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A Prospective Randomised Observational Study of Obstructed Total Anamalous Pulmonary Venous Connection (TAPVC) Repair Patients with Milrinone Versus Milrinone and Inhaled Nitric Oxide

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ABSTRACT

Background: Obstructed total anomalous pulmonary venous connection (OTAPVC) typically presents with severe cardiovascular decompensation and requires urgent surgical management. Pulmonary arterial hypertension (PAH) is a major risk factor affecting mortality. Perioperative management focuses on providing inotropic support and managing potential pulmonary hypertensive episodes. The aim of this study was to determine the outcome of patients with high pulmonary arterial pressure (PAP) with milrinone alone and a combination of milrinone and inhaled nitric oxide (INO). **Material and Methods:** After the approval of the ethical committee, this single-centre prospective randomised and observational study was conducted over a period of two years among eighty-six patients with obstructed TAPVC repair with severe PAH. Group-I patients received milrinone, and Group-II patients received both milrinone (after aortic cross clamp removal) and INO during the post-operative period at the cardiac care unit (CCU). Clinical outcomes such as ventilation time, length of stay (LOS) in the CCU, LOS in the hospital, complications, and hospital mortality were compared between the two groups. **Result:** The average ventilation time, LOS in CCU, and LOS in hospital for group I were 96.82 ± 19.46 hours, 10.91 ± 7.53 days, and 14.46 ± 7.58 days, respectively, and for group II, it was 85.14 ± 15.79 hours, 7.28 ± 3.68 days, and 10.21 ± 3.14 days, respectively, which was statistically significantly lower for group II. Reintubation, RV dysfunction, and hospital mortality were 16.3%, 37.2%, and 6.9% in group I, and 4.8%, 14.6%, and 2.4% in group II, respectively. The P value for each variable was significant < 0.05 (except mortality). **Conclusion:** Preoperative obstruction is a risk factor for postoperative obstruction, as 235 patients with obstructed TAPVC had severe PAH (39.98%) in this study. Management of severe PAH with a combination of milrinone and INO had a better outcome than milrinone alone.

KEYWORDS: Cyanotic congenital heart disease, TAPVC, Milrinone, Inhaled Nitric Oxide

INTRODUCTION

Total anomalous pulmonary venous connections (TAPVC) is a cyanotic congenital heart disease where all the pulmonary veins drain directly or indirectly into the right atrium. [1] There is a complete mixture of pulmonary and systemic venous return in the right atrium and an obligate right-to-left atrial shunting to sustain life. TAPVC, as reported in the literature, is a rare congenital malformation accounting for 1–3% of all congenital heart disease [2] and approximately 7 per 100,000 live births. [3] Anatomically, TAPVC can be divided into four subtypes based on the level of the anomalous connection, which was originally described by Craig & Darling. [4] The most common type, accounting for

45-55% of all TAPVC cases, is supracardiac; 20-30% are cardiac; 13-25% are infracardiac; and less than 10% of cases are mixed. [5]

Obstruction may be intrinsic due to the narrowing of the lumen of the confluent vessel or extrinsic due to the passage of vein through tissue like the diaphragm, as in the infracardiac type of TAPVC, or by intrathoracic structures such as the left pulmonary artery in supracardiac type TAPVC. Obstruction may also be present at the entry point of the pulmonary venous system into the systemic venous system. The infracardiac type of TAPVC is mostly associated with obstruction, usually at the level of the diaphragm, as a vertical vein passes via the esophageal orifice. About 50% of supracardiac types of TAPVC are associated with obstruction. Obstruction is rarely associated with the intracardiac type of TAPVC. It is present at the level of entry of the vertical vein into the coronary sinus, or right atrium. Patients are further classified as obstructed based on the evidence of pulmonary venous obstruction, and drainage is described as obstructed when there is a mean Doppler velocity of $\geq$2 m/s (or a gradient by catheterization of $\geq$4 mmHg) by two-dimensional echocardiography (EoCG) in the circulation of blood. [6]

Pulmonary artery hypertension (PAH) is a pathological hemodynamic condition defined as an increase in mean pulmonary arterial pressure (MPAP) $\geq$25 mmHg at rest, assessed using the gold standard investigation by right heart catheterization. [7] Pulmonary hypertension could be a complication of cardiac or pulmonary disease or a primary disorder of small pulmonary arteries. Pulmonary hypertension in congenital heart disease is commonly secondary to left-to-right shunt defects or left heart obstructive disease-causing postcapillary hypertension. PAH is widely accepted as one of the major risk factors leading to mortality in OTAPVC patients. It is imperative to maintain lower pulmonary vascular resistance to improve the outcome of the patients.

