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Original Article

Comparison of Vasopressin and Nor-Adrenaline for Hemodynamic Effects during Beating Heart Bypass Surgery

[1]Dr.Savita Chandrakant Pandit , [2]Dr.Kirti Arvind Kundalwal , [3]Dr.Surendra Dhanaji Nikhate , [4]Dr.Nanasaheb Khandu Bhangare

[1]Dept of Anaesthesia, BJGMC & SGH,Pune
[2]Dept of Anaesthesia BJGMC & SGH,Pune
[3]Dept of OBGY, DYPMC,Pune
[4]Dept of Pharmacology BJGMC & SGH,Pune
Corresponding Author: Dr.Kirti Arvind Kundalwal

ABSTRACT

Introduction- Coronary artery bypass graft (CABG) surgery is usually performed either stopping the heart or beating heart which is also known as "off-pump" bypass surgery. Anaesthesia for Off-pump CABG (OPCABG) is challenging as appropriate choice of inotrope plays a vital role in maintaining hemodynamic stability during surgery. We compared vasopressin and noradrenaline for the same purpose.

Materials and Methods- After obtaining Ethics Committee approval, 60 patients between 40- 60 years of age of either sex belonging to American society of Anaesthesiology (ASA) physical status class II and III scheduled for OPCABG, were enrolled in this prospective, randomized and double blind study. They were randomly divided into two equal groups. Group A received injection noradrenaline 0.02-0.12 µg/kg / min. while Group B received injection vasopressin 0.01-0.06 U /min. during surgery as pressor support. Aims and objectives of study were to compare hemodynamic effects of Vasopressin and Noradrenaline by studying blood pressure, systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), PVR/SVR ratio during OPCABG, to compare postoperative renal functions by studying serum creatinine, blood urea level, urine output. Chi-square test and Student's *t*-test was used for analysing categorical and continuous data respectively. $P < 0.05$ was considered as statistically significant.

Results- We found that both the drugs were potent vasopressors. But, noradrenaline failed to decrease PVR/SVR ratio and the drug deranged postoperative renal functions.

Conclusion- From present study it was concluded that low dose vasopressin had a better and more cardiovascular stability and more favourable renal functions when compared to noradrenaline during off-pump CABG surgeries.

Keywords: Vasopressin, Nor-adrenaline, Off-pump CABG, Systemic vascular resistance, pulmonary vascular resistance

INTRODUCTION

Coronary artery bypass graft surgery is a surgical procedure done in a patient suffering from coronary artery disease. Atherosclerotic segment was bypassed by grafting normal coronary arteries to the arteries and vein elsewhere in the body and thus coronary circulation was improved. This surgery is usually performed either stopping the heart or on beating heart which is also known as "off pump" coronary artery bypass graft (OPCABG) surgery.

On May 2, 1960 the first coronary artery bypass surgery was performed. It was conducted by a team led by Dr. Robert Goetz and Dr. Michael Rohman at the Albert Einstine College of medicine.[1,2] In this technique the vessels were held together with circumferential ligatures over an inserted metal ring. The internal mammary artery was used as the donor vessel and was anastomised to the right coronary artery. The actual anastomosis with the Rosenbach ring took fifteen seconds and did not require cardiopulmonary bypass. The disadvantage of using the internal mammary artery was that, occlusion of internal mammary artery itself by an atheromatous plaque which was seen at autopsy nine months later

In 1964 Dr. Vasilli Kolesov, performed the first successful coronary artery bypass graft.[3] This technique was quickly superseded by Dr. Rene Favaloro who pioneered the bypass grafting procedure in 1967.[3] In his technique saphenous vein auto graft was used as a donor vessel to replace a stenotic segment of the right coronary artery. This is the typical bypass technique we know today. Later left coronary arteries were bypassed by Dr. Dudley Johnson.[3]

Anaesthesia for coronary bypass surgery is challenging as we have to maintain the hemodynamic stability at any cost to avoid cardiovascular accident during surgery. Many a times we come across severe hypotension during these surgeries which require pressor support. Recently vasopressin has gained increasing interest in the same and may provide better hemodynamic control than other vasopressors like noradrenaline.

