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COMPARISON OF PHENOXYBENZAMINE AND SODIUM NITROPRUSSIDE FOR AFTERLOAD REDUCTION IN PEDIATRIC CARDIAC SURGERY

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ABSTRACT

Objectives*:* To compare the intraoperative hemodynamic and afterload reduction effects of the α-adrenergic receptor blocker, phenoxybenzamine with a direct acting arterial dilator sodium nitroprusside in paediatric cardiac surgical patients. Design: A prospective, observational study. Setting: Tertiary care teaching hospital. Participants: 60 infants scheduled for elective congenital cardiac surgery repair requiring cardiopulmonary bypass (CPB) divided into two equal groups, receiving nitroprusside group (SNP) or phenoxybenzamine group (POB). Interventions: The infants received either sodium nitroprusside 1µg/kg/min infusion intraoperatively (30 infants) or received phenoxybenzamine 1 mg/kg slowly intravenously before the aortic cannulation (30 infants) prior to initiation of CPB. A non-invasive cardiac output monitor was used to derive hemodynamic value at baseline and at selected time point's upto ICU admission. Measurement and Main Results: Both groups had comparable hemodynamics at baseline. Hemodynamic responses seen included the following: group POB had greater reduction in SBP, DBP, MAP, SVR, SVRI and more tachycardia. Group SNP had controlled decrease of SBP, DBP, MAP, SVR, SVRI and less tachycardia. Cardiac index and SI increased in both the groups but it was always maintained higher in SNP group. Requirement of volume and vasopressor bolus to maintain hemodynamics was higher in POB group compared to SNP group. Conclusion: SNP is safer vasodilator for afterload reduction in cardiac surgery. We found that SNP infusion fulfilled the requirement of decrease in SVR and SVRI while maintaining hemodynamics compared to POB. SNP infusion caused less tachycardia, controlled hypotension; controlled reduction in afterload while maintaining the cardiac index.

Key Words: Intraoperative hemodynamic, After load reduction effects, α-Adrenergic receptor blocker.

INTRODUCTION

Vasodilators are commonly used in paediatric cardiac surgery. The indications for use of vasodilators includes: (l) reduction of left ventricular afterload in low output states, (2) control of intraoperative and postoperative hypertension (which may result in increased postoperative bleeding), (3) pulmonary vasodilation and (4) uniform cooling and rewarming, avoiding temperature gradient in various organs.

A transient and reversible reduction in cardiac output – low cardiac output state (LCOS) often occurs Following surgery for congenital heart diseases [1]. This reduction in cardiac output is due to a transient "myocardial dysfunction" following cardiopulmonary bypass (CPB). Factors implicated in the development of myocardial dysfunction include: (1) intense inflammatory response associated with CPB, (2) myocardial ischemia from prolonged aortic cross clamping, (3) inadequate

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myocardial protection, (4) reperfusion injury, (5) hypothermia and (6) large ventriculotomy. Further reduction in cardiac output may occur due to a residual or undiagnosed structural lesion or in instances of late presentation for surgery with pre-existing right ventricular, left ventricular or biventricular dysfunction [2]. Therapy for LCOS is well described, including, Preload optimization with fluid augmentation, inotropic support and afterload reduction to ensure better hemodynamics.

Afterload is the sum of forces that oppose systolic performance [3]. Afterload can be estimated by the resistance of the vascular bed (systemic or pulmonary) against which the ventricle is working. An increase in systemic vascular resistance or pulmonary vascular resistance can significantly reduce both stroke volume and the extent and velocity of wall shortening; the result is decreased cardiac output and ventricular function. Increased vascular resistance is common after CPB in neonates and adults. Aggressive afterload reduction is the mainstay of management in severe systolic ventricular dysfunction. Afterload reduction has been shown to be particularly useful to augment stroke volume and overall cardiac output in neonatal heart as well as in those with poor myocardial contractility.

Historically afterload reduction in the intraoperative and postoperative period in pediatric cardiac surgery was achieved with the alpha receptor blocker phenoxybenzamine but intraoperative phenoxybenzamine had fallen into dispute over the last many years due to the prolonged vasodilation, difficult to titrate acutely, associated tachycardia, associated hypotension and absence of an effective antidote. Although phenoxybenzamine is a historical drug but it is still use in large number of cardiac centers in South East Asia region because of its low cost.