Milrinone is an intravenously active selective phosphodiesterase III inhibitor that increases the intracellular concentration of cyclic adenosine monophosphate in vascular smooth muscle cells and cardiomyocytes. [8] It's an efficient medication for patients with pulmonary hypertension and depressed cardiac function as it helps to relax vascular smooth muscles (systemic and pulmonary) and improves both diastolic and systolic function with very weak or non-existent inotropic and lusitropic properties. It is used as the first-line treatment for pulmonary hypertension. [8, 9]

Until 1970, nitric oxide (NO) was considered a toxic environmental pollutant. In 1998, Dr. Ferchgott et al. were awarded the Nobel Prize for their discovery of NO's role in the cardiovascular system. [10] The clinical use of NO for the relaxation of smooth muscle cells in the vasculature and selective pulmonary vasodilation has been shown in many studies and is used for the treatment of pulmonary hypertension. [11, 12] Higher systemic concentrations of NO cause toxicity such as elevated methaemoglobin >6% of total haemoglobin, systemic hypotension and increased ionotropic requirement, low cardiac output syndrome, and progressive metabolic acidosis. [11–15] Inhaled nitric oxide (INO) causes selective pulmonary vasodilation, does not enter the systemic circulation, does not cause any systemic effects, has a short half-life, but has logistical problems and a high cost. [11–16]

In obstructed TAPVC, the lungs are edematous with dilated lymphatic channels and thick alveolar walls. [13, 14, 16] Thus, a few days of postoperative mechanical ventilation should be anticipated. The aim of this study was to determine the clinical outcome of patients being operated on for OTAPVC with high pulmonary artery pressure postoperatively treated with milrinone alone versus milrinone with inhaled nitric oxide.

MATERIALS AND METHODS

This study was carried out from September 2021 to August 2023 after obtaining ethical approval from the Ethical Clearance Committee on Human Research (Number: CAU/2417/P/2021) at SAMSRI, as per the Helsinki Declaration and revised guidelines of 2000. The nature of the study was explained to the guardians of the patients included in the study, and written informed consent was obtained from them.

I. Study Design: This study was a single-centre prospective randomised observational study. A prevalence of 25% was adopted for obstructed TAPVC corrective surgery with severe post-surgery PAH. The sample size estimation in this study, with reference to the previous studies, was determined as follows:Required sample size:$n = \frac{z^2pq}{d^2}$, where the z = z score corresponding to the 95% significance level, p = the estimated proportion (as referenced in the previous study) = 1 minus p, and d = precision, or the tolerated margin of error. Therefore, z=1.96, p=0.25, q= (1-0.25), d=0.1 Substituting these values into the above equation: $n = \frac{(1.96)^2\ (0.25)\ (1-\ 0.25)}{(0.1)^2} = 72.03$Considering a 19% dropout rate = 19/100 $\times$ (72) = 13.68, and the dropout rate 14. The required sample size (n): [estimated 72 + dropout 14] = 86.

Patients were identified by searching the daily surgical list of TAPVC (652 patients), echocardiographic, and catheterization databases for obstructed TAPVC (235 patients). Postoperatively, 94 patients had PAH, and eighty-six patients were identified from obstructed TAPVC who had undergone corrective surgery with PAH, which met the study criteria. Patients were randomly divided into two groups using a computer-generated randomization table. "A" group prepared the study drugs and managed the patients in the operating room, and "B" group was responsible for the patients' and their records in the cardiac care unit (CCU), while "C" group participated in the randomization process of patients among the two study groups. The surgeon and surgical technique were not the same for all the patients.

