockers[10] sodium nitroprusside[11], nitroglycerine[10,12] milrinone[12,13], and phenoxibenzamine[14] have been studied, compared, and used both topically and intraluminally to treat the perioperative spasm of the arterial conduits. Papaverine is a phosphodiesterase inhibitor with a half-life of 100 minutes, and it is widely used during or after IMA harvesting to reverse spasm. Sodium nitroprusside is an arterial dilator. This study was designed to compare the early and late effects of papaverine and sodium nitroprusside solution as topical vasodilators for internal mammary artery.

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PATIENTS AND METHODS

Patient Selection and Data Collection

Since 2003 in our institution, we have routinely used papaverine and sodium

nitroprusside as an antispasmodic agent for the IMAs. Between January 2009 and March 2009, 241 patients underwent adult cardiac surgery operations, 197 of them had coronary artery bypass grafting (CABG) operation. Of this series, 50 consecutive patients were enrolled having elective operation, as isolated and primary CABG.

Patients undergoing emergency CABG and those with rapid onset of ischemic events that necessitated emergency bypass during the elective operation were excluded from this study. All patients were assigned by randomization charts to one of two categories: group N (n=25), treatment with sodium nitroprusside solution; group P (n=25) treatment with papaverine. The local Ethics Research Committee approved the study in December 2008, and each patient included in the study gave a written consent. Demographic and clinical data are listed in Table 1.

There is no conflict of interest in this study. The study was wholly sponsored by the institute.

Operative Technique

The left IMA was harvested as a pedicle from the subclavian vein to just beyond the bifurcation into the superior epigastric artery and musculophrenic arteries, with the aid of diathermy and metal clips. Five minutes after systemic heparinization (300 units/kg) ,the artery was divided beyond its bifurcation, free flow was measured by bleeding the artery into an inverted 25 ml syringe without a plunger for 15 seconds (Flow 1) at time (T1=0 min), free flow per minute was calculated accordingly, and then the IMA was clipped at its distal end.

The solutions used were prepared as the following mixtures. The nitroprusside solution contained 5 mL of drug (10mg/mL) in 50 ml 0.9% normal saline. The papaverine solution contained 2 mL of drug (0.025g/mL) in 50 ml 0.9% normal saline. The temperature of each solution during delivery was the same as the temperature of the operating room. (20° to 22°C).

The pedicled LIMA was then sprayed with the test solution and later wrapped with a gauze strip soaked with the study drug and then placed beneath the left sternal edge. The second flow (Flow 2) at time T2 (min) was measured just before commencing CPB. CPB was established and core temperature was reduced to 34°C. Ante grade warm blood cardioplegia was used for myocardial preservation. The pedicle was then wrapped again in the drug soaked gauze until the time of anastomosis of the LIMA to the LAD when the final 3rd flow (Flow 3) at time T3 (mins) was measured. In all patients, the left IMA was grafted to the LAD and was the last distal anastomosis. Rewarming of the patient was commenced shortly after the LIMA-LAD anastomosis was begun. The time interval between the three measurements, mean arterial pressure (MAP) and cardio pulmonary bypass flow (CPQ) were all recorded.

Statistical Analysis

Patients were randomly assigned to two groups to obtain approximately the same number of patients in each group. Results were expressed as mean ± standard error, in order to analyze statistically, signifcant differences in mean continuous parameters (age, body surface are (BSA), number of grafts, time, CPQ, etc.) between the two groups (papaverine, and sodium nitroprusside). Analysis of variance was done using the Levene's Test for Equality of Variances Multiple comparison option.

Independent sample t-test was used to compare the numeric variables between the two groups. Paired sample t-test was done in order to analyze statistically significant differences between first, second and third flow measurements specific for each group. P-values less than or equal to 0.05 were considered statistically significant.

RESULTS

Patients were divided into two groups; N (sodium nitroprusside solution) and group P (papaverine) each containing 25 patients respectively. Demographic, hemodynamic and CPB data between the two groups are shown in Table 1. No statistically significant differences were found between the groups with respect to age, body surface area (BSA), time intervals

between the three flow measurements, and CPB flow. Mean arterial pressure (MAP) at the time of the first, second and third flow measurements were not significantly different either within or between the groups.

In group N the flows 1, 2 and 3 were 32.72±27.67 ml, 63.92±33.40 ml and 62.44±38.38 ml whereas in group P the flows were 23.44±15.16 ml, 38.88±25.54 ml and 49.52±30.29 ml respectively. In both the groups the initial flow before treatment with test drug (Flow 1) was the lowest. There was a significant increase in Flow 2 and Flow 3 in the groups as compared to the initial flow, (Table 2 and 3). However the quantity of flow increase between Flow 1 and Flow 2 was much more in Nitroprusside group as compared to papaverine group. There was a steady flow increase of papaverine group from flow I through Flow 3.

Comparison of flow increase between groups (Table 4) Flow1-2, was 11.64±22.65 ml in papaverine group and 31.20±28.10 ml in Nitroprusside group, Flow 1-3 was18.50±34.63 ml in papaverine group and 29.72±34.17ml in Nitroprusside group and Flow2-3, was 6.85 ±18.55ml in papaverine group and a decrease in flow of 1.48 ±37.64 ml in Nitroprusside group.