The present study was designed to test the hypothesis that the administration of Sodium nitroprusside (SNP) may better improve the hemodynamic profile because SNP is titrable_vasodilator due to its shorter half life. SNP causes only modest increase in the heart rate and rapidity of onset and offset of action. These favorable qualities and low cost make it a preferred afterload reduction agent in cardiac surgery but till now there is no study comparing these two commonly used vasodilator drugs for afterload reduction using noninvasively measured parameters of SVR, SVRI, HR, SBP, DBP, MAP, SI,and CI. The purpose of this observational study was to compare the intraoperative hemodynamic and afterload reduction effects of phenoxybenzamine with sodium nitroprusside in pediatric cardiac surgical patients.

MATERIALS AND METHODS

After approval by the institutional human research ethics board, written consent was obtained from the guardians of each participating pediatric patient. 60 pediatric patients (up to 12 months) scheduled for elective cardiac surgery on CPB were studied .The children were divided into 2 groups according to the vasodilator they received. Due to a prospective observational study, choice of vasodilator for each case was known to care givers. Initially 30 consecutively patients were treated with SNP and thereafter 30 consecutive cases were treated with POB. In Group SNP (30), SNP 1µ/kg/min infusion was initiated just after sternotomy and it was continued in pediatric intensive care unit (PICU). In the PICU, SNP was slowly tapered and discontinued over 24 hour after surgery. Group POB (30) received phenoxybenzamine 1 mg/kg intravenously in 2ml/kg normal saline over a period of 10 minutes just after sternotomy. All patients enrolled in the study received a standardized anesthetic regimen. Anaesthesia was induced with ketamine and fentanyl, rocuronium bromide was given to facilitate tracheal intubation. Maintenance of anesthesia was achieved with oxygen/air/isoflurane mixture, high-dose narcotics (fentanyl up to 20µg/kg), benzodiazepines (midazolam (0.1-0.3mg/kg), and vecuronium (0.1 mg/kg). After intubation anesthesiologist placed a femoral artery catheter for continuous systemic arterial pressure monitoring. A triple lumen central venous catheter was placed in femoral vein. The ICON monitor (OSPYKA, Berlin, Germany) was attached with 4 electrodes to each patient and manual demographic and hemodynamic parameters were entered in it and continuous measurement of hemodynamic variables were taken. The bladder was drained with a Foley catheter. Following a stabilization period of 5 minutes, ICON hemodynamic data were recorded. Sternotomy response was blunted with 2µ/kg of fentanyl bolus doses. The vasodilator selected according to study group was started. Although the ICON provides continuous hemodynamic data, Hemodynamic variables were recorded at 2, 5 and 10 minutes. If hypotension (fall in blood pressure more than 20% baseline) occured, it was managed with 2ml/kg saline bolus and if persistent then 2µg titrated multiple bolus of vasopressor noradrenaline was used to restore SVR. SNP infusion was not interrupted and continued as a steady dose. No reading was taken just after the bolus of vasopressor. The authors compared the SVR, SVRI, HR, SBP, DBP, MAP, SI, CI, after drug administration and afterwards till ICU admission.

Infants who underwent surgical repair of a left-sided obstructive lesion, and/ or single ventricle physiology or those who received no or smaller doses of POB or SNP were excluded from the study.

Primary outcome measures of the study were comparison of baseline parameter (SVR, SVRI, HR, SBP, DBP, MAP, SI and CI) with the parameter obtained after drug administration. Secondary outcomes measured were the requirement of volume bolus or vasopressor to maintain adequate hemodynamics.

The iCON monitor (OSPYKA, Berlin, Germany) was used continuously to measure hemodynamic variables

like cardiac index (CI), stroke index (SI), systemic vascular resistance (SVR) and systemic vascular resistance index (SVRI). Electrical Cardiometry (EC) [4] is the name of the method used by the ICON monitor. Electrical Cardiometry is a non-invasive method of measuring continuous beat-to beat left sided cardiac output based on measurement of thoracic electrical bioimpedance. Bioimpedance CO is based on the principle that cyclical increases in blood volume in the great vessels, as well as alignment of red blood cells in the thoracic aorta resulting from increased velocity, cause concomitant decreases in the electrical impedance in the chest. An alternating current of low amplitude is introduced and simultaneously sensed by electrodes placed around the neck, and laterally on the thorax to measure thoracic electrical bioimpedance. Changes in thoracic bioimpedance are induced by ventilation and pulsatile blood flow, and processing of the signal results in a characteristic impedence (Z) waveform. For measurement of SV, only the cardiac-induced pulsatile component of the total change in electrical impedance is analyzed (dZ/dt), as the respiratory component is filtered out. EC interprets the maximum change in thoracic electrical bioimpedance as the ohmic equivalent of the mean aortic blood flow acceleration and further transforms it into an equivalent of mean aortic blood flow velocity. Stroke volume and cardiac output are then calculated.

