# The Efficacy and Safety of intravenous Levosimendan compared with Milrinone in preventing low cardiac output after corrective cardiac surgery in Tetralogy of Fallot: A prospective open-label study.

***(Thesis submitted for the partial fulfilment for the requirement of the Degree of DM (Cardiothoracic and Vascular Anaesthesia)***


**BY**

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**DM CARDIOTHORACIC AND VASCULAR ANAESTHESIA RESIDENT 2019 – 2021**

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## Declaration

I hereby declare that this thesis entitled, "***The Efficacy and Safety of intravenous Levosimendan compared with Milrinone in preventing low cardiac output after corrective cardiac surgery in Tetralogy of Fallot: A prospective open-label study.***" has been prepared by me under the supervision and guidance of Prof. Unnikrishnan. K.P., Division of Cardiothoracic and Vascular Anaesthesiology, Department of Anaesthesiology, at Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram, Dr Baiju S Dharan, Professor and Head, Division of Cardiothoracic and Vascular Surgery and Dr Sabarinath Menon, Additional Professor, Division of Cardiothoracic and Vascular Surgery Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvanthapuram.

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## List of Abbreviations:

**A-VSO2: Arterio-Venous Oxygen Saturation Difference**

**ABG: Arterial Blood Gas**

**ADR: Adrenaline**

**AF: Atrial Fibrillation**

**AKI: Acute Kidney Injury**

**ASD: Atrial Septal Defect**

**BSA: Body Surface Area**

**CI: Cardiac Index**

**CO: Cardiac Output**

**CPB – Cardiopulmonary Bypass**

**CVP – Central Venous Pressure**

**EF: Ejection Fraction**

**ICR: Intra Cardiac Repair**

**ICR+TAP+MCR: Intracardiac repair +Trans Annular Patch closure + Mono cusp reconstruction**

**IS: Inotropic Score**

**JET: Junctional Ectopic Tachycardia**

**L: Levosimendan**

**LCOS: Low Cardiac Output Syndrome**

**LOS: Length Of Stay**

**M: Milrinone**

**µg. : Microgram**

## List of Abbreviations:

**MV: Mechanical Ventilation**

**NT pro BNP: N-terminal prohormone of Brain Natriuretic Peptide**

**NORADR: Nor Adrenaline**

**PA: Pulmonary Artery**

**PFO: Patent Foramen Ovale**

**PI: Pulmonary insufficiency**

**POD: Post-Operative Day**

**RA: Right Atrium**

**RACHS: Risk Adjustment for Congenital Heart Surgery**

**RPI: Rate Pressure Index**

**RV: Right Ventricle**

**RVOT: Right Ventricular Outflow Tract**

**RVOTO: Right Ventricular Outflow Tract Obstruction**

**SCVO2: Central venous saturation**

**SV: Stroke Volume**

**SVI: Stroke Volume Index**

**VF: Ventricular Fibrillation**

**VSD: Ventricular Septal Defect**

**VT: Ventricular Tachycardia**

**TEE – Trans Esophageal Echocardiography**

**TOF: Tetralogy of Fallot**

**VIS: Vasoactive Inotropic Score**

## CERTIFICATE

This is to certify that the thesis entitled "***The Efficacy and Safety of intravenous Levosimendan compared with Milrinone in preventing low cardiac output after corrective cardiac surgery in Tetralogy of Fallot: A prospective open-label study***" has been prepared by Dr Aspari Mahammad Azeez, DM Cardiothoracic and Vascular Anaesthesiology, Division of Cardiothoracic and Vascular Anaesthesiology, Department of Anaesthesiology at Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvanthapuram.

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## CERTIFICATE

This is to certify that this thesis entitled, **"The Efficacy and Safety of intravenous Levosimendan compared with Milrinone in preventing low cardiac output after corrective cardiac surgery in Tetralogy of Fallot: A prospective open-label study"** Is Dr Aspari Mahammad Azeez's Bonafede work, Senior resident, conducted in the Division of Cardiothoracic and Vascular Anaesthesiology, Department of Anaesthesiology, at Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram, under our supervision and guidance. He has shown a keen interest in preparing this project.

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## INTRODUCTION

Low cardiac output syndrome (LCOS) is a common complication after cardiac surgery on cardiopulmonary bypass, and 25% of children after cardiac surgery have a CI of less than 2.0 L/min/m.[1] Especially in the paediatric age group, it is a significant contributor to morbidity and mortality. Among patients undergoing repair of TOF, approximately 1/3 will experience LCOS due to RV diastolic dysfunction or "Restrictive RV physiology".[20]

Preoperative RV hypertrophy, Cardiopulmonary bypass induced myocardial injury, and oedema after right ventriculotomy all decrease right ventricular compliance and result in diastolic dysfunction. Arrhythmias, residual anatomic lesions such as VSD, RVOTO, tricuspid regurgitation, pulmonary insufficiency (PI) and increased airway pressure in mechanical ventilation may also add to the cardiopulmonary dysfunction. Patients with RV diastolic dysfunction require elevated RA pressures for adequate RV filling in diastole. Decreased RV filling leads to decreased LV preload and resultant low cardiac output.

LCOS is recognised by a group of signs such as decreased mixed venous saturation, reduced urine output, elevated lactate, heart rate and low blood pressure. No definitive diagnostic criteria exist at present for the diagnosis of LCOS within the paediatrics population.

An appropriate agent to manage LCOS should improve cardiac output without increasing myocardial oxygen demand. LCOS is managed by maintaining adequate preload, sinus rhythm, various catecholamines, inodilators and vasopressors. The catecholamines, commonly used, increase myocardial oxygen consumption, heart rate, afterload and risk of arrhythmia, hyperglycaemia, and lactic acidosis; hence has an unfavourable haemodynamic profile. Subsequently, phosphodiesterase-3 inhibitors milrinone and amrinone are used, but Milrinone also increases heart rate and oxygen consumption through its action on cAMP. For patients with RV

diastolic dysfunction, the noncompliant RV acts more like a passive conduit than a compliant chamber and results in antegrade diastolic flow into the pulmonary arteries during atrial systole, which plays a crucial role in maintaining cardiac output in corrective cardiac surgery for Tetralogy of Fallot.[20]Hence, Levosimendan is an attractive alternative to catecholamines because it may improve cardiac output without increasing myocardial oxygen demand.