Vasopressin is an exogenous parental form of ADH (Anti Diuretic Hormone) which favourably increases SVR (Systemic Vascular Resistance) without any side effects on pulmonary vasculature. Though known as an antidiuretic hormone, vasopressin has shown to actually increase urine output. [4] Failure of noradrenaline to decrease PVR (Pulmonary Vascular Resistance) / SVR (Systemic Vascular Resistance) ratio in bypass surgery patients and associated adverse effects on renal function is discouraging it's use.

MATERIALS AND METHODS

After obtaining approval from the Hospital Ethics Committee along with written and informed consent from patients, patients between 40 to 60 years of age and 130 to 180 cm of height of either sex belonging to American society of Anaesthesiology (ASA) physical status class II and III scheduled for elective beating heart bypass surgery under general anaesthesia, were enrolled in this prospective, randomized and double blind study. We excluded patients with LVEF (Left Ventricular Ejection Fraction) less than 45%, serum creatinine>1.2mg/dl, hepatic derangements, neurological diseases, endocrine disorders, pulmonary hypertension, COPD and asthma, allergy to any drug used. The drugs used for study were FDA approved.

Study period

The study was conducted between Oct. 2008 - April 2010.

Study sample

Out of 100 patients attending /reporting /referred to CVTS OPD for elective beating heart bypass surgery, 60 patients were chosen for study as remaining 40 patients having co-morbidities under exclusion criteria were excluded from study. Considering a limited period of time for study, the sample size might be inadequate.

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60 patients were randomly divided into two groups of 30 each by computer generated random table number. Group A received injection noradrenaline while Group B received injection vasopressin during the surgery as pressor support.. On preoperative day all the patients were investigated for haemoglobin, bleeding and clotting time, prothrombin time, platelet count, urine -routine and microscopy, blood urea level , serum creatinine, blood sugar level, liver function tests, ECG, serum proteins, left ventricular ejection fraction (2D ECHO).

All the patients were given tab.lorazepam 2 mg and tab.ranitidine 150 mg orally on preoperative night.On the day of surgery, after confirming patient's consent and nil by mouth status patients were premedicated in cardiac ICU under observation with glycopyrrolate 5 µg/kg intramuscular 30 min before, ondanesetron 0.08mg/kg, midazolam 0.04 mg/kg iv, fentanyl 0.5µg/kg iv just before taking to operation theatre. In operation theatre a pulmonary artery catheter was inserted through right internal jugular vein and radial arterial line was secured and connected to cardiac monitors. Other parameters monitored were ECG, oxygen saturation(spo2), endtidal co2(etco2), urine output. Baseline values of blood pressure, systemic vascular resistence(SVR), pulmonary vascular resistence(PVR) and urine output were noted. Also preoperative serum creatinine and blood urea levels were noted. Induction of anaesthesia was done with iv propofol 2mg/kg and under direct laryngoscopic vision, tracheal intubation was facilitated using inj. vecuronium 0.08 mg/kg as skeletal muscle relaxant. Maintenance of anaesthesia was done with 1% sevoflurane in O2 as inhalational agent with continuous infusion of inj.fentanyl 1mcg/kg/hr, inj.midazolam 0.02 mg/kg/hr, inj.vecuronium 0.0005-0.0012 mg/kg/min.