Electrical Cardiometery (EC) is often confused with the traditional bioimpedance technology most commonly known as Impedance Cardiography (ICG). Though both methods use sensors placed on the thorax, traditional bioimpedance or ICG methods rely on the assumption of periodical volumetric changes in the aorta to determine stroke volume (SV) and cardiac output (CO). In short, ICG attributes the steep increase in the conductivity waveform (dZ) to a volumetric expansion of the aorta during systole, while EC contributes the increase in conductivity to the orientation change of the RBCs to determine the velocity of the blood flow. Thus, the algorithm and evident accuracy of EC compared to ICG is what separates the two methods. EC has proven as an accurate method for measuring cardiac output in a wide spectrum of patient conditions and patient populations including neonates [5] and children [6], while ICG is limited to relatively healthy adults.

The advantages of Electric cardiometry based ICON monitor are: it is Easy to use, Non invasive, Continous measurement of parameters, can be used in neonates, children and adults, no preparation of patient, no side effect or complication, works in patient with atrial fibrillation, arrhythmia, pacing.

Stastical analysis

Continuous hemodynamic variables were compared using repeated measures analysis of variance to determine whether significant changes occurred or not. For those variables with significant changes, paired t-tests with the Bonferroni correction were used to isolate pairwise differences. Fisher's exact test was used for categorical data. Tests were performed using Statistical Analysis System software. Power of the study was 100% so, this sample size found to be adequate in each group. Significance was set at a P value < 0.05.

RESULTS

Sixty infants were enrolled consecutively and divided into 2 groups according to the vasodilator they received. The demographic data of the infants shows that the 2 groups were comparable for age, height, weight, sex, and type of surgery (Table 1). HR, SBP, DBP, MAP, SVR, SVRI, CI and SI were measured before drug administration as baseline for defining further changes. (The hemodynamic data over the different time intervals is given in Table 3 & 4). The baseline hemodynamic values of studied variables did not show significant differences between two groups using t –test ($P > 0.05$) except in mean SBP values (Table 2).

As both the drugs are vasodilators so, the hemodynamic changes that occurred in the groups were in the same direction but the greatest differences between the groups were changes in SVR, SVRI, HR and systemic arterial pressures. After drug administration the SVR was decreased in both groups but decrease in SVR was more pronounced in the POB group compared to SNP group, and this difference was found to be statistically significant ($p<0.0001$) at 2 minutes, 5 minutes and 10 minutes after drug administration. The decrease in SVR was maintained even after completion of POB infusion (Fig 1 & Table 4).

The SVRI was also significantly ($p \leq 0.0001$) reduced in the POB group compared with the SNP group at all points studied (Fig 2 & Table 4).

The SBP, DBP and MAP reduced significantly ($p<0.001$) compared to baseline values in both the groups but between the two groups these values declined more significantly in the POB group. Reduction of these pressures in POB group compared to SNP group was accounted by a significantly greater decrease in SVR and SVRI in the POB group (Figure 3, 4, 5 & Table 3).

In the POB group, immediate and significant increase ($p<0.001$) in heart rate was observed and it was not normalized afterwards at all points of time however in the SNP group, there was comparatively lesser increase in heart rate. (Figure 6 & Table 3)

The CI and SI both are increased at 2 minutes, 5 minutes and 10 minutes time point, after drug administration in both SNP and POB group but these values remained comparatively higher in SNP group (Figure 7,8 & Table 3) .

In the POB group, all the 30 children needed extra volume infusion of ringer lactate (RL) (2ml/kg) and noradrenaline boluses to treat hypotension occurring after POB administration. out of which 13 children needed single nor adrenaline bolus and 17 children needed two

noradrenaline bolus whereas in the SNP group 16 children needed extra volume infusion of RL (2ml/kg) and only 4 children needed noradrenaline boluses at one time as shown in Table no 5 . This Difference in the requirement of extra RL fluid infusion and vasopressor boluses in both observed groups were statistically significant. (P=0.001).

Table 1. Demographic Data

	POB	SNP	P value
No. patients	30	30	1.00
Age (months)	2.53 (2.34)	2.58 (2.08)	0.43
Weight (kg)	5.3 (2.64)	5.07 (2.43)	0.46
Height (cm)	64.6 (8.10)	65.1 (8.56)	0.82
Gender (M/F)	16/14	13/17	0.43
ASO & VSD closure	25	24	0.73
Rastelli procedure	1	1	1.00
TAPVC repair	3	4	1.00
AP Window repair	1	1	1.00

Data are mean (±SD).