DISCUSSION

This study confirms previous observations[15-17] that IMA flow is low initially after its harvest from the chest wall. This most probably is due to vasospasm triggered by

Table 1: Patients' clinical characteristics and hemodynamic data

	GROUP N Nitroprusside	GROUP P Papaverine	P value
MALE/FEMALE	24/1	22/3	0.297
AGE	56.2±9.6	56.8±8.7	0.819
BSA	.1840±.013	.1791±.014	0.212
BMI	25.9±3.42	25.7±2.46	0.842
EF	53.16±7.56	53.60±8.85	0.851
TI	0	0	0
T2	17.20± 5.361	17.92± 4.339	0.603
T3	50.52± 14.858	47.04 ±6.680	0.291
MAP 1 mm Hg	81.92±11.694	79.48 ±12.035	0.471
MAP 2 mm Hg	72.52 ± 9.618	70.04 ± 8.507	0.339
MAP 3 mmHg (On CPB)	64.24 ±12.129	69.56 ±14.771	0.170
CPQ L/min	4.60917 ±1.015	4.65440 ±.333	0.834

Table 2: IMA flow rates before and after treatment

TIME	Group N Nitroprusside	Group p Papaverine	P value
FLOW 1 ml/min (Before treatment)	32.72±27.67	23.44±15.16	0.148
FLOW 2 ml/min (After treatment)	63.92±33.40	38.88±25.54	0.004
FLOW 3 ml/min (After treatment)	62.44±38.38	49.52±30.29	0.193

Table 3: Comparison between groups

No.	Groups	Nitroprusside/ P Value	Papaverine/ P Value
1	Flow1-Flow2	0.000	0.001
2	Flow1-Flow3	0.000	0.000
3	Flow2-Flow3	0.846	0.061

Table 4: Comparison of flow change between groups

	GROUP N Nitroprusside	GROUP P Papaverine	P value
FLOW 1-FLOW2 (ml/min)	31.20±28.10	11.64±22.65	0.007
FLOW1-FLOW 3 (ml/min)	29.72±34.17	18.50±34.63	0.242
FLOW2- FLOW3 (ml/min)	-1.40±37.64 (Decrease in flow)	6.85±18.55	0.303

mechanical manipulation of the artery and physical factors such as diathermy[18.19]. However, this study shows that with application of topical vasodilator drugs the spasm subsides, the artery dilates, and its flow increases by two to three-folds.

Green[20] introduced papaverine in surgery in 1971. Since then, many cardiac surgeons have used this drug to treat the spasm both of IMA and vein grafts. Papaverine is a nonspecific vasodilator and relaxes the vascular smooth muscles through multiple mechanisms[21-23] and this vasodilator can be used topically and intraluminally, but its solution is acid (pH 4.4 to 4.8)[24] and can be damaging to the vascular endothelium[25, 26].

SNP is effective against a wide range of vasoconstrictor stimuli. SNP causes release of nitric oxide (NO) a strong stimulant of gunylate cyclase, which rises cGMP in smooth muscle cells, this decreases intracellular calcium levels and relaxes vascular smooth muscles.[27]

The design of this study varies from other studies in that a series of flow readings were taken from the division of the IMA off the chest wall to the time just before the LIMA was anastomosed to the LAD. This showed the behavior of the LIMA smooth muscle to the drug over a period of time initially with systemic pulsatile pressures and later on laminar CPB flow.

In the Nitroprusside group the flow increased two to three folds on the second reading and thereafter there was a gradual plateau in flow till the time of LIMA –LAD anastomosis. With regard to the onset of the effect for vasodilators, nitrates are the fastest, calcium antagonists are intermediate, and papaverine the slowest[28] and this was confirmed by our study.

This initial rapid effect in SNP group is due possibly to its better absorption and rapid onset of action on the vascular smooth muscles. Whereas in the papaverine group there was a gradual step up of flow with time till the LIMA-LAD anastomosis.

On the basis of our results, Papaverine and Nitroprusside solutions could be used indifferently to treat arterial conduit spasm. Nevertheless, in two recent reports, Mayranpand colleagues[29] and Gao and coworkers[30] have described two different types of damage induced by papaverine. Mayranpand described the evidence of endothelial damage of human radial graft in terms of endothelial denudation or "porosity." This damage could be caused by low pH of papaverine. Gao and colleagues have demonstrated that papaverine could induce apoptosis in porcine coronary endothelial cells and in rat aortic smooth cells. They have concluded that papaverine itself and not its acidity is responsible for apoptosis.

For severe spasm it is essential to use a dilator drug, preferably a fast-acting one suitable for intraluminal use, to determine whether the IMA should be discarded or alternatively relegated to graft a minor vessel. Maximal pharmacologic dilation of the IMA allows the surgeon to evaluate the flow-carrying capacity of the IMA and provides a relaxed, dilated distal vessel that facilitates a precise anastomosis. Vasodilatation of the IMA pedicle may also unmask small bleeding points at the time of surgery and thus improve hemostasis.[27]

Our study suffers from a few limitations. First, a simple system to collect the free flow was adopted: blood free flow in a 25-mL syringe in 15 seconds and flow per minute was calculated accordingly. By using more sophisticated systems, better measurements could be obtained. Second, arterial spasm is a multifactor phenomenon; we studied the indications to treat the mechanical spasm, but factors such as preoperative medications, endogenous catecholamine, and body temperature could modify the response of the arterial conduit to the tested vasodilators.

CONCLUSION

Papaverine is the oldest vasodilator used in cardiac surgery to treat the internal mammary artery spasm. Nevertheless, in the last years, data about its potential damage to endothelium have encouraged many surgeons to utilize

other vasodilators to reduce the risks of intimal damage and early graft closure. Nitroprusside solution is rapidly acting and should represent a valid alternative to papaverine.

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