**Hypothesis:** We hypothesised that Levosimendan was superior or equal to Milrinone in preventing LCOS and arrhythmias after corrective cardiac surgery in Tetralogy of Fallot

## AIM AND OBJECTIVES

**Primary objectives:** To the study the Efficacy and Safety of intravenous Levosimendan compared with Milrinone in preventing/managing low cardiac output syndrome by evaluating below given components of LCOS

1. LCOS:
    a. Blood lactate levels
    b. Central venous oxygen saturation
    c. Arterial to central venous oxygen saturation difference
    d. Urine output
    e. Peripheral skin temperature to core body temperature
2. Arrhythmias in both Milrinone and Levosimendan: SVT, Ectopic atrial tachycardias, AF, accelerated junctional rhythms, JET, VT and VF

## Secondary objectives:

i. Post repair evaluation of right ventricular restrictive physiology by measuring end-diastolic forward flow in the pulmonary artery (PA) by Doppler echocardiography,

ii. Immediate Post CPB evaluation of RVOT to the pulmonary artery pressure gradient in both groups.

iii. Tricuspid and mitral inflow E/A values

iv. The direction of the PFO shunt

v. RVOT to the pulmonary artery pressure gradient

vi. Rate pressure index during inodilator infusion

vii. **Adverse events** due to inodilator infusions:

Hypotension, hypokalemia, and thrombocytopenia

viii. In CHICU, Transthoracic Echocardiography was done on POD 1, 2 &3 to evaluate RVOT to the pulmonary artery pressure gradient in both groups.

ix. Re-Interventions

x. Length of intensive care unit (ICU) stay.

xi. Length of hospital stay.

xii. Duration of mechanical ventilation

xiii. Duration of a chest drain.

xiv. Vasoactive-Inotrope score [37] by

VIS = dopamine dose (mcg/kg/min) +dobutamine dose (mcg/kg/min) +100×epinephrine dose (mcg/kg/min) +10×milrinone dose (mcg/kg/min) +10,000×vasopressin dose (U/kg/min) +100×norepinephrine dose (mcg/kg/min) +50×levosimendan dose (mcg/kg/min).

xv. Number of patients requiring mechanical circulatory support -ECMO

## Justification of the study:

- Only very few studies are available globally on Levosimendan utilisation in post-cardiac surgery in Tetralogy of Fallot patients.
- There are only very few studies available globally comparing Levosimendan with Milrinone in preventing LCOS in post-cardiac surgery in Tetralogy of Fallot patients
- Only one study in our country compared Levosimendan with Milrinone in preventing LCOS in post-cardiac surgery in the paediatric population. This study included a heterogeneous paediatric population with a broad spectrum of congenital heart disease. In our study, we were confined to a more homogenous single congenital heart disease -TOF.
- Levosimendan administration was cost-effective compared with other inodilators such as Milrinone and amrinone.

## PHARMACOLOGY

**Milrinone:** Milrinone, a phosphodiesterase III inhibitor currently used to treat paediatrics patients with cardiac diseases, increases the level of cyclic adenosine monophosphate in the myocardium and vascular smooth muscle. High levels of cyclic adenosine monophosphate enhance the contractility of the myocardium by increasing calcium influx and relaxing vascular smooth muscles, therefore, increasing cardiac output and decreasing afterload.[2] Milrinone also has a lusitropic property, which improves myocardial relaxation.[3] unlike other inotropes such as dopamine, dobutamine, and epinephrine, Milrinone is not associated with increased myocardial oxygen consumption.[4]

Milrinone has a relatively long half-life of 2 to 4 hours.[24,25] Most studies using intravenous doses suggest that bolus doses of 25-75 μg/kg or infusion doses of up to 0.7 μg/kg/min produce the optimal therapeutic response.[7] Volume of distribution was 0.32 L/kg after intravenous bolus administration of Milrinone in healthy subjects, and 0.3 to 0.42 L/kg (intravenous bolus), 0.47 L/kg (intravenous infusions) and 0.53 to 0.56 L/kg (oral) in congestive heart failure patients. Bio-availability is approximately 85 to 92% after oral administration.[28]

Animal studies have shown that the major metabolic pathways for milrinone metabolism appear to be oxidation and glucuronidation, the primary path of bio-transformation. However, the parent drug is the primary excretion product. The elimination half-life of Milrinone is approximately 48 to 56 minutes in healthy subjects following intravenous or oral administration of 10 to 125 μg/kg and 1.0 to 12.5mg, respectively, but is extended to 3.2 hours in patients with chronic renal failure.[29] In patients with congestive heart failure, elimination half-lives of 1.2 to 2.7 hours are seen.[30] Plasma clearance following oral and intravenous administration of Milrinone is

about 18 to 24 L/h in healthy subjects, about 7.8 to 12 L/h in congestive heart failure patients and about 1.8 L/h in patients with chronic renal failure.[29]

Milrinone is widely used due to its inotropic, vasodilatory, and lusitropic properties. It is frequently prescribed after cardiac surgery due to its Efficacy in preventing low cardiac output syndrome.[5]

**Levosimendan**: Levosimendan is a calcium sensitiser and potassium channel opener. Levosimendan has a half-life of 1 hour in the adult population and is metabolised into OR-1896, an active metabolite, with a longer half-life of 75 to 80 hours.[21,22] Levosimendan and OR-1896 improve myocardial contractility by sensitising troponin C to the intracellular calcium during systole without affecting diastolic function.[23] Its action as a potassium channel opener in vascular smooth muscle cells causes coronary vasodilatation and pulmonary vasodilatation.[6]Therefore, Levosimendan elevates cardiac contractility; meanwhile, it does not cause chronotropic and does not increase cardiac oxygen consumption. Treatment with Levosimendan is usually initiated with a loading bolus of 3 to 12 mcg/kg for 10 min followed by a continuous infusion of 0.05 to 0.2 mcg/kg per min. The most common adverse reactions in clinical trials were headache and hypotension, and the majority of adverse reactions were seen within 3 days after the start of the infusion**.** The benefits appear to be through its positive inotropy with well-controlled heart rate and low incidence of arrhythmia, probably due to its beta-1 sparing action.

# REVIEW OF LITERATURE

Low cardiac output syndrome (LCOS) is defined as the clinical manifestation of mismatched oxygen supply and demand due to cardiovascular dysfunction following cardiac surgery and a common adverse outcome following cardiac surgery in the paediatric population, incidence as high as 25%.[1] No definitive diagnostic criteria exist at present for the diagnosis of LCOS within the pediatric population. The existing criteria are based on hemodynamic measurements instead of an objective measurement of cardiac output. This is in contrast to the adult population, where a definition relies on objective measurement of cardiac index exists. The mainstays of treatment include catecholamine and inodilators such as calcium sensitizers (Levosimendan) and phosphodiesterase inhibitors (Milrinone).[17]

**Therapeutic trials of Milrinone in pediatric cardiac surgery:**

Milrinone in the paediatric population was first described in 1995 by Chang et al. in ten neonates following cardiac surgery.[26] The authors used a thermodilution pulmonary artery catheter (Baxter Edwards Critical-Care, Irvine, CA) to measure cardiac index. An increase in the cardiac index from 2.1 (+ 0.5) to 3.0 (+ 0.8) L/m2 /min with the use of 0.5 μg /kg/min milrinone and 3 to 7 μg /kg/min dopamine, without increased myocardial oxygen consumption was observed. Then in 1998, a pharmacokinetic study in 19 infants and children confirmed therapeutic plasma levels with both 0.5 and 0.75 μg /kg/min milrinone with reduced clearance compared to adults, especially in infants. [27]