After internal mammary artery (IMA) dissection and after noting first SVR measurement infusion of vasopressin or noradrenaline was started. Drug preparations were made by anaesthesiologist who was not involved in study. 4mg of noradrenaline was diluted in 400ml of 5% dextrose, similarly 40U of vasopressin was diluted in 400ml of 5% dextrose which gave rise to 10µgm/ml and 0.1U/ml of concentration of noradrenaline and vasopressin respectively. The minimum starting infusion rate was 6ml/hr which correspond to 0.02 µgm/kg/min and 0.01U/min dose of noradrenaline and vasopressin respectively. During the infusion drugs were titrated every 15min by increasing rate by 6ml/hr with a goal of MAP above 60-65mmHg. Maximum dose allowed was 0.12 µgm/kg/min for noradrenaline and 0.06U/min for vasopressin that is 36ml/hr of infusion rate. Continuous cardiac output studies monitored during surgery for measuring SVR & PVR.

Aims and objectives of study were to Compare hemodynamic effects of both the drugs by studying blood pressure(systolic and diastolic), systemic vascular resistance(SVR), pulmonary vascular resistance(PVR), PVR/SVR ratio during beating heart bypass surgery, to compare postoperative renal functions by studying serum creatinine, blood urea level, urine output, to study any side effects of vasopressin.

SVR was calculated by formula

$$SVR = \frac{MAP - CVP}{CO}$$

SVR = Systemic vascular resistance (dyne.sec.cm^{-5})

MAP = Mean arterial pressure (mm Hg)

CVP = Central venous pressure (mm Hg)

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CO = Cardiac output (L/min)

PVR was calculated by formula,

$$PVR = \frac{MPAP - PAWP}{CO}$$

PVR = Pulmonary vascular resistance (dyne.sec.cm^{-5})

MPAP = Mean pulmonary artery pressure (mm Hg)

PAWP =Pulmonary artery wedge pressure (mm Hg)

CO = Cardiac output (L/min)

Observations were noted at following intervals

1) Before LAD Lift up
2) LAD Lift up
3) Post LAD grafting
4) Right ventricle lift up
5) Post Right Coronary grafting
6) Heart lift up for OM grafting
7) Post OM grafting

OM : Obtuse Marginal Artery

LAD : Left Anterior Descending Artery

Levels of serum creatinine, blood urea and urine output were noted on 1st, 2nd and 3rd postoperative day.

Statistical Analysis

The recorded data were tabulated and expressed in mean ± standard deviation (SD). Microsoft Excel for windows was used for statistical analysis. The demographic data for categorical variables were compared using Chi-square test. Student's *t*-test was used for analysing statistical significance in time related variables. $P < 0.05$ was considered as statistically significant.

RESULTS

The demographic data of the both groups were comparable statistically. Average age of the patients in group A was 55±4.08years while it was 56±3.8years in group B. Average weight of the patients in group A was 71.7±5.18kg while it was 70.96±6.2kg in group B. Other parameters like height, sex, ASA status were also comparable.

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Table no. 1: COMPARISON OF SYSTOLIC & DIASTOLIC BLOOD PRESSURE AT DIFFERENT STAGES

BP	STAGES	Nor adrenaline		Vasopressin		Unpaired t	P Value
		Mean	SD	Mean	SD		
SBP (mmHg)	Before LAD Lift Up	121.27	2.318	120.40	5.715	0.77	0.445 NS
	LAD Lift up	104.33	6.910	106.80	6.759	1.398	0.168 NS
	Post LAD grafting	114.13	8.565	110.13	6.663	2.019	0.048 Sig
	Rt.Ventricle Lift up	103.53	18.884	109.67	9.657	1.584	0.119 NS
	Post Rt. Caronary grafting	122.28	2.433	106.53	9.669	8.51	<0.001 HS
	Heart lift up for OM grafting	107.20	7.604	107.93	6.695	0.396	0.693 NS
	Post OM grafting	118.93	3.269	115.33	4.766	3.412	0.001 Sig
DBP (mmHg)	Before LAD Lift Up	79.93	2.947	80.00	2.573	0.093	0.926 NS
	LAD Lift up	75.0667	5.13899	70.1333	3.71143	4.263	<0.001 HS
	Post LAD grafting	71.8667	3.52071	68.1333	3.40115	4.177	<0.001 HS
	Rt.Ventricle Lift up	68.9333	3.13966	70.6667	4.34172	1.772	0.082 NS
	Post Rt. Caronary grafting	75.3333	3.07754	63.6667	5.40966	10.267	<0.001 HS
	Heart lift up for OM grafting	73.3333	3.45746	66.4000	4.53036	6.664	<0.001 HS
	Post OM grafting	71.8000	2.98733	67.0000	5.98273	3.932	<0.001 HS