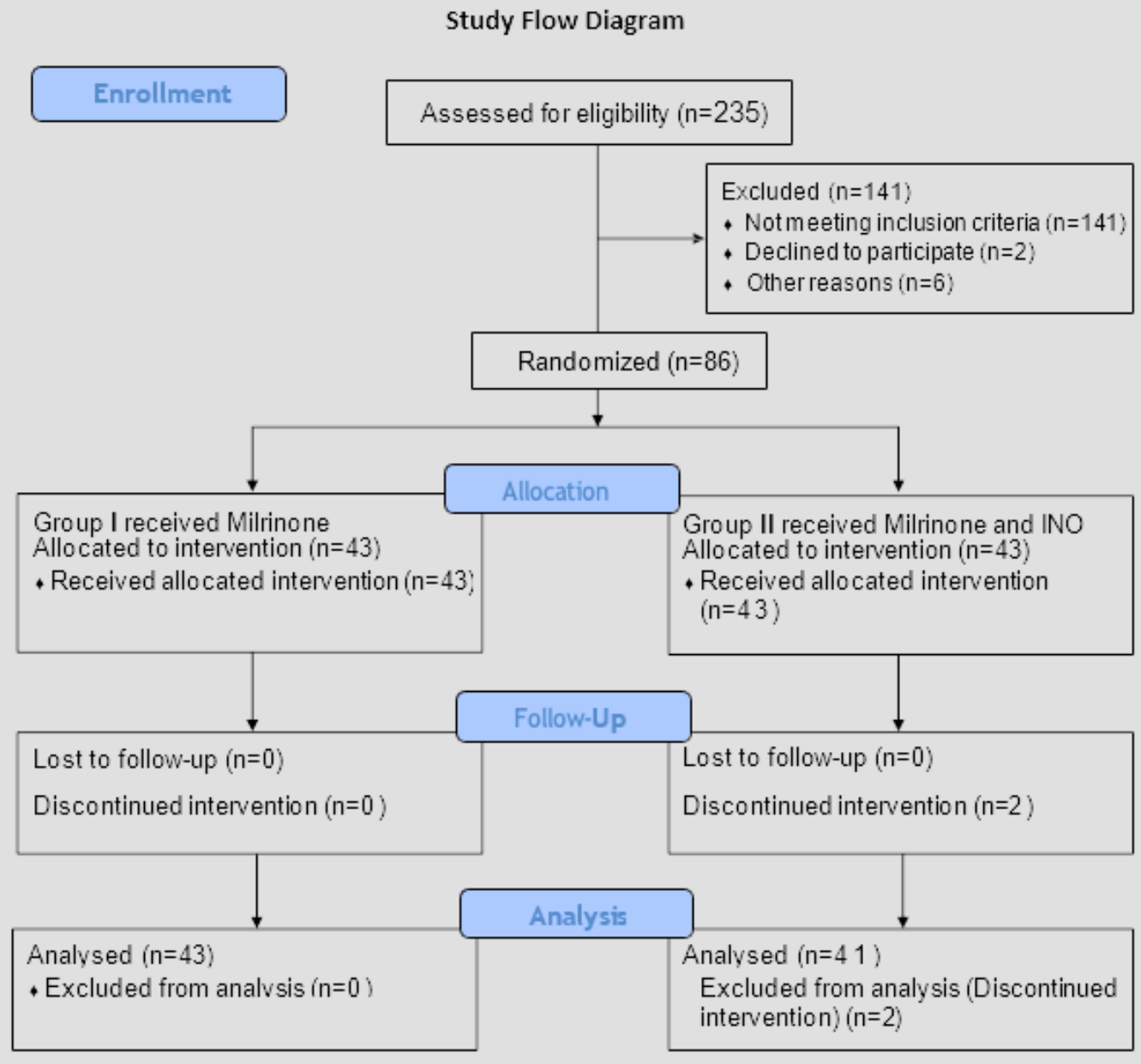

Figure 1: Study Flow Chart

II. Inclusion Criteria and Exclusion Criteria: The study population consisted of the physical status III and IV of the American Society of Anesthesiologists (ASA), of either sex between the ages of 8 and 100 days, with a mean pulsed doppler gradient of >4 mmHg by two-dimensional and EoCG anywhere in the circulation of blood from the pulmonary veins to the right atrium with or without a restrictive interatrial communication considered obstructed TAPVC with severe post-surgery PAP (more than or equal to systemic pressure, RVSP >60 mmHg) under general anaesthesia.

Patients with unobstructed TAPVC corrective surgery, revision surgery due to any cause, PAP less than systemic pressure (RVSP <60 mmHg), age less than 8 days or more than 100 days, emergency surgery, co-infection, preoperative hemodynamic instability, preoperative respiratory disease, abnormalities found in the lung, liver, kidney, or coagulation function, and refusal to provide consent to participate in the study were excluded from the study.

III. Preoperative Preparation: All patients underwent a pre-anaesthetic evaluation a day before surgery, with particular consideration to elicit any new complications and review previous anaesthetic history and drug sensitivity. All routine investigations were re-checked, and procedures were explained to the guardians. The patients were fasted according to hospital protocol for 3 hours before elective surgery.