Abbreviations: ASO & VSD closure, Arterial Switch operation & ventricular septal defect closure; TAPVC repair, total anomalous pulmonary venous connection (TAPVC) repair; AP window repair, aortopulmonary window repair.

Table 2. Summary of Baseline Hemodynamic Parameters

	POB	SNP	*P* Value
HR	142.00 ±3.80	140.33 ±3.30	0.07
SBP	96.93±14.18	90.93±6.09	0.03*
DBP	55.17±11.02	55.53±5.27	0.46
MAP	70.60±13.96	66.13±3.14	0.09
SVR	6836.43 ±497.10	7050.40 ±799.40	0.21
SVRI	1421.47±160.70	1420.83±156.26	0.98
CI	3.55±0.37	3.58±0.68	0.83
SI	27.93±3.91	29.03±6.69	0.31

Data are mean± SD.

Abbreviations: HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; SVR, systemic vascular resistance; SVRI, systemic vascular resistance index; CI, cardiac index; SI, stroke index; NS, not significant, *, $p \leq 0.05$.

Table 3. HR, SBP, DBP and MAP at various time intervals

Time	Group	HR	SBP	DBP	MAP
Baseline	POB	142.00 ±3.80	96.93±14.18	55.17±11.02	70.60±13.96
	SNP	140.33 ±3.30	90.93±6.09	55.53±5.27	66.13±3.14
2 minutes after drug	POB	150.00 ±4.65	77.10±7.21	43.80±5.45	55.67±6.49
	SNP	140.70 ±3.43	77.07±12.47	50.63±10.86	59.63±10.50
5 minutes after drug	POB	159.97 ±2.89	62.40±11.05	35.93±7.11	45.90±10.31
	SNP	142.60 ±3.12	71.80±12.46	49.00±8.07	56.80±9.12
10 minutes after drug	POB	161.27 ±6.97	59.20±13.12	34.20±8.22	43.47±11.91
	SNP	143.87 ±3.69	70.87±11.27	45.20±7.88	53.90±8.59
CPB off	POB	152.73 ±5.03	64.47±12.59	39.77±7.59	50.13±8.89
	SNP	135.33 ±5.63	70.83±21.31	40.33±6.45	50.73±10.87
ICU admission	POB	156.37 ±5.07	71.10±8.65	40.87±6.56	51.90±7.58
	SNP	143.03±10.53	77.37±10.80	42.20±9.11	53.77±9.90

Data are mean± SD.

Abbreviations: HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; CPB off, cardiopulmonary bypass off; ICU admission, just after shifting the patient in intensive care unit.

Table 4. SVR, SVRI, CI and SI at various time intervals

Time	Group	SVR	SVRI	CI	SI
Baseline	POB	6836.43 ±497.10	1421.47±160.70	3.55±0.37	27.93±3.91
	SNP	7050.40 ±799.40	1420.83±156.26	3.58±0.68	29.03±6.69
2 minutes after drug	POB	4894.03 ±604.24	1109.90±134.12	3.6±0.42	27.54±4.95
	SNP	6791.17 ±835.80	1285.23±166.19	3.65±0.82	30.07±5.95
5 minutes after drug	POB	3840.90 ±1050.96	1041.93±91.49	3.55±0.55	28.79±3.79
	SNP	6460.97 ±804.68	1102.30±43.68	4.07±0.86	29.63±8.10
10 minutes after drug	POB	3322.87 ±716.32	933.87±126.95	3.64±0.72	28.39±3.90
	SNP	6440.70 ±888.36	1089.33±67.80	3.88±0.58	29.3±8.01
CPB off	POB	3919.23 ±838.33	1074.97±615.80	3.18±0.40	24.39±3.86
	SNP	6524.93 ±945.25	1171.70±97.68	4.09±1.49	28.43±0.89
ICU admission	POB	3888.73 ±856.545	925.00±251.08	3.20±0.43	28.03±9.05
	SNP	6496.10±845.14	1184.77±108.65	3.93±1.20	28.17±1.34

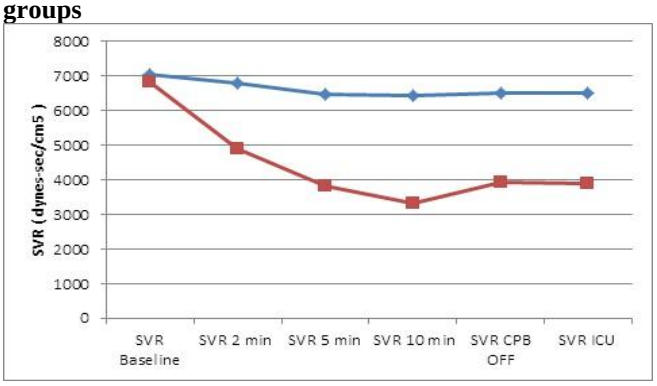
Data are mean± SD.