NS- Not significant,

Sig- Significant,

HS- Highly Significant

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Table no.2: COMPARISON OF SVR AT DIFFERENT STAGES

SVR(dyne.sec.cm-5)	Nor adrenaline		Vasopressin		Unpaired t	P Value
	Mean	SD	Mean	SD		
Before LAD Lift Up	1394.63	63.877	1409.87	129.463	0.578	0.566 NS
LAD Lift up	1315.63	23.492	1109.80	91.061	11.988	<0.001 HS
Post LAD grafting	1244.37	24.051	1122.13	42.198	13.784	<0.001 HS
Rt.Ventricle Lift up	848.57	13.821	743.50	44.770	12.282	<0.001 HS
Post Rt. Caronary grafting	797.93	24.234	775.90	19.655	3.868	<0.001 HS
Heart lift up for OM grafting	732.20	21.188	687.13	47.315	4.761	<0.001 HS
Post OM grafting	869.23	13.853	830.43	58.033	3.562	0.001 Sig

NS- Not significant,

Sig- Significant,

HS- Highly Significant

Table no. 3: COMPARISON OF PVR AT DIFFERENT STAGES

PVR(dyne.sec.cm-5)	Nor adrenaline		Vasopressin		Unpaired t	P Value
	Mean	SD	Mean	SD		
Before LAD Lift Up	131.33	4.908	120.60	8.463	6.009	<0.001 HS
LAD Lift up	123.13	3.665	113.83	6.232	7.046	<0.001 HS
Post LAD grafting	110.43	4.216	105.03	5.543	4.247	<0.001 HS
Rt.Ventricle Lift up	93.87	2.886	81.47	2.030	19.252	<0.001 HS
Post Rt. Caronary grafting	86.73	4.042	71.10	2.820	17.372	<0.001 HS
Heart lift up for OM grafting	81.53	3.181	69.10	8.057	7.861	<0.001 HS
Post OM grafting	82.00	3.353	77.37	7.175	3.204	0.002 Sig

Sig-Significant,

HS-Highly Significant

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Table no.4: COMPARISON OF PVR/SVR RATIO AT DIFFERENT STAGES

PVR/SVR RATIO	Nor adrenaline		Vasopressin		Unpaired t	P Value
	Mean	SD	Mean	SD		
Before LAD Lift Up	.094313	.0055047	.087206	.0112561	3.107	0.003 Sig
LAD Lift up	.093573	.0032327	.105783	.0151430	4.319	<0.001 HS
Post LAD grafting	.088643	.0037990	.117833	.1426564	1.120	0.267 NS
Rt.Ventricle Lift up	.110700	.0040269	.109877	.0070787	0.554	0.582 NS
Post Rt. Caronary grafting	.108830	.0049766	.091843	.0051918	12.937	<0.001 HS
Heart lift up for OM grafting	.140457	.1562685	.101610	.0104642	1.359	0.180 NS
Post OM grafting	.088147	.0214094	.093350	.0086422	1.234	0.222 NS