**Timothy M Hoffman et al.** in their Double-blind, placebo-controlled, PRIMACORP

trial with 3 parallel groups (low dose, 25 μg /kg bolus over 60 minutes followed by a 0.25 μg /kg per min for 35 hours; high dose, 75 μg /kg bolus followed by a 0.75 μg /kg per min for 35 hours; or placebo) conducted in paediatric congenital heart surgery supported the frequent use of High-dose milrinone. The authors observed that high-dose Milrinone reduced the risk of LCOS development by 55% in children after biventricular repair compared with placebo.[7] However, there was no significant difference in lactate clearance, duration of MV, hospital LOS and mortality. Low-dose Milrinone (0.25 μg/kg/min) showed no benefit over placebo.

**Cavigelli-Brunner, Anna et al. in a** Prospective, single-centre, double-blinded, randomised clinical pilot study, 50 patients (age, 0.2-14.2 yr.; median, 1.2 yr.) undergoing open-heart surgery for congenital malformations were included. After cardiopulmonary bypass, a continuous infusion of either dobutamine 6 μg/kg/min. Or milrinone 0.75 μg/kg/min. was administered for the first 36 postoperative hours. Efficacy was defined as needing additional vasoactive support, which did not differ between groups (dobutamine 61% vs Milrinone 67%; p = 0.71). Sodium nitroprusside was used more often in the dobutamine group (42% vs 13%; p = 0.019). Systolic blood pressure showed a trend toward higher values in the dobutamine group, whereas both drugs increased heart rate early postoperatively. The study concluded that Dobutamine and Milrinone are safe, well-tolerated, and equally effective in preventing low cardiac output syndrome after paediatric cardiac surgery. [19]

**Therapeutic trials of Levosimendan in paediatric cardiac surgery:**

Levosimendan, a calcium sensitiser, enhances myocardial function by generating more energy-efficient myocardial contractility than through adrenergic stimulation with catecholamines. Thus, Levosimendan is a beneficial alternative to standard medication for preventing low cardiac output syndrome in paediatric patients after open-heart surgery.

**A** randomised controlled trial evaluated the Efficacy of Levosimendan in neonates with congenital heart disease undergoing cardiac surgery. Sixty-three patients (32 cases and 31 controls) were randomised to receive either a 72 h continuous infusion of 0.1 μg/kg/min Levosimendan or standard post-CPB inotrope infusion. Low cardiac output syndrome observed in 37 % of Levosimendan patients and in 61 % of controls ($p = 0.059$, OR 0.38, 95 % CI 0.14-1.0). Post-surgery heart rate measured at 6 ($p = 0.008$), 12 ($p = 0.037$), and 24 h ($p = 0.046$), and lactate levels at PCICU admission ($p = 0.015$) and after 6 h ($p = 0.048$), were lower within the Levosimendan group. Inotropic scores were significantly lower within the Levosimendan group at PCICU admission, after 6 h and after 12 h ($p < 0.0001$). The Authors concluded that Levosimendan was well tolerated with a potential benefit on postoperative hemodynamic and metabolic parameters of risk-adjusted classification for congenital heart surgery( RACHS )3–4 procedures in neonates.[8]

**Wang et al.** conducted a meta-analysis of six randomised controlled trials and one case-control trial including 436 patients. The results found that Levosimendan did not significantly decrease all-cause mortality compared with control drugs(Milrinone, Dobutamine and placebo) in children undergoing cardiac surgery ($P = 0.403$). Perioperative prophylactic Levosimendan administration

significantly decreased the low cardiac output syndrome (LCOS) incidence ($P = 0.016$) but did not considerably reduce acute kidney injury (AKI) incidence ($P = 0.251$) and shorten mechanical ventilation and ICU stay time compared with other inotropes and placebo .[15]

**Hummel J et al** in their meta-analysis of studies using Levosimendan in paediatric cardiac surgery, published in the Cochrane Database of Systematic Reviews in 2017, included 5 studies and had a total number of only 212 infants and children less than 5 years.[18] The study showed Levosimendan had no clear effect on risk of mortality (risk ratio (RR) 0.47, 95% confidence interval (CI) 0.12 to 1.82; participants = 123; studies = 3) and no clear effect on low cardiac output syndrome (RR 0.64, 95% CI 0.39 to 1.04; participants = 83; studies = 2) compared to standard treatments . Even though the effect of Levosimendan not reflected on mortality and LCOS incidence but Levosimendan groups had shorter length of intensive care unit stays (mean difference (MD) 0.33 days, 95% CI -1.16 to 1.82; participants = 188; studies = 4; $I^2 = 35\%$), length of hospital stays (0.26 days, 95% CI -3.50 to 4.03; participants = 75; studies = 2), and duration of mechanical ventilation (MD -0.04 days, 95% CI -0.08 to 0.00; participants = 208; studies = 5; $I^2 = 0\%$)

**Comparison of Levosimendan vs Milrinone in Paediatric Cardiac Surgery:**

**Momeni et al.**, in their prospective, double-blind, randomized trial conducted in congenital heart surgery of children 0–5 years age, patients were administered a continuous infusion of either Levosimendan at 0.05 μg /kg/min, or Milrinone at 0.4 μg /kg/min started at the begging of CPB. Epinephrine was started at 0.02 μg kg/min in both groups after aortic cross-clamp release. There was no significant difference between serum lactate levels (1±0.3 (L), 1±0.5 (M) )of groups. The

rate-pressure index, which is an indicator of myocardial oxygen demand, was significantly lower at 24 hours and 48 hours in the Levosimendan group ($p < 0.001$) in comparison to the milrinone group. [9]

**Lechner et al**. In a Prospective, single-centre, double-blind, randomised pilot study.

They compared the effects of Levosimendan and Milrinone on Fractional shortening (FS) and the cardiac index in 40 infants after cardiac surgery. At weaning from cardiopulmonary bypass, either a 24-hr infusion of 0.1 μg/kg/min Levosimendan or 0.5 μg/kg/min Milrinone was administered. Cardiac output was evaluated at 2, 6, 9, 12, 18, 24, and 48 hrs after cardiopulmonary bypass using a transoesophageal Doppler technique.