Abbreviations: SVR, systemic vascular resistance; SVRI, systemic vascular resistance index; CI, cardiac index; SI, stroke index; CPB off, cardiopulmonary bypass off; ICU admission, just after shifting the patient in intensive care unit.

Table 5. Number of patients in whom extra volume or Nor adrenaline was required

Requirement	SNP	POB
Extra volume (ringer lactate) 2ml/kg	16	30
Noradrenaline only single bolus	4	13
Noradrenaline with repeat bolus	0	17

Figure 1. comparison of mean SVR between two study groups



Blue color line – shows SNP (sodium nitroprusside) trends, Brown color line- shows POB (phenoxybenzamine) trends.

Figure 2. comparison of mean SVRI between two study groups

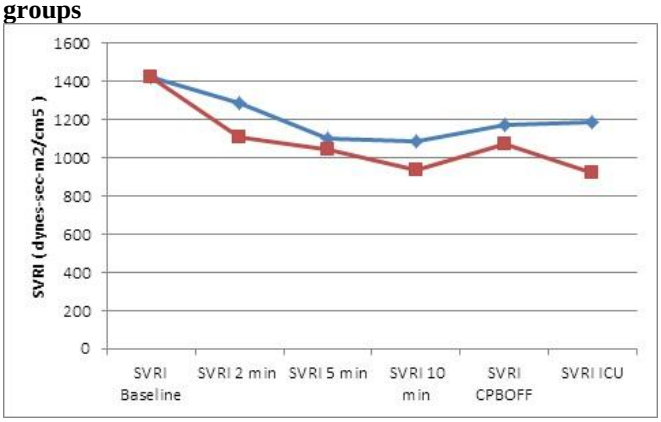


Figure 3. comparison of mean SBP between two study groups

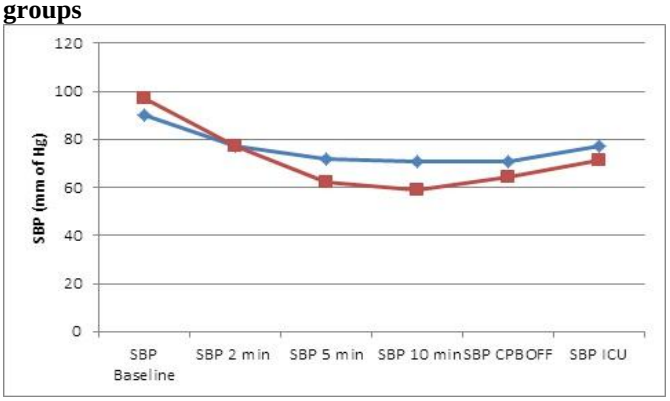


Figure 4. comparison of mean DBP between two study groups

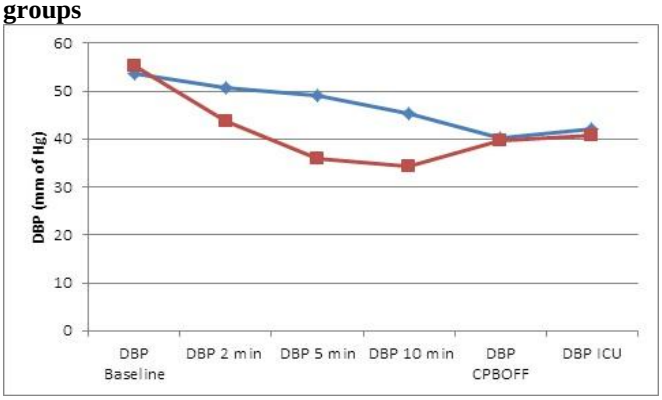


Figure 5. comparison of mean MAP between two study groups

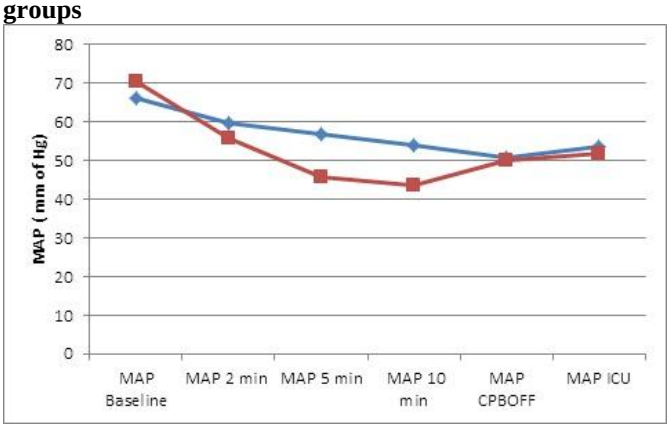


Figure 6. comparison of mean HR between the two study groups

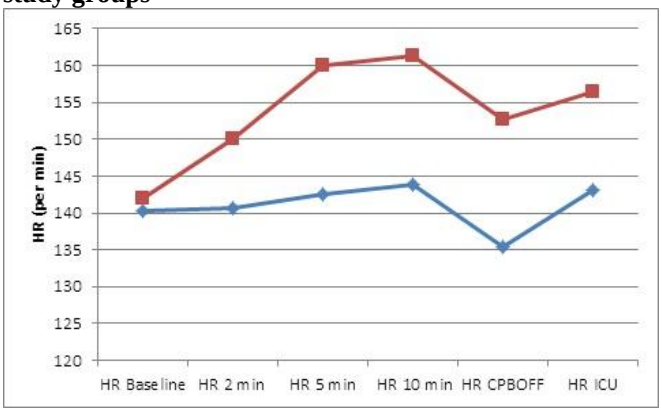


Figure 7. comparison of mean CI between the two study groups

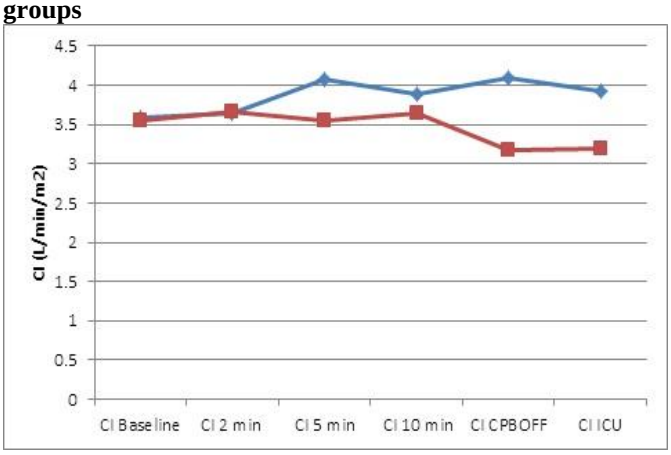
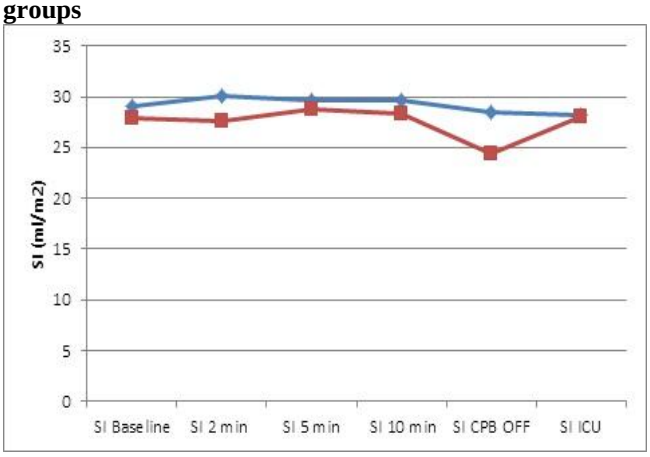


Figure 8. comparison of mean SI between the two study groups



DISCUSSION

Vasodilator therapy is a valuable component of afterload reduction, in the pediatric cardiac surgical patient. Benefits of vasodilator therapy include increased organ perfusion on CPB, improved cardiac output post-CPB by decreasing the afterload without affecting the contractility, and pulmonary bed vasodilatation [7], avoidance of temperature gradients while cooling and rewarming.

In our study we compared the hemodynamic effects of clinically used doses of SNP and POB. Using the ICON monitor, the afterload parameter SVR and SVRI were directly measured. There is no study in literature till date evaluating the hemodynamic and afterload assessment parameters between SNP and POB. A comparable baseline data was obtained for meaningful comparison of the hemodynamic effects of POB and SNP. The mean SVR and SVRI before study drug administration, between the 2 groups were comparable. Although there was baseline differences in the associated parameters of systolic blood pressure between the 2 groups. Differences in baseline measurements can occur by chance and are more likely when multiple hemodynamic parameters are being compared rather than simply the hemodynamic entry criteria. Our result showed that both drugs decreased the afterload as was indicated by decreased SVR and SVRI. In our study, POB caused greater decrease in SVR and SVRI as compared to SNP and greater increases in HR. POB was associated with a significantly greater degree of hypotension.