IV. Anaesthesia and Surgical Protocol: Identification of the patient in the operation theatre (OT), a short preoperative history was taken along with the clinical examination, and routine investigations were re-checked. Oxygen saturation in four limbs was checked without oxygen and with oxygen. All patients underwent a pre-anaesthetic evaluation a day before surgery, with particular consideration to elicit any new complication and review previous anaesthetic history. All routine investigations were re-checked, and the procedure was explained to the guardians. The patients were fasted according to hospital protocol for 3 hours before elective surgery. On the day of surgery, all participants were premedicated by oral route with midazolam 0.5 mg/kg in OT. The patient's vital signs were monitored, including blood pressure, electrocardiogram, and oxygen saturation. Induction of anaesthesia was performed with ketamine 1-2 mg/kg, opioids (inj. fentanyl 4-5 μg/kg), and benzodiazepine (inj. midazolam .1 mg/kg). For muscle relaxation, inj. pancuronium (0.1 mg/kg) was used. Intubation was performed after adequate muscle relaxation. Anaesthesia was maintained with oxygen and sevoflurane (1%–3%) in addition to bolus doses of fentanyl (1–2 μg/kg) given as per patient requirement. The end-tidal CO_2 was maintained between 30 and 35 mmHg. Additional monitoring included invasive blood pressure, central venous pressure, and rectal and nasal temperatures.

After sternotomy, the patient's vena cava and ascending aorta were cannulated for venous drainage and arterial perfusion. The patients were heparinated with 3 mg/kg and taken on the pump after ACT > 480 seconds. The CPB technique was standardised for all patients. Supplemental heparin was administered into the CPB circuit from time to time to maintain ACT > 480 seconds. The CPB flow was maintained at 2 litres per minute per meter^2, and the pressure was >30 mm Hg. Core cooling was used in all patients; rectal or esophageal probes monitored temperature. In all patients, PAP was measured directly through a 2.5-F soft catheter placed directly in the main PA at the time of surgery. This allows continuous real-time monitoring of the PA pressure postoperatively in the CCU. Repair of obstructed TAPVC was performed by the surgical team. Modified ultrafiltration was performed in all patients after separation from the bypass, as its advantages were proven by many studies.[17] Injection Adrenaline infusion was also started as per requirement. Invasive PAP, CVP, and MAP were recorded as per study protocol. An aggressive management strategy was adopted to deal with severe PAP (more than or equal to systemic pressure), and our unit policies were as follows:

- Optimise ventilation by lung recruitment; check for collapse, consolidation, pneumothorax, endotracheal tube (ETT) position, and plural effusion. Target SpO_2 >95% by adjusting FiO_2, and target $PaCO_2$ 30–35 mmHg with ventilation setting adjustments.
- Check for ventricular function by echocardiography and optimise by adding or modifying inotropes. We have used a milrinone infusion loading dose of 50 μg/kg given over 10 minutes, followed by a maintenance dose of 0.5 μg/kg/min continued till 24 hours after extubation as an inodilator, and an adrenaline infusion (dose range: 0.04 to 0.1 μg/kg/min) as an inotrope in both study groups I and II.
- Group II received INO immediately postoperatively in the CCU with 20–40 ppm and titrated as per the requirement to achieve an adequate oxygenation ratio (PaO_2/FiO_2 ratio), SpO_2, and hemodynamics, and continued for 48 hours along with milrinone.
- The methemoglobin levels and platelet count were monitored in patients on INO. Weaning of INO started after 48 hours at 1 ppm/hour.
- Sildenafil infusion (dose: 1–1.6 mg/kg/day) started during the weaning of milrinone in group I and INO in group II.

We adopted early extubation as one of the strategies to deal with postoperative PAH management, as an ETT in position is one of the strong stimuli for high PAP. Before extubation, as a unit policy, we document the normalisation of ventricular function and diaphragm movement by EoCG. Early use of noninvasive ventilation was adopted if the patient remained tachypneic with high $PaCO_2$ or low PaO_2 within the first 4 hours of extubation. In the postoperative period, pulmonary artery pressure was measured using a transthoracic echo.

V. Statistical analysis: Collected data were analysed using IBM SPSS version 22.0 software (SPSS Inc., Chicago, IL, USA). These data were presented as mean $\pm$ standard deviation (SD) or proportion according to their distribution characteristics. Categorical variables were described using counts and percentages as appropriate. A paired Student's t-test was used to compare continuous variables. The chi-square test was used for categorical variables. $P < 0.05$ was considered to be statistically significant.

