ORIGINAL ARTICLE

THE EFFECT OF INHALED MILRINONE ON PULMONARY ARTERIAL PRESSURE IN PATIENTS UNDERGOING CARDIAC SURGERY

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ABSTRACT

Objective: To find out the effect of inhaled Milrinone on pulmonary arterial pressure in patients undergoing cardiac surgery.

Methods: A randomized controlled trial was done at Peshawar Institute of Cardiology in 78 patients who had preoperative pulmonary hypertension and had undergone cardiac surgery between the ages of 3 months and 60 years. Divided into 2, group 1 received Intravenous (IV) Milrinone and group 2 received Inhalational (IN) Milrinone. MANOVA was used to compare the difference between two groups across six dependent variables i.e., Heart rate (HR), systolic arterial pressure (SAP), Central venous pressure (CVP), Systolic pulmonary arterial pressure (SPAP), Diastolic pulmonary arterial pressure (DPAP) and mean pulmonary arterial pressure (MPAP) at three stages; baseline, end of nebulization, and after cardiopulmonary bypass (labeled as stages 1,2 and 3). Intraoperative complications like weaning from cardiaopulmonary bypass (CPB) machine, use of vasopressor, insertion of intra-aortic balloon pump (IABP), and cardiopulmonary re-initiation were also observed in both the groups. Analysis of the data was done through SPSS-23.

Results: In a total of 78 patients (39 in each group), an insignificant change was observed regarding the effects of IN Milrinone on HR, SAP, and CVP whereas significant effects of Inhaled Milrinone on SPAP, DPAP, and MPAP were observed (P-values <0.05).

Conclusion: The use of inhaled Milrinone was beneficial in patients with pulmonary hypertension in the prevention of Intraoperative complications like difficulty in weaning from CPB, insertion of IABP, and use of vasopressors, while CPB re-initiation was observed less in patients with inhalational milrinone as compared with intravenous administration while reducing their length of stay in ICU.

Key Words: inhaled Milrinone, pulmonary artery pressure, cardiac surgery.

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INTRODUCTION

Patients who have cardiac surgery are significantly more likely to experience preoperative morbidity and mortality if they have pulmonary hypertension (PHT).[1] It has been hypothesized that PHT may account for up to 58 percent of early postoperative mortality.[2] PHT, which is brought on by high left atrial pressure, is a common and serious consequence following cardiac operations, particularly in the context of congenital heart disorders.[3] It is typically observed in people who have mitral valve disease and may be made worse by endothelial dysfunction brought on by cardiopulmonary bypass-associated lung injury following mitral valve replacement and other cardiac procedures.[4]

Nitric oxide (INO) inhalation, injectable phosphodiesterase inhibitors, and inhaled epoprostenol are used to treat PHT in clinical settings (IPGI2).[5] A type III phosphodiesterase inhibitor called milrinone affects vascular smooth muscle cells by raising the level of cyclic adenosine inside the cells. [6] Intravenous Milrinone increases the risk of systemic hypotension, increases inotropy, and increases the need for adrenaline and non-adrenaline. [7] Additionally, in developing nations like Pakistan, the routine use of inhaled nitric oxide and epoprostenol is expensive and complicated. On the other hand, Milrinone for inhalation is less expensive and more widely accessible. [8] Milrinone is demonstrated to reduce pulmonary reperfusion syndrome more effectively when inhaled than when administered intravenously before and during CPB. [9] The use of inhaled

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Milrinone in heart transplant patients undergoing cardiac catheterization has not been shown to have any significant side effects in only two investigations. [10]

In the context of cardiothoracic anesthesia, medications that reduce pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR) while having no effect on systemic vascular resistance (SVR) are of particular therapeutic importance. [11] Inhalation as a route of PHT treatment as well as the introduction of innovative strategies to maximize drug administration has been the focus of recent studies. [12] By focusing primarily on pulmonary circulation, inhaled vasodilators may avoid potentially harmful systemic side effects.

The aim of this study was to show that inhaled Milrinone administered before CPB could be helpful in weaning patients of CPB in high-risk patients.

MATERIAL AND METHOD

After ethical approval from the hospital ethical committee, a randomized controlled trial of 78 patients undergoing cardiac surgery receiving both intravenous and inhaled Milrinone from September 2020 to November 2021 was conducted at Peshawar Institute of Cardiology (PIC). Patients were equally divided into 2 groups, where group-1 (n=39) received Intravenous (IV) Milrinone and group-2 (n=39) received Inhalational (IN) Milrinone. All patients had preoperative risk assessment by the ASA scoring system. In group 1, 46% were male, 35% were female and 17% were children, whereas group 2 had 56% male, 20% female, and 20% children under 6 years of age.

All patients were monitored by electrocardiogram, radial artery catheter, pulse oximetry, and capnography. Anesthesia was induced with fentanyl, midazolam, and rocuronium and maintained with isoflurane. Blood cardioplegia was used in all included patients. Temperature 32° C was controlled for coronary artery bypass procedures. Weaning from cardiopulmonary bypass was attempted after sustaining a temperature of >36° C.