Although both drugs produced an increase in cardiac index with the doses employed, POB accomplished this at the expense of a significantly greater increase in heart rate.

One other difference between POB and SNP was in the requirement of volume and vasopresser. All the 30 children in the POB group needed extra RL volume (2ml/kg) and nor‑adrenaline bolus to increase the SVRI for maintaining adequate MAP and CI, indicating that POB infusion given over 10 minutes without a loading bolus dose produces significant vasodilation. Conversely, only 4 children needed anor adrenaline bolus and 16 children needed extra volume infusion (2ml/kg) of RL in the SNP group indicating relatively less vasodilation with SNP. The requirement of volume and vasopressors was proportionally less in the SNP group to maintain hemodynamics. SNP produced controlled vasodilation because noradrenaline bolus was not repeated to

maintained hemodynamics, on the contrary in 17 children of POB group noradrenaline bolus was repeated to treat the hypotension occurring after POB administration.

These observations are in accord with the known effects of both drugs on the vasculature. Nitroprusside [8] is a nitrovasodilator that acts by releasing nitric oxide (NO). NO activates the guanylyl cyclase-cyclic GMP-PKG pathway, leading to vasodilation, mimicking the production of NO by vascular endothelial cells, which is impaired in many hypertensive patients. The mechanism of release of NO is not clear and likely involves both enzymatic and nonenzymatic pathways. Nitroprusside dilates both arterioles and venules, and the hemodynamic response to its administration results from a combination of venous pooling and reduced arterial impedance. In subjects with normal left ventricular function, venous pooling affects cardiac output more than does the reduction of afterload; cardiac output tends to fall. In contrast, in patients with severely impaired left ventricular function and diastolic ventricular distention, the reduction of arterial impedance is the predominant effect, leading to a rise in cardiac output. Sodium nitroprusside is a nonselective vasodilator, and regional distribution of blood flow is little affected by the drug. In general, renal blood flow and glomerular filtration are maintained, and plasma renin activity increases. Sodium nitroprusside usually causes only a modest increase in heart rate and an overall reduction in myocardial demand for oxygen. Sodium nitroprusside is an unstable molecule that decomposes under strongly alkaline conditions or when exposed to light. The drug must be given by continuous intravenous infusion to be effective. Its onset of action is within 30 seconds; the peak hypotensive effect occurs within 2 minutes, and when the infusion of the drug is stopped, the effect disappears within 3 minutes.

The short-term adverse effects of nitroprusside are due to excessive vasodilation, with hypotension and the consequences thereof. Close monitoring of blood pressure and the use of a continuous variable-rate infusion pump will prevent an excessive hemodynamic response to the drug in the majority of cases. Less commonly, toxicity may result from conversion of nitroprusside to cyanide and thiocyanate. Toxic accumulation of cyanide leading to severe lactic acidosis usually occurs when sodium nitroprusside is infused at a rate greater than 5 μg/kg per minute, but also can occur in some patients receiving doses about 2 μg/kg per minute for a prolonged period. In our study dose of sodium nitroprusside was limited to 1 μg/kg per minute that was far less than toxic doses. The limiting factor in the metabolism of cyanide appears to be the availability of sulfur-containing substrates in the body (mainly thiosulfate). The concomitant administration of sodium thiosulfate can prevent accumulation of cyanide in patients who are receiving higher-than-usual doses of sodium nitroprusside; the efficacy of the drug is unchanged. The risk of thiocyanate toxicity increases when sodium nitroprusside is infused for more than 24 to 48 hours, especially if renal function is impaired. The plasma concentration of thiocyanate should be monitored during prolonged infusions of nitroprusside and should not be allowed to exceed 0.1 mg/ml. In patients with renal failure, thiocyanate can be removed readily by hemodialysis.

Thomas J. Bixler [9] et al in their study found that that in patients with postoperative left ventricular failure, nitroprusside alone can improve cardiac output by reducing systemic vascular resistance without significantly lowering arterial blood pressure. These findings are comparable to our study.

Maseda J [10] et al, showed that in postoperative cardiac surgical patients, SNP administration can be expected to improve renal blood flow and the decline in systemic arterial pressure is not excessive. In our study we also found that there is also less hypotension.

At the other end of the Spectrum, Phenoxybenzamine is a haloalkylamine that blocks α1 and α2 receptors irreversibly [11]. Although phenoxybenzamine may have slight selectivity for α1 receptors, it is not clear whether this has any significance in humans.