They found no significant difference in postoperative FS, cardiac index, lactate clearance and inotropic requirement measured up to 48 hours after CPB between the two groups. However, there was a significant increase in CO over time ($p<0.005$) in the Levosimendan group. [10]

**Himanshu et al.,** in their Comparative study of Levosimendan versus Milrinone for paediatric cardiac surgery patients aged 2–12 years, divided into two groups. Group L (n=25) received in. Levosimendan 12μg/kg over 10 minutes after cross-clamp removal and 0.1μg/kg/min started after that. Group M (n=25) received in. milrinone 50μg/kg of bolus dose for 10 minutes and 0.5 μg/kg/min infusion after that. Both the group received in. Dopamine 5-8 μg/kg/min from the beginning. Noradrenaline 0.1μg/kg/min was added as a rescue drug for hypotension. Both drugs were compared for hemodynamic (including echocardiography parameters), respiratory parameters (including ABG), fluid requirements, urine output, temperature monitoring and also for routine laboratory investigations (including platelet count) postoperatively. Time taken for extubating after shifting the patient was also observed. They concluded that the Levosimendan

results in improved cardiac output by increasing stroke volume, low troponin I, improved Lactate clearance, and a significantly lower requirement of pressor observed in the Levosimendan group. [11]

**Nirav Parikh et al.** conducted a prospective observational study in 100 paediatric patients undergoing complex congenital cardiac surgeries to evaluate the Efficacy of Milrinone and Levosimendan on intraoperative and postoperative outcomes. The study showed postoperative period heart rate and meant arterial pressure at three different periods (T1- 1hr, T2 -24 hrs and T3-48 hour postoperatively) were comparable in both the groups. The VIS score after 48 hours was less in Group L ($p = 0.0005$). Serum creatinine estimated at T2 and T3 showed a statistically significant difference. [16]

**Jothinath et al**., in their single centre, the randomised study recruited forty infants undergoing corrective surgery for congenital heart disease. They randomised them into two groups (group L and group M). During rewarming, a loading dose of Levosimendan or Milrinone was administered followed by a 24-hour infusion of the chosen inotrope. 4 patients (20%) treated with Levosimendan had LCOS in comparison with 6 (30%) patients in those treated with Milrinone. Echocardiographic parameters in both groups L and M were comparable (cardiac index 3.47 ± 0.76 vs 3.72 ± 1.05 L/min/m2, EF 66.10 ± 7.82% vs 59.34 ± 10.74%, stroke volume index 25.4 ± 6.3 vs 27.74 ± 10.35 mL/m2). The duration of ventilation, ICU stay, and hospital stay was lesser in group L (12.75 ± 9.69, 35.95 ± 12.11, 119.10 ± 46.397 vs 23.60 ± 22.03, 51.20 ± 29.92, 140.20 ± 52.65 hours). The study concluded that LCOS incidence was lesser in those patients treated with Levosimendan when compared with Milrinone. Thus, Levosimendan provides a non-inferior alternative to Milrinone when used as the primary inotrope following paediatric cardiac surgery.

In a secondary analysis of a randomised, prospective, double-blinded clinical drug trial, E.M. Thorlacius et al. compared the differential effects of intraoperative administration of Milrinone and Levosimendan on myocardial function in 72 infants after paediatric cardiac surgery by using biventricular longitudinal strain (LS) with 2-dimensional speckle tracking Transthoracic echocardiography. [12] They reported that there were no significant differences between the groups for early (Postoperative day 1 (POD 1)) or late (hospital discharge) LV-LS or RV-LS but found a significant correlation between preoperative NTproBNP and LV-LS on POD1. They concluded that Levosimendan was comparable with Milrinone for left and right ventricular inotropic support in paediatric cardiac surgery.[12]

A post hoc, non-prespecified exploratory secondary analysis of the Milrinone versus Levosimendan-1 trial (ClinicalTrials.gov Identifier: NCT02232399) compared the effect of Levosimendan and Milrinone on the plasma levels of myocardial injury biomarkers, that is, high-sensitivity troponin T and heart-type fatty acid-binding protein, and on N-terminal prohormone of brain natriuretic peptide as a biomarker of ventricular function in infants, diagnosed with ventricular septal defect, complete atrioventricular septal defect, and Tetralogy of Fallot undergoing corrective surgery with cardiopulmonary bypass. Plasma levels of cardiac biomarkers were measured prior to the initiation of cardiopulmonary bypass and 2, 6, and 24 hours after weaning from cardiopulmonary bypass. In both groups, the amount of high-sensitivity troponin T and heart-type fatty acid-binding protein were highest at 2 hours post cardiopulmonary bypass. In contrast, the maximum level of N-terminal prohormone of brain natriuretic peptide occurred at 24 hours post cardiopulmonary bypass. There was no statistically significant difference in the biomarkers' plasma levels between the study groups over time.[14]

After extensive review of the literature to our knowledge, there is no literature available in comparing Efficacy and Safety of Levosimendan with Milrinone in Tetralogy of fellow patients

# MATERIALS AND METHODS

**Study Design**: Prospective open label study.

**Study Setting**: This study was conducted in the Department of Anesthesiology, Cardiothoracic and Vascular Anaesthesia Division, *Sree Chitra Tirunal Institute for Medical Sciences and Technology*, Trivandrum, India – A tertiary referral center, university-level hospital, operating about 60-70 intra cardiac repairs for Tetralogy of Fallot cases per year)

**Ethical Considerations:**

The study was started after obtaining clearance from the Institutional Ethical Committee, (IEC Regn. No. ECR/189/Inst/KL/2013/RR-16), Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, India. (IEC certificate No.SCT/IEC/1395/August 2019)(Annexure , Pg.). The background, purpose, procedures involved in the study, measures which were taken to ensure confidentiality of the study participants, the voluntary nature of the study and applicability of findings were explained. The study complied with the revised Helsinki Declaration (2013) and Good Clinical Practice Guidelines.

Informed and written consent (Consent form, Annexure , Pg.. ) was sought from the participants of the study. The participants were informed of the purpose and importance of the study in English and Malayalam and were enrolled in the study only if they accepted. Those who declined to participate in the study underwent routine surgery as per institutional protocol.

**Study Participants**: 0-12 years age group scheduled to undergo corrective cardiac surgery for Tetralogy of Fallot were prospectively included in this study.

**Study Sample size:** Previous studies by Himanshu et al. in their Comparative study of Levosimendan versus milrinone for pediatric cardiac surgery patients taken 50 as total sample size and concluded that Levosimendan results in improved cardiac output by increasing stroke volume, improved Lactate clearance, significant lower requirement of pressor and significant lower arrhythmias(L-8%vsM24%) was observed in the Levosimendan group. Concerning the study mentioned earlier, to get a 16% difference in arrhythmia,5%significant and 90% study power required 20 subjects in each group and 40 as the total sample size. Patients fulfilling the inclusion criteria were selected for the proposed the study.