RESULTS

The cohort included eighty-six patients who underwent an operation that included obstructed TAPVC repair at our institution from September 2021 to August 2023. They were divided into two groups of 43 each. Study group I received milrinone, and group II received milrinone and INO immediately after shifting to CCU. The demographic parameters, such as the mean age at the time of surgery, were 54.5 $\pm$ 7.89 days. The mean weight (kg) of the patients was 3.32 $\pm$ 0.59 and the mean height (cm) was 50.6 $\pm$ 5.20. All demographic parameters were comparable in two study groups (Table 1). There was a male preponderance of 58.2% vs. 41.8% in this study.

TAPVC cases were classified as supracardial, with 51.13% of cases, and is the most common type. Infracardiac type 42.94% of cases, mixed type 3.55% of cases, and cardiac type 2.38% of TAPVC, as shown in Table 2 andFigure 2.

Variables	Group-I (n=43)	Group-II (n=43)	p-value
Age (days)	53±8.26	56±7.53	0.481
Weight (Kg)	3.25±0.57	3.38±0.61	0.638
Height (cm)	49.8±4.62	51.4±5.78	0.572
BSA (m^2)	0.25±0.06	0.26±0.08	0.946
SpO_2	70.85±8.9	73.18±7.4	0.382
Sex (F/M) F: M	17/26 1:1.53	19/24 1:1.26	0.437

Age, weight and Height as means ± standard deviation (SD), percentages and ratio. Kg = kilogram, cm-centimetre, BSA- body surface area, m^2-squaremetre M = male, F = female, p is significant <0.05.

Table 1: Demographics of the patient population:

	Group-I	Group-II	Percent
Obstructed (n=)	43	41	-
Supracardiac	53.48%	48.78% (1*)	51.13
Cardiac	2.34%	2.44%	2.38
Infracardiac	39.53%	46.34% (1*)	42.94
Mixed	4.65%	2.44%	3.55

* -Technical difficulties prevented completion of study protocols. Severe hypoxemia developed in 2 patients upon separation from bypass after TAPVC repair because of severely hypoplastic pulmonary veins and were excluded from the study.

Table 2: Pre-Operative diagnosis:

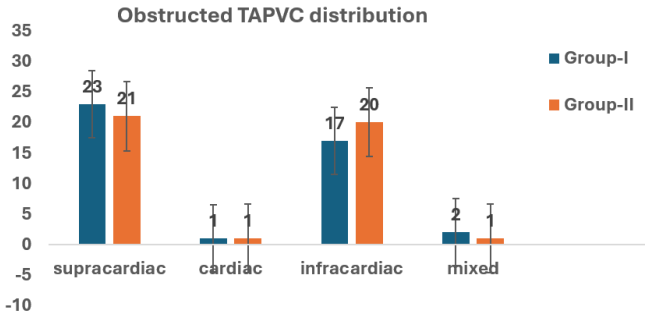

Figure 2: Obstructed total anomalous pulmonary venous connection (n=86). TAPVC -obstructed total anomalous pulmonary venous connection

The intraoperative variables such as CPB duration, ACCT, minimum core temperature, total heparin, and urine output were comparable for both groups (Table 3). Preoperative obstruction is a risk factor for postoperative obstruction, as 235 patients with obstructed TAPVC had severe PAH (39.98%) in this study (Figure 3).

Variables	Group-I	Group-II	p-value
CPB duration (min)	148.93±68.73	145±65.41	0.397
ACCT (min)	68±27.35	69±31.8	0.582
Minimum core temperature (°C)	25.6±4.1	25.3±3.8	0.739
Total heparin (units)	5387±843	5643±1294	0.494
Urine output on CPB (ml/kg)	11.5±6.8	12.7±5.2	0.583

Data are presented as means ± standard deviation (SD), ACCT= Aortic cross clamp time, CPB= cardiopulmonary bypass, °C = celsius, ml=millilitre, kg= kilogram. P is significant <0.05.