NS-Not significant,

Sig-Significant,

HS-Highly Significant

Table no.5: COMPARISON OF RENAL FUNCTION TESTS (RFT) ON DIFFERENT DAYS

RFTs	Days	Nor adrenaline		Vasopressin		Unpaired t	P Value
		Mean	SD	Mean	SD		
BUL(mg/dl)	Pre_op	32.07	3.423	32.97	3.846	0.96	0.342 NS
	Post.op Day_1	44.97	4.958	31.37	3.378	12.41	<0.001 HS
	Post.op Day_2	47.53	3.170	31.97	2.906	19.82	<0.001 HS
	Post.op Day_3	51.13	3.288	30.67	2.106	28.71	<0.001 HS
Serum Creatinine (mg/dl)	Pre_op	0.91	0.150	0.91	0.189	0.0	1.0 NS
	Post.op Day_1	1.447	0.2529	1.007	0.2067	7.38	<0.001 HS
	Post.op Day_2	1.600	0.2421	0.977	0.1851	-11.20	<0.001 HS
	Post.op Day_3	2.33	0.631	0.95	0.176	11.52	<0.001 HS
URINE OUTPUT(ml)	Pre_op	951.50	96.196	965.67	71.036	0.65	0.52 NS
	Post.op Day_1	888.33	78.886	960.00	91.350	3.25	0.002 Sig
	Post.op Day_2	869.50	58.639	960.00	51.528	6.35	<0.001 HS
	Post.op Day_3	820.33	36.998	957.00	90.188	7.68	<0.001 HS

NS- Not significant,

Sig- Significant,

HS- Highly Significant

DISCUSSION

The essential goal of an anaesthetic management in cardiac surgery is hemodynamic stability. Anaesthetics and techniques for anaesthesia should be selected with consideration of patient's cardiac pathophysiology. In the present study, 60 patients were studied to look for the hemodynamic effects of noradrenaline and vasopressin in hypotension during OPCABG.

1. BLOOD PRESSURE

Table no.1 shows comparison of the systolic and the diastolic blood pressure.

In present study, group A showed that there was increase in both systolic and diastolic blood pressure when compared with group B. The difference was statistically significant.

2. SVR (SYSTEMIC VASCULAR RESISTANCE)

Present study showed that there was statistically significant increase in SVR in group A as compared to group B as shown in Table no.2. Coronary artery bypass grafting by using cardiopulmonary bypass (CPB) may be complicated by persistent hypotension due to low systemic vascular resistance.[5] Different causes have been associated with this situation, like hypothermia, total duration of cardiopulmonary bypass and total volume of cardioplegia solution infused, patients on angiotensin-converting enzyme inhibitors preoperatively, deranged left ventricular function, and systemic inflammatory response syndrome (SIRS), or inappropriate low arginine-vasopressin secretion. All these factors lead to reduced pressor effect of catecholamines due to cellular acidosis, opening of ATP sensitive channels, efflux of K+ and hyperpolarization of the myocytes, which prevents Ca++ channels from opening.[6,7] Independent of CPB, surgical trauma has a major role in activating inflammatory process in case of OPCABG[8]. Present study suggests that both noradrenaline and vasopressin are potent vasopressors.

3. PVR (PULMONARY VASCULAR RESISTANCE)

There was statistically significant increase in PVR in group A as compared to group B as shown in Table no.3. Our study also showed that pulmonary vascular resistance was not affected by the vasopressin infusion rather, there was decrease in PVR. It may attributed to vasodilation due to vasopressin in the pulmonary vasculature,[9,10] and is due to a release of NO by the endothelial pulmonary capillaries.[11] Because of the pulmonary vasodilatory action, vasopressin has been successfully used by Tayama E, et al,[12] in cardiac surgical patients with preoperative pulmonary hypertension.

In surgical correction of obstructed total anomalous pulmonary venous return(TAPVR) vasopressin had shown to inhibit pulmonary hypertension and improve systemic circulation as studied by Mark A. Scheurer, et al [13] (2005). In animal models of hypoxic pulmonary constriction, vasopressin has been shown to have properties of pulmonary vasodilation as well as systemic vasoconstriction. In no. of animal experiments it is observed that vasopressin mediated selective vasodilation of pulmonary vasculature under hypoxia is due to a V_1 receptor–mediated release of NO.[14,15] Additionally, a model of chronic hypoxia suggests that the selective pulmonary vasodilatory action of vasopressin is enhanced through altered receptor-mediated processes during prolonged hypoxia.