**Inclusion criteria**:

- All Patients admitted in the cardiac surgery intensive care after corrective cardiac surgery for Tetralogy of Fallot was included in the study
- Age group 0-12yrs with TOF

**Exclusion criteria:**

- **TOF** with other congenital cardiac anomalies
- History of anaphylactic reaction to Levosimendan or Milrinone
- Preoperative renal impairment.
- Preoperative hepatic impairment.

## Funding:

Funding is not required. The patients were not incurred additional expenses as ABG analysis is a part of routine postoperative management.

## The study protocols

- Patients/patient guardians were educated about the study. An informed consent form was signed by the patient or relative of the patient as per the Institute protocol.
- According to the inclusion criteria, patients were selected, and the inodilator (Levosimendan or Milrinone) received by a participant was decided by attending anesthesiologist and surgical team during a surgical time out, which is a routine institutional practice.
- Induction and myocardial protection strategy was similar in both groups
- Patients were monitored intraoperatively for ECG, heart rate, and mean arterial pressure.
- Baseline saturation and post-induction ABG was taken.
- TEE was used to measure restrictive RV physiology intraoperatively after TOF repair, like an end-diastolic forward flow in the pulmonary artery (PA) by Doppler echocardiography.
- In both the groups, stroke volume (SV), cardiac index/cardiac output CO, Tricuspid and mitral inflow E/A values, and RVOT to the pulmonary artery pressure gradient in immediate post-CPB was measured.

- Group L was received inj. Levosimendan 12 µg/kg iv. after cross-clamp removal followed by 0.1 µg/kg/min for 48 hrs.
- Group M was received inj. Milrinone 50 µg/kg of bolus dose after cross-clamp removal and followed by 0.5 µg/kg/min infusion for 48 hrs.
- In both groups, open label milrinone infusion was used as a rescue inodilator after 48 hrs. if required.
- After the surgery, patients were monitored for the urine output, Arterial blood gas, central venous saturation and lactate parameters in the postoperative period at an interval of 0,6,12,18, 24 ,36 and 48 hours after shifting to CHICU
- In CHICU, Transthoracic Echocardiography was done on POD 1, 2 &3 to evaluate Stroke volume (SV), cardiac index/cardiac output, Tricuspid and mitral inflow E/A values and RVOT to the pulmonary artery pressure gradient in both groups.

## The study groups

Two study groups:

1. **L-Group**: TOF patients managed postoperatively with intravenous Levosimendan infusion was included in this study
2. **M-Group**: TOF patients managed postoperatively with intravenous Milrinone infusion was included in this study

## Observations:

### Primary Observations:

I. LCOS:

a) Blood lactate levels

b) Central venous oxygen saturation

c) Arterial to central venous oxygen saturation difference

d) Urine output

e) Peripheral skin temperature to core body temperature

II. Arrhythmias in both Milrinone and Levosimendan: SVT, Ectopic atrial tachycardias, AF, accelerated junctional rhythms, JET, VT and VF.

### Secondary Observations:

1) Post repair evaluation of right ventricular restrictive physiology by measuring end-diastolic forward flow in the pulmonary artery (PA) by Doppler echocardiography,

2) Immediate Post CPB evaluation of Tricuspid and mitral inflow E/A values and RVOT to the pulmonary artery pressure gradient in both groups.

3) Rate pressure index during inodilator infusion

4) **Adverse events** due to inodilator infusions: Hypotension, hypokalemia, and thrombocytopenia

5) Transthoracic Echocardiography on POD 1,2 &3 to evaluate Tricuspid and mitral inflow E/A values and RVOT to the pulmonary artery pressure gradient in both groups.

6) Re-Interventions

7) Length of intensive care unit (ICU) stay.

8) Length of hospital stay.

9) Duration of mechanical ventilation

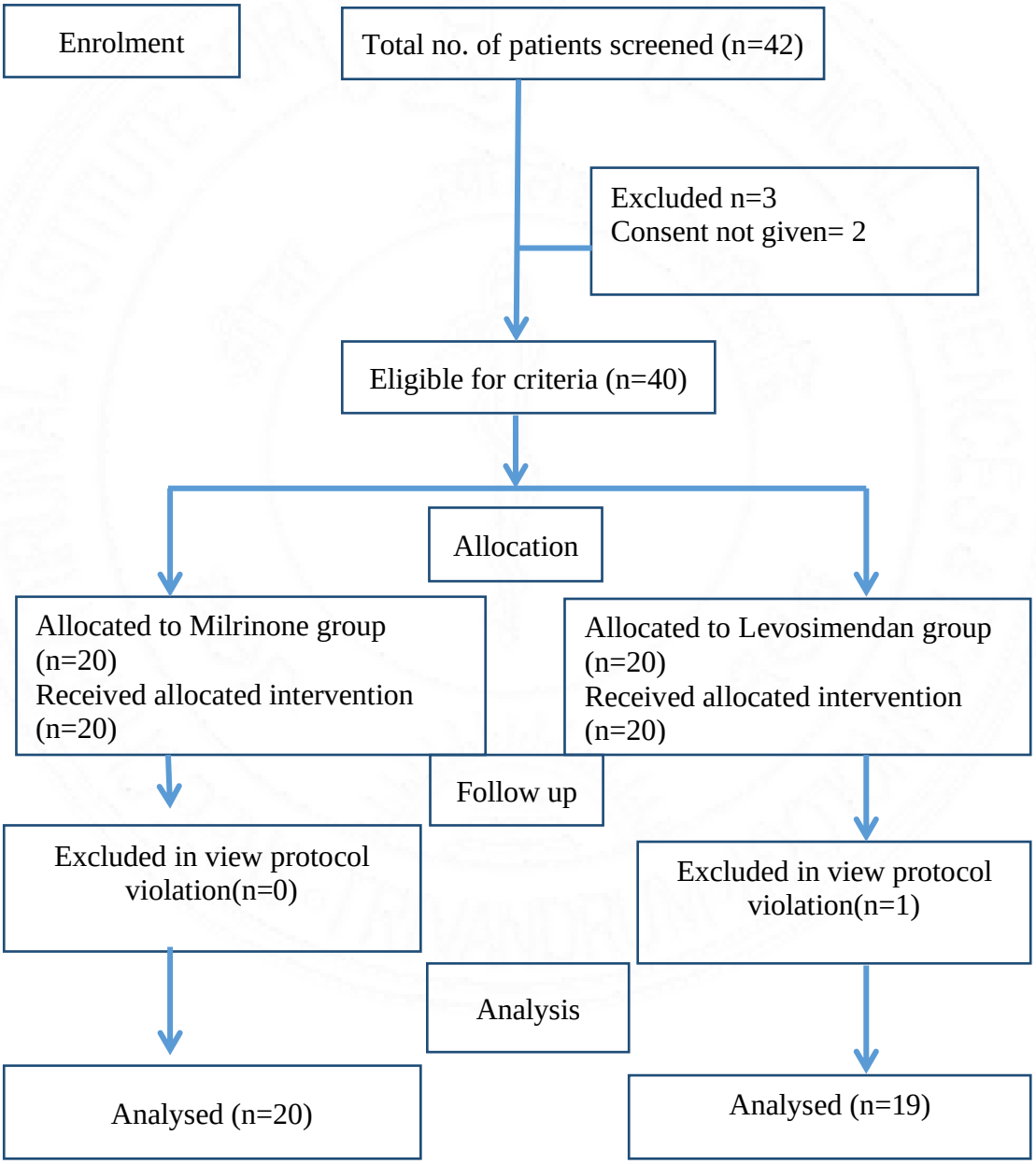
## Statistical analysis:

Statistical analysis was done from the collected data. Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables. Non normally distributed quantitative variables were summarized by median and interquartile range (IQR). Data was also represented using appropriate diagrams like bar diagrams, pie diagram and box plots. For normally distributed Quantitative parameters, the mean values were compared between the study groups using an Independent sample t-test (2 groups)P-value $< 0.05$ was considered statistically significant. IBM SPSS version 22 was used for statistical analysis.[13]

## RESULTS

A prospective randomised clinical trial was conducted in thirty-nine patients undergoing elective intracardiac repair for Tetralogy of Fallot from July 2019 to June 2021 in the congenital heart surgery operation theatres in Sree Chitra Tirunal Institute for Medical Sciences and Technology Thiruvananthapuram, Kerala, India.

**Figure 1:Consort diagram**



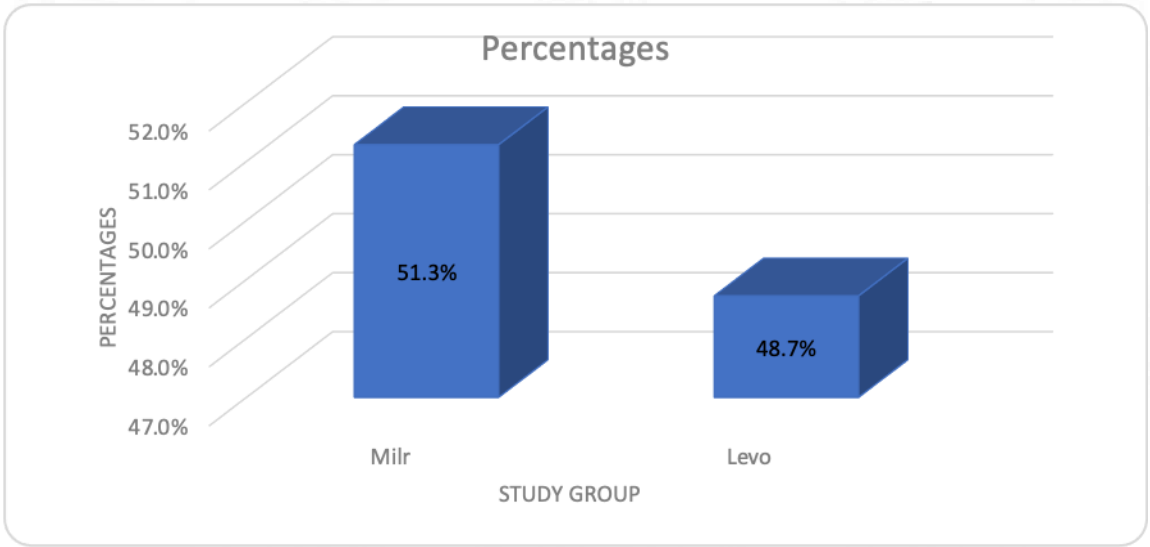
## Demographics of the study population

After obtaining Ethical Committee approval, 42 patients were screened, out of which 39 patients were randomized into Milrinone 20 (51.3%) and Levosimendan 19 (48.7%) groups. Table 1 and Figure 2 shows descriptive analysis of the study group in the study population.

**Table 1: Descriptive analysis of the study group in the study population (N=39)**

| The study group | Frequency | Percentage |
|---|---|---|
| Milrinone | 20 | 51.3% |
| Levosimendan | 19 | 48.7% |

**Figure 2: Bar chart of The study group in the study population (N=39)**




There was no statistically significant difference between the two groups as regards the demographic data. The demographic data in both the groups have been represented in Table 2

**Table 2: Demographic data of the study population**

| Parameter | Study group (Mean ± SD) | | P-value |
|---|---|---|---|
| | Milrinone (N=20) | Levosimendan (N=19) | |
| Age (months) | 20.55 ± 21.38 | 25.47 ± 30.78 | 0.564 |
| Male¥ | 10 (50%) | 11 (57.89%) | 0.621 |
| Female¥ | 10 (50%) | 8 (42.11%) | |
| Weight (kg) | 10.33 ± 5.79 | 10.08 ± 6.1 | 0.897 |
| Height (cm) | 79.6 ± 19.05 | 79.37 ± 18.01 | 0.969 |
| BSA (kg/m2) | 0.47 ± 0.18 | 0.46 ± 0.18 | 0.898 |

Data expressed as mean± SD for quantitative variables and ¥ - qualitative data defined as number (percentage). P<0.05 is considered statistically significant.

BSA – Body Surface Area ($m^2$).

**Baseline $o_2$ saturation & Haemogram** :

We Compared two groups for mean baseline O2 saturation and Preoperative haemoglobin, Total leucocyte count and platelet count. The mean baseline saturation in groups M and L were 83.95 ± 10.65 and 82.16 ± 7.29, respectively. They were comparable in both groups (p=0.546).Pre-operative haemogram (15.07 ± 2.16 ,in group M and 15.24 ± 3.13 in group L , p=0.842),Total leucocyte count (10275.5 ± 2363.59 Cells/Cumm in group M and 10228.95 ± 3668.69 Cells/Cumm in group L,p=0.962) and Platelet count (3.53 ± 1.45 Lakhs/Cumm in group M and 3.04 ± 0.82 in group L, p=0.204) were comparable in both groups.

**Table 3: Comparison of mean of baseline O2 saturation%, HB, TLC and platelets between the study group (N=39)**

| Parameter | Study group (Mean± SD) | | P-value |
|---|---|---|---|
| | Milrinone(N=20) | Levosimendan(N=19) | |
| Baseline O2 saturation % | 83.95 ± 10.65 | 82.16 ± 7.29 | 0.546 |
| Pre-op HB(g%) | 15.07 ± 2.16 | 15.24 ± 3.13 | 0.842 |
| TLC cells/Cumm | 10275.5 ± 2363.59 | 10228.95 ± 3668.69 | 0.962 |
| Platelets Lakhs/Cumm | 3.53 ± 1.45 | 3.04 ± 0.82 | 0.204 |

Data expressed as mean± SD for quantitative variables . P<0.05 was considered statistically significant.