All the cases were performed on a cardiopulmonary bypass machine (CPB). Pulmonary hypertension in the post-operative period was managed with intravenous Milrinone only in our study due to the non-availability of other products such as nitric oxide, prostaglandin, and inhaled clopidogrel used in developed countries. Intra-operative events such as hemodynamic stability, difficulty in weaning from CPB, Post-operative respiratory support, mortality, and length of ICU stay were analyzed. Intra-operative Hemodynamic instability was defined as systolic pressure < 90 mmHg, pulmonary artery diastolic pressure > 18mm Hg after weaning of CPB. High inotropic support along with the use of an intra-aortic balloon pump (IABP) was considered a difficulty in weaning from CPB.

Transthoracic echo was used to obtain PA pressures preoperatively and pressures >20mmHg were considered Pulmonary Hypertension. Left ventricular functions were noted as well. EF >50% were considered normal.

Inhaled Milrinone at a dose of 0.1mg/kg was used in group 2 patients. The drug was administered via endotracheal tube using a nebulization chamber just before the termination of CPB. Nebulization was performed with a jet nebulizer attached to the inspiratory limb of the ventilator using a flow of 10 liters of oxygen. Nebulization was initiated when the temperature reached 34° C. The minute ventilation was adjusted to achieve peak airway pressure of <30cm of water. The patients` characteristics were expressed in frequencies and percentages. Multivariate Analysis of Variance (MANOVA) was used to compare the difference between two groups (Intravenous milrinone vs. Inhalation milrinone) across six dependent variables i.e., HR, SAP, CVP, SPAP, DPAP and MPAP at three stages; baseline, end of nebulization, and after cardiopulmonary bypass (labelled as stages 1,2,3 for each variable). MANOVA analysis bring out the mean difference and statistical significance of differences among groups (Garcia, 2017). [13] It uses multivariate F-test (Pillai's trace, Wilk's Lambda, Hoteling's Trace, Roy's largest root) to check the differences in HR, SAP, CVP, SPAP, DPAP and MPAP among patients given Intravenous milrinone and Inhalation milrinone.

RESULTS

A total of 78 patients, both male and female were divided into two groups with 39 patients in each had similar preoperative characteristics as shown in table No.1. Types of cardiac surgeries in both groups are shown in Table No. 2.

Table No 3, shows that complications like difficulty in weaning from CPB, insertion of IABP, use of vasopressor, CPB re-initiation, and Intensive care in hospital were less in patients receiving inhalational milrinone as compared to patients receiving intravenous milrinone.

Hemodynamic Variables between 2 groups with their level of significance are shown in table No.4. It shows the overall and group means and standard deviations for each dependent variable. The mean and standard deviation of HR-1 for Intravenous milrinone (IVM) is 74.79 ± 6.37 and 73.59 ± 4.71 for Inhalation Milrinone (INM).

Figure 1 and table 4 shows that there is no significant effect of Inhaled milrinone and Intravenous milrinone on HR-1, HR-2, HR-3, SAP-1, and CVP-1, while the p-values of SAP-2, SAP-3, CVP-2, CVP-3, SPAP-1, SPAP-2, SPAP-3, DPAP-1, DPAP-2, DPAP-3, MPAP-1, MPAP-2, and MPAP-3 are less than 0.05 that suggest a significant effect of Inhaled milrinone and Intravenous milrinone on these variables.

Table 1: Preoperative characteristics

Preoperative characteristics	Intravenous Milrinone group		Inhaled Milrinone group	
	n = 39	%	n = 39	%
Male	18	46%	22	56%
Female	14	35%	8	20%
children	7 (6 male, and 1 female)	17%	9 (6 male, and 3 females)	23
Hypertension	25	64.1%	21	53.8%
Left ventricular dilatation	17	43.5%	23	58.5%
Left ventricular hypertrophy	27	69.5%	20	51%
ASA score	3.4	8.7%	3.4	8.7%

Table 2: Operative procedures

Types of operation	Intravenous Milrinone group 1 n= 39	Inhaled Milrinone group 2 n= 39
CABG	15	14
Aortic valve replacement (AVR)	10	7
Mitral valve replacement (MVR)	7	9
Atrial Septal Defect (ASD)	3	6
Total corrections	4	3

Table 3: intra operative complications

Complications	IV Milrinone	Inhalation Milrinone
Difficulty weaning from CPB	16	10
Insertion of IABP	9	7
Use of Vasopressor	7	5
CPB re-initiation	6	4
Hospital Stay(days)	10 days	5 days