Table 3: Intraoperative characteristics of the patient population:

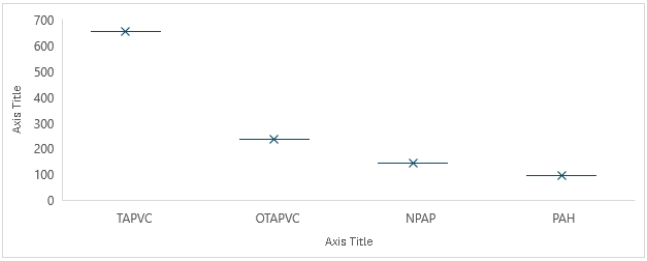

Figure 3: Obstructed TAPVC with postoperative PAH: OTAPVC -obstructed total anomalous pulmonary venous connection, TAPVC- total anomalous pulmonary venous connection, NPAP- normal pulmonary arterial pressure, PAH-Pulmonary arterial hypertension

Mean arterial pressure (MAP) and pulmonary arterial pressure (PAP) are comparable immediately after coming off CPB (Table 4). However, at 24 hours and 48 hours, a significant reduction in PAP pressure and a significant improvement in MAP in group II were seen (Figure 4).

In the postoperative period of the of the pulmonary artery, the pressure was measured using a transthoracic echo with the help of tricuspid regurgitation jet velocity (RVSP + CVP) or pulmonary regurgitation velocity (Figure 5).

The average mechanical ventilation time, LOS in the CCU, and LOS in the hospital for group I were 96.82 ± 19.46 hours, 10.91 ±7.53 days, and 14.46 ±7.58 days, respectively, and group II were 85.14 ±15.79 hours, 7.28 ±3.68 days,