HB-Haemogram, TLC-Total leucocyte count.

## Intraoperative variables

In our institute, two surgical procedures were performed in Tetralogy of Fallot patients based on intraoperative pulmonary valve inspection. Patient with normal morphological pulmonary valve underwent Intra Cardiac Repair (ICR), consisting of VSD closure and Right ventricular outflow tract (RVOT) patch closure. Patients with abnormal pulmonary valve anatomy underwent intracardiac repair, Trans Annular Patch closure with Mono cusp reconstruction (ICR+TAP+MCR). The two groups were compared in surgical procedures performed. The % of ICR was 60% in group M and 78.95% in group L. Similarly, ICR +TAP+MCR was 40% in group M compared with 21.05% in group L . There was no statistically significant difference between

both groups with p=0.2. Comparison of surgery between groups was depicted in stacked bars in figure 3.

**Table 4: Comparison of surgery between the study group (N=39)**

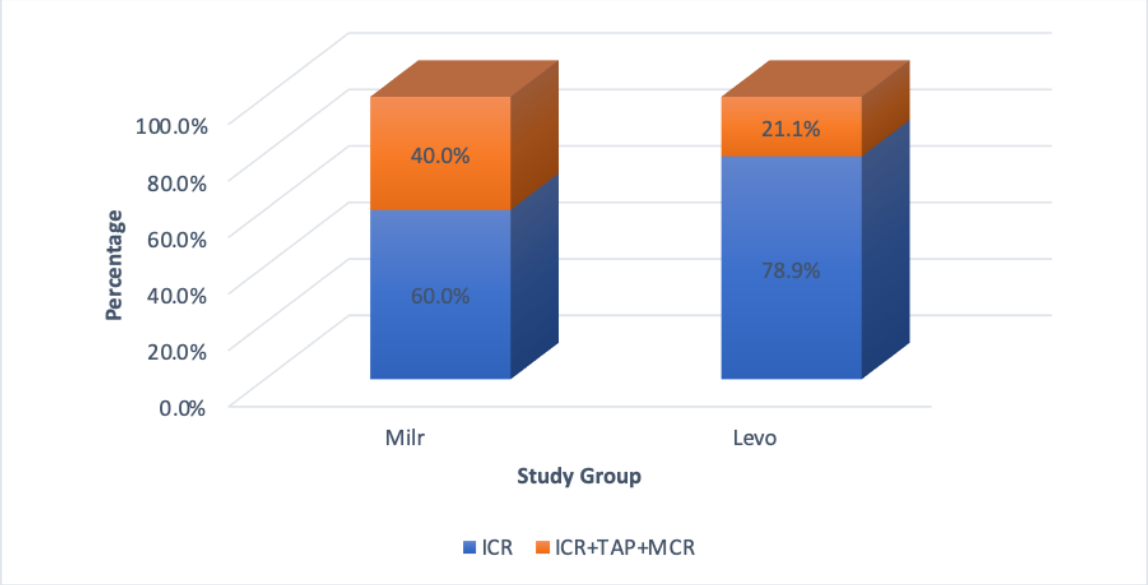
| Surgery | Study Group | | Chi-square | P-value |
|---|---|---|---|---|
| | Milrinone(N=20) | Levosimendan(N=19) | | |
| ICR | 12 (60%) | 15 (78.95%) | 1.642 | 0.200 |
| ICR +TAP+MCR | 8 (40%) | 4 (21.05%) | | |

Data expressed as number (percentage). P<0.05 considered statistically significant

ICR: Intra Cardiac Repair

ICR+TAP+MCR: Intracardiac repair +Trans Annular Patch closure + Mono cusp reconstruction

**Figure 3: Stacked bar chart of comparison of surgery between the study group (N=39)**



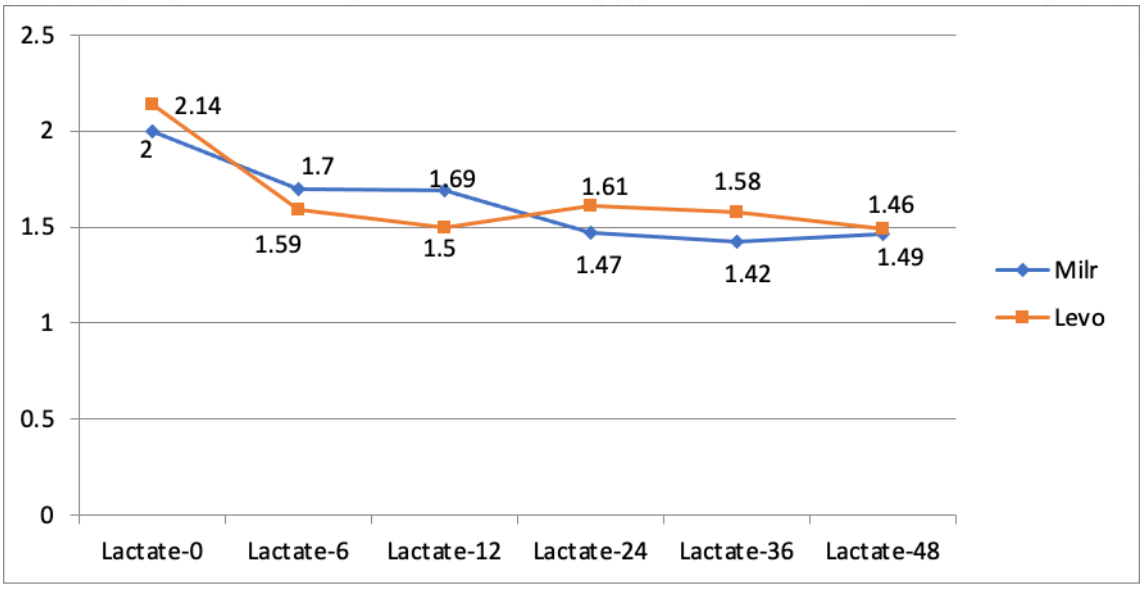

**Primary outcomes:**

**Lactate clearance :** There was no statistically significant difference in Mean Lactate level at every time point between the study groups with (P-value > 0.05) (Table 5 & Figure 4)

**Table 5: Comparison of mean of lactate mmol/L at different periods between the study groups (N=39)**

| Parameter | Study group (Mean± SD) | | P-value |
|---|---|---|---|
| | M (N=20) | L (N=19) | |
| Lactate-0 hrs | 2 ± 0.69 | 2.14 ± 0.67 | 0.535 |
| Lactate-6 hrs | 1.7 ± 1.06 | 1.59 ± 0.73 | 0.722 |
| Lactate-12 hrs | 1.69 ± 1.19 | 1.5 ± 0.48 | 0.522 |
| Lactate-24 hrs | 1.47 ± 0.5 | 1.61 ± 0.66 | 0.458 |
| Lactate-36 hrs | 1.42 ± 0.45 | 1.58 ± 0.61 | 0.362 |
| Lactate-48 hrs | 1.46 ± 0.53 | 1.49 ± 0.59 | 0.847 |