Table 4: Hemodynamic Variables between 2 groups with their level of significance

Hemodynamic Variable	IV Milrinone (mean values with SD) n= 39	Inhaled Milrinone (mean values with SD) n= 39	P. Value
HR-1	74.79 ± 6.371	73.59 ± 4.711	.345
HR-2	70.51± 4.893	70.59 ± 5.646	.949
HR-3	81.36 ± 5.358	80.59 ± 4.296	.486
SAP-1	77.64 ± 7.325	76.90 ± 5.688	.618
SAP-2	86.41± 5.861	89.00± 4.460	.031
SAP-3	85.21± 4.311	78.21 ±6.075	.000
CVP-1	15.49 ± 3.068	15.51± 2.684	.969
CVP-2	13.79± 2.802	11.26 ± 1.390	.000
CVP-3	14..24 ± 2.192	12.00 ± 2.128	.000
SPAP-1	39.56 ± 6.958	42.95 ± 5.083	.016
SPAP-2	20.33± 3.405	23.08± 4.035	.003
SPAP-3	20.33 ± 3.405	28.67 ± 5.142	.000
DPAP-1	41.92± 6.788	36.38 ± 5.019	.002
DPAP-2	21.62 ± 3.566	19.15 ± 4.301	.000
DPAP-3	28.00± 4.707	24.62± 4.452	.002
MPAP-1	42.21± 5.786	34.59 ± 5.369	.000
MPAP-2	41.64 ± 5.728	16.23 ± 2.924	.000
MPAP-3	28.44± 3.235	22.00 ± 3.606	.000

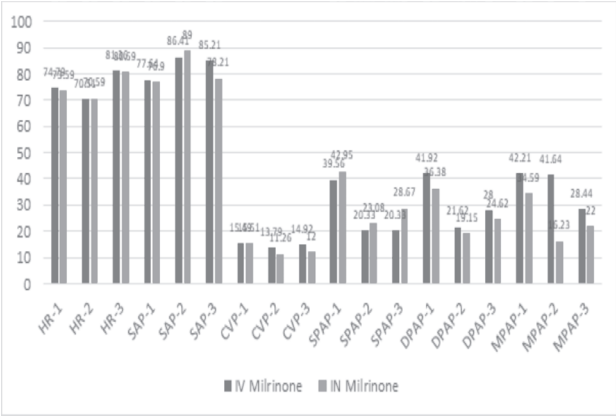

Fig 1: Hemodynamic parameters in both groups at 3 stages

DISCUSSION

The major findings of the study are that patients with pulmonary hypertension in cardiac surgery can benefit from a single dose of 0.1 mg/kg during Cardiac surgery in terms of separation from CPB, length of stay, and hemodynamic stability. The use of the inhaled route for milrinone (INM) has been described in two animal and human studies. [14, 15] In both the studies, the mean pulmonary arterial pressure (mPAP) was above 30 mmHg with 2 mg IVM in heart transplant surgery. A 1mg of inhaled milrinone was administered to patients undergoing different congenital cardiac procedures showing reduced pulmonary arterial pressure, and higher MAP over mPAP ratio before CPB. Administration of milrinone in smaller doses before and during CPB would result in uniform distribution and penetration in the lung parenchyma, protecting pulmonary vasculature during weaning from CPB when most ischemic reperfusion injury occurs. [16] Administration of the drug during CPB leading to diversion of the blood from the pulmonary arterial bed could explain this longer duration as the drug would diffuse in poorly irrigated lung parenchyma during the CPB run.

As an alternative to inhaled nitric oxide and inhaled prostacyclin, inhaled milrinone (INM) is also less expensive and does not require a complex setup and monitoring of toxic metabolites. It is readily available in operating rooms and needs no special preparation, as opposed to inhaled prostacyclin.

Administration of (INM) has the advantage of protecting pulmonary vasculature during weaning from CPB when ischemic reperfusion injury occurs through a more uniform distribution and penetration in mechanically ventilated lungs. INM Before CPB could prevent the reperfusion syndrome. [17] Our Study data support the efficacy and clinical use of inhaled milrinone in cardiac surgery, and it has the advantage over Nitric oxide, Epoprostenol, and other inhaled agents used in patients to treat pulmonary hypertension in cardiac surgery. Inhaled milrinone has the advantage of being simpler, cheaper, and easily available in operation rooms rather than other expensive inhaled medications which require a complex setup during operative procedures.

One of the limitations of the study is that it is a single-center experience, and covered many surgeries where proper group comparison might not be possible. Multicenter, large-scale RCTs are required to further validate these observations.

CONCLUSION

The use of inhaled Milrinone was beneficial in patients with pulmonary hypertension in separating them from the coronary bypass machine. Intraoperative complications like difficulty in weaning from CPB, insertion of IABP, use of vasopressor, duration in ICU, and CPB re-initiation in patients were less with inhalational milrinone, as compared to intravenous administration. Nebulized milrinone is simpler and more cost-effective than nitric oxide. This makes inhaled milrinone an attractive option in cardiac surgeries.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under

Anwar K: Data collection, literature search, writing up.

Shah SSA: Conceived the idea

Ehtisham S: Data analysis

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.