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4. PVR / SVR RATIO

In group B, there was increase in the ratio in initial stages; towards end of surgery, there was decrease in the ratio in group B which was statistically significant as shown in Table no.4. In comparative study studied by Yunseok Jeon , et al[16] both low dose vasopressin and norepinephrine increased SVR after milrinone induced hypotension in OPCABG patients. However, only low-dose vasopressin decreased the PVR/SVR ratio that was increased by milrinone. So they concluded milrinone–vasopressin combination provide better hemodynamic conditions by maintaining systemic perfusion pressure and reducing right heart afterload compared to milrinone–norephinephrine combination in right heart failure patients.

5. RENAL FUNCTION TESTS:

Postoperative renal dysfunction is relatively common and one of the serious complications of cardiac surgery. Renal dysfunction or failure occurs nearly in 8% of all patients undergoing CABG.[17] It is multifactorial in origin.[18] Though OPCABG technique avoids cardiopulmonary bypass (CPB) circuit induced adverse effects on renal function, multiple other factors cause postoperative renal dysfunction in these group of patients.[19,20] Each year, 600,000 patients worldwide undergo coronary artery bypass surgery,[17] which includes higher no. of elderly population increasing the perioperative challenges like renal failure. Intensive care unit and hospital ward stay is doubled in patients with postoperative renal dysfunction as compared to those who don't have and mortality is significantly increased from 1% to 19%. [20,21] Furthermore, approximately 1 out of 6 patients with renal dysfunction will need dialysis and two third of them will not survive their hospitalization.[22,23] Many more patients suffer from occult, subclinical, and transient renal injury without requiring hemodialysis. In spite of advancement in surgical techniques and better understanding of the pathophysiology of acute renal failure (ARF), mortality and morbidity associated with ARF have not decreased in the last decade.[24] These data highlight the necessity of identifying the risk factors associated with CABG and implementing specific therapies that are based on the knowledge of well designed clinical trials.

Mangano CM, et al[17] (1998) studied renal dysfunction after myocardial revascularization .Out of 2222 patients , 171 patients (7.7%) had postoperative renal dysfunction; 30 of these (1.4% overall) had oliguric renal failure that required dialysis.

1) SERUM CREATININE

There was statistically significant increase in postoperative serum creatinine in group A as compared to group B (Table no.5)

2) BLOOD UREA LEVEL

There was statistically significant increase in postoperative BUL in group A as compared to group B (Table no.5)

3) URINE OUTPUT

Group A showed statistically significant decrease in postoperative urine output as compared to group B (Table no.5) The increased urine output represents a remarkable result of infused vasopressin due -

according to several studies- to the increased mean arterial pressure of the patient and therefore to the improvement of glomerular filtration rate.[25,26] Many studies have proven that vasopressin receptors are located in the efferent arterioles of the renal vasculature, in contrast to the catecholamine receptors, which are located in the afferent arterioles.[27] Therefore, the vasoconstrictive action of catecholamines leads to a decrease in the filtration fraction, the action of vasopressin leads to an increase in the filtration fraction and hence, to an increase of urine output. [25,26,27]

Comparing effects of noradrenaline and vasopressin, from present study, it is suggested that use of vasopressin gives better hemodynamic control and favourable renal functions.

CONCLUSION

In the present study when we compared the hemodynamic effects of low dose Vasopressin and Noradrenaline in patients undergoing elective beating heart bypass surgery there was increase in systolic blood pressure and SVR in both the groups but there was, increase in the diastolic blood pressure, increase in PVR, increase in PVR/SVR ratio in later stages of the surgery, increase in postoperative serum creatinine and blood urea levels, and decrease in urine output in noradrenaline group as against the vasopressin group. So we can conclude that low dose vasopressin had a better and more cardiovascular stability and more favourable renal functions when compared to noradrenaline.

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