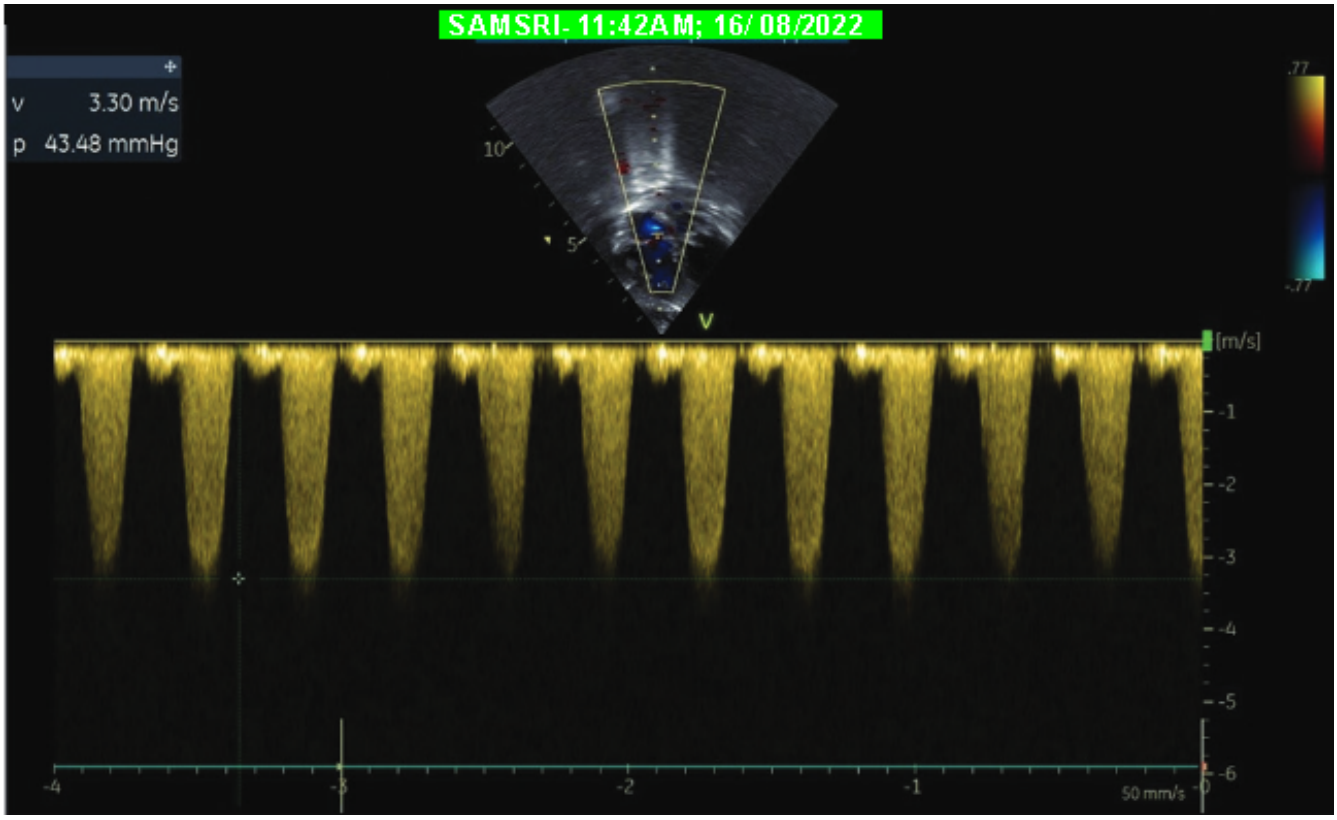

Figure 5: Postoperative transthoracic echo showing TR jet velocity

Haemodynamic data (mmHg)	Group-I	Group-II	p-value
MAP in OT	42.26±5.31	43.51±4.67	0.247
MAP in CCU at 24 hrs.	44.05±7.35	47.63±5.73	0.006*
MAP in CCU at 48hrs.	47.52±5.57	53.14±5.85	0.002*
PAP in OT	46.36±5.82	46.97±5.62	0.835
PAP in CCU at 24 hrs	40.33±4.96	34.91±5.16	0.006*
PAP in CCU at 48hrs.	34.27±3.82	27.42±5.14	0.384*

Data are presented as means ± standard deviation (SD), MAP= mean arterial pressure, PAP= pulmonary artery pressure., mmHg= millimetre of mercury, P is significant * < 0.05.

Table 4: Haemodynamic data:

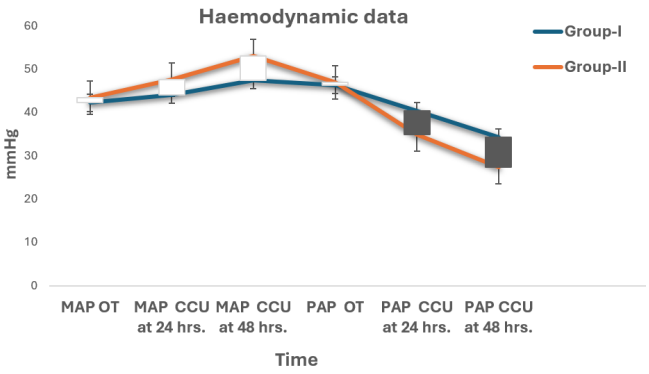

Figure 4: Mean arterial pressure (MAP) and Pulmonary artery pressure (PAP) in millimetre of mercury (mmHg) at operation theatre (OT) at end of surgery, at cardiac care unit CCU at 24 and 48 hours, respectively

and 10.21 ±3.14 days, respectively, which were statistically significantly lower for group II as seen inTable 5.

Table 6 shows the postoperative outcomes of patients. Reintubation, RV dysfunction, and hospital mortality were (16.3%), (37.2%), and (6.9%) in group I and (4.8%), (14.6%), and (2.4%) in group II, respectively, with a statistically significant p- value (p<0.05). In our cohort, 30-day mortality was less in group II (2.4%) compared with group II (6.9%) and was comparable in both study groups.

DISCUSSION

TAPVC is a subset of complex congenital cardiac defects where all pulmonary veins have no direct connection with the left atrium, and they drain into one of the systemic veins or directly to the right atrium or coronary sinus. In

Variable	Group-I	Group-II	p-value
Duration of mechanical ventilation (hr)	96.82 ± 19.46	85.14± 15.79	0.013*
Average CCU LOS (days)	10.91 ±7.53	7.28±3.68	0.028*
Chest tube drain in first 48 hours (ml)	102.59±47.82	103.11±44.93	0.529
Average Hospital LOS (days)	14.46±7.58	10.21 ±3.14	0.003*

Data are presented as means ± standard deviation (SD), and percentages, LOS= Length of Stay; OR- operating room; hr= hours, P -* is significant <0.05.

Table 5: Comparison of mechanical ventilation and Length of Stay (LOS) in CCU

Variable	Group-I (n=43)	Group-II (n=41)	p-value
Reintubation	7 (16.3%)	2 (4.8%)	0.037
Open chest	4 (9.3%)	5 (12.2%)	0.582
Re-exploration	3 (6.9%)	2 (4.9%)	0.631
RV dysfunction	16 (37.2%)	6 (14.6%)	0.019
Mortality	3 (6.9%)	1 (2.4%)	0.285

Table 6: Perioperative Complications and outcome

the literature, supracardiac TAPVC is the most common type reported, accounting for about 45% to 55% of the total TAPVC. [2] Our study partially mirrored these observations, with supracardiac (51.16%) being the most common. This may probably be due to our centre being one of the tertiary referral centres for complex congenital cases. The infracardiac type was the second most common, accounting for about 43.02% of cases.