The haloalkylamine adrenergic blocking drugs are closely related chemically to the nitrogen mustards. The molecular configuration directly responsible for blockade probably is a highly reactive carbonium ion formed upon cleavage of the three-membered ring. It is presumed that the arylalkyl amine moiety of the molecule is responsible for the relative specificity of action of these agents, since the reactive intermediate probably reacts with sulfhydryl, amino, and carboxyl groups in many proteins. Because of these chemical reactions, phenoxybenzamine is covalently conjugated with α receptors. Consequently, receptor blockade is irreversible, and restoration of cellular responsiveness to α receptor agonists probably requires the synthesis of new receptors [12]. Pressor responses to exogenously administered catecholamines are impaired. Indeed, hypotensive responses to epinephrine occur because of unopposed β receptor-mediated vasodilation. Although phenoxybenzamine has relatively little effect on supine blood pressure in normotensive subjects, there is a marked fall in blood pressure on standing because of antagonism of compensatory vasoconstriction. In addition, the ability to respond to hypovolemia and anesthetic-induced vasodilation is impaired. Phenoxybenzamine inhibits the uptake of catecholamines into both sympathetic nerve terminals and extraneuronal tissues. In addition to blockade of α receptors, substituted β haloalkylamines irreversibly inhibit responses to 5-HT, histamine, and ACh. However, somewhat higher doses of phenoxybenzamine are required to produce these effects than to produce blockade of α receptors. The half-life of phenoxybenzamine probably is less than 24 hours. However, since the drug irreversibly inactivates α receptors, the duration of its effect is dependent not only

on the presence of the drug, but also on the rate of synthesis of α receptors [13]. Many days may be required before the number of functional α receptors on the surface of target cells returns to normal. Blunted maximal responses to catecholamines may not be as persistent, since there are "spare" α1 receptors in vascular smooth muscle.

The major adverse effect of phenoxybenzamine is postural hypotension. This often is accompanied byreflex tachycardia and other arrhythmias. Hypotension can be particularly severe in hypovolemic patients or under conditions that promote vasodilation. The major effects of POB result from blockade of α1- and α2-receptors in smooth muscle. Prolonged vasodilation with POB can be explained because of the noncompetitive α-blockage refractory to catecholamines such as norepinephrine. All of these factors support our findings that phenoxybenzamine appears to have a more profound effect on vasculature due to increased α-blockade and reflex increase in heart rate due to uninhibited beta receptor activity. Infusion of POB in normal volunteers induced a marked hemodynamic response characterized by a fall in systemic vascular resistance, central venous pressure, and a secondary increase in heart rate and cardiac index. The dose of POB used was 1 mg/kg intravenously because of previous experience with the drug in the our center and in other institutions.

Phenoxybenzamine has become part of a strategy for early recognition and treatment of decreased systemic output after stage I palliation of HLHS. Phenoxybenzamine is used for afterload reduction, to control SVRI, and pulmonary-tosystemic flow ratio [14]. In humans, after the early neonatal period (_7 days of age), there is a progressive increase in the afterload with reduction in the contractility, reaching a plateau at age 4 years [15]. It also has a limited preload reserve related to decrease passive left ventricular compliance [16]. Significant increase in α-adrenergic receptor density also seen over time in children with congenital heart disease [17]. Because of this less efficient contractile mechanism, vasodilatory therapy can play a key role in pediatric cardiac surgery, improving cardiac output by decreasing the afterload without affecting the contractility.

Studies comparing the effects of SNP and POB in surgical patients for afterload reduction assessment have not been reported yet now, and only Motta [18] et al compare the 2 drugs on cardiopulmonary bypass for CPB flow and perfusion assessment. Motta [18] et al illustrated that POB was more effective than SNP in improving peripheral circulation as shown by reduced temperature gradients and less base deficits after CPB and in the PICU. POB increases flow during CPB and can improve perfusion and ventricular function postoperatively but they did not study the associated hemodynamic compromise and afterload reduction with either of the drugs. Motta18 et al studied the parameter on CPB where perfusion pressure and hemodynamics are mechanically assisted by CPB machine but in our study we compared these parameters in the actual patient condition before the onset of CPB. Our findings suggest that SNP may be preferable to decrease afterload and increase ventricular performance. In equivalent doses it induces far less tachycardia than POB and is not associated with uncontrolled hypotension.

Limitations.

There are some limitations of this study, Although ICON is a newer non invasive monitoring tool but if any error in measurement of parameters occurs, it will be reflected in both the groups for that parameter.

CONCLUSION

Comparison of vasodilators after CPB may be affected by inotropic agents such as dopamine and dobutamine, which are started at that time and their effect on vasculature may serve as confounding factor in assessment of SVR and SVRI.

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