These patients are at significant risk of pulmonary hypertensive crisis as endothelial dysfunction is induced by ischemia, complement activation, micro-emboli, and pulmonary leuko-sequestration during CPB, further exacerbate neonatal pulmonary vasoreactivity. [3, 5] The degree of pulmonary hypertension is related to the presence of preoperative pulmonary hypertension and the duration of CPB. The mean ACCT was 148.93±68.73 and 69±31.80 min, and the mean CPB time was 148.93±68.73 and 145±65.41 min in groups I and II, respectively. This was high due to the fact that TAPVC complex anatomy takes more time for repair. CPB and ACCT were comparable for both study groups.

MAP and PAP at 24 hours and 48 hours were statistically significantly low and high in group I. This supports that milrinone alone is not very effective in patients with elevated pulmonary vascular resistance with PH, as it relaxes vascular smooth muscles both systemic and pulmonary. Our findings confirm that milrinone alone has slower, weaker, and systemic effects as compared to milrinone + INO group II. Similar findings were supported by Cai J. et al. [18]

Until 1970, NO clinical use was limited due to its short half-life, logistical problems, high cost [16], high affinity for haemoglobin and producing methaemoglobin, which impairs oxygen transport. [19] Long-term therapy causes pulmonary epithelial cell damage, interstitial atrophy, fibrosis, sepsis, and ARDS. [20, 21] The antiplatelet effect in premature infants increases their bleeding risk. [22, 23] Kharitonov et al. reported that INO < 80 ppm reduces PAP and pulmonary vascular resistance without toxicity. [16, 24] In our study of OTAPVC repair, milrinone with INO was titrated up to 40 ppm according to the requirement for 48 hours after surgery. None of our patients had signs or symptoms of INO toxicity due to its short-term use. Paediatric patients undergoing congenital cardiac surgery showed a positive impact on reducing pulmonary hypertension and a better clinical outcome with INO. [24]

Our study has shown a statistically significant decrease in the average mechanical ventilation time, LOS in the CCU, and LOS in the hospital for group II. But there are some studies that did not find any statistically significant correlation. [4, 9, 25] Surgical correction for OTAPVC is usually done as an emergent or semi-emergent procedure. There may be inadequate time for preoperative stabilisation; we included in our study only elective or semi-emergent OTAPVC repairs. There is also an increased incidence of delayed sternal closure, ventricular dysfunction, and significant ventilation/perfusion mismatch perioperatively. These factors may have contributed to the altered morbidity parameters.

The surgical mortality of TAPVC in the early literature was in the range of 10% to 80%. [8, 18], but most recent reports revealed a surgical mortality of <10%. [8] In our study, out of a total of four deaths, two children had postoperative infections (one developed ventilator-associated pneumonia, the other had blood stream infections, renal failure, and eventually multiorgan failure), and two had succumbed to low cardiac output, of which one child was put on veno-arterial extracorporeal support postoperatively but could not be salvaged. In our analysis, we found lower body surface area and low cardiac output to be major risk factors for mortality. A similar observation was made by White et al. [6] In our study, 30-day mortality was 4.7%, which is comparable to recent reports of mortality rates. Pulmonary hypertensive crises are associated with increased mortality and should be managed aggressively. [4, 5] The factors that have improved

OTAPVC outcomes in our centre are the availability of a dedicated children's cardiac team that works in a coordinated manner to deliver outcomes. Another factor is the appropriate usage of pulmonary vasodilators like milrinone, inhaled nitric oxide (INO), and sildenafil protocol for managing high PA pressure. Early extubating strategies, which have brought down our morbidity parameters, including the use of non-invasive ventilation and early discharge from the CCU, have reduced the incidence of infections, complications, and mortality rates. [23]

CONCLUSION

Most of the patients with obstructed TAPVC had severe PAH. Management of severe PAH with a combination of milrinone and INO had a better outcome than milrinone alone.

STUDY LIMITATIONS

There are some limitations to this study. The surgical technique and surgical team were not the same for all the patients, but the anaesthesia team, post-operative management CCU team, and protocols were fixed. INO was not started immediately at the end of surgery in the OT but was started after shifting the patient from the OT to the CCU, as we do not have the facility available inside the OT to administer INO. We have not measured the plasma level of milrinone because of the unavailability of the kit in our hospital laboratory, which would have given greater insight into pharmacokinetics. Another limitation is the population of the study, which was relatively small.

DATA AVAILABILITY

All data are available within the manuscript. The data sets used and analyzed during the current study are available from the corresponding author on reasonable request.

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