**Figure 4: Line chart for comparison of mean Lactate levels between The study group (N=39)**

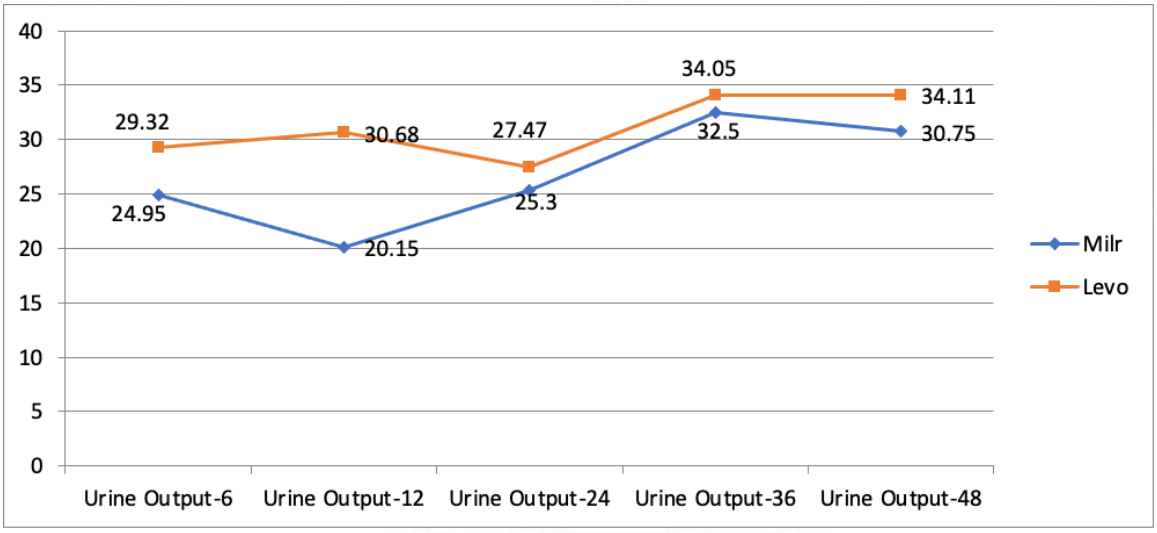


**Urine output:** There was no statistically significant difference in Mean Urine Output at every time points between The study group with (P-value > 0.05) (Table 6 & Figure 5)

**Table 6: Comparison of mean of urine output ml/hr at different time points between the study groups (N=39)**

| Parameter | Study group (Mean± SD) | | P-value |
|---|---|---|---|
| | M (N=20) | L(N=19) | |
| Urine Output-6 | 24.95 ± 23.24 | 29.32 ± 15.51 | 0.497 |
| Urine Output-12 | 20.15 ± 16.11 | 30.68 ± 20.97 | 0.086 |
| Urine Output-24 | 25.3 ± 19.22 | 27.47 ± 20.66 | 0.736 |
| Urine Output-36 | 32.5 ± 17.72 | 34.05 ± 21.92 | 0.809 |
| Urine Output-48 | 30.75 ± 17.1 | 34.11 ± 24.69 | 0.623 |

**Figure 5: Line chart for comparison of mean Lactate levels between The study group (N=39)**

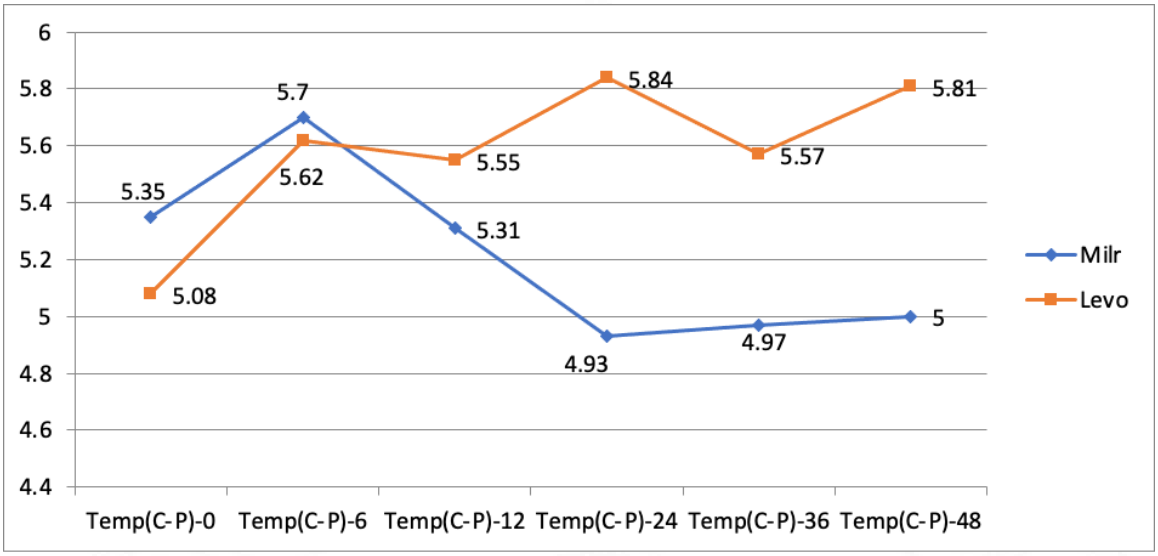


**The core to peripheral temperature (Temp C-P) difference:** There was no statistically significant difference in Mean Temp(C-P) at every time points between The study group with (P-value > 0.05) (Table 7& Figure 6)

**Table 7: Comparison of mean of the core to peripheral temperature (Temp C-P) in ºC difference at different time points between the study group(N=39)**

| Parameter | Study group (Mean± SD) | | P-value |
|---|---|---|---|
| | M (N=20) | L(N=19) | |
| Temp(C-P)-0 | 5.35 ± 1.85 | 5.08 ± 2.07 | 0.675 |
| Temp(C-P)-6 | 5.7 ± 2.67 | 5.62 ± 1.97 | 0.917 |
| Temp(C-P)-12 | 5.31 ± 2.39 | 5.55 ± 1.5 | 0.702 |
| Temp(C-P)-24 | 4.93 ± 2.39 | 5.84 ± 2.09 | 0.213 |
| Temp(C-P)-36 | 4.97 ± 2.01 | 5.57 ± 1.76 | 0.327 |
| Temp(C-P)-48 | 5 ± 1.98 | 5.81 ± 1.94 | 0.204 |

**Figure 6: Line chart for comparison of the mean core to peripheral temperature (c-p) difference between The study group (N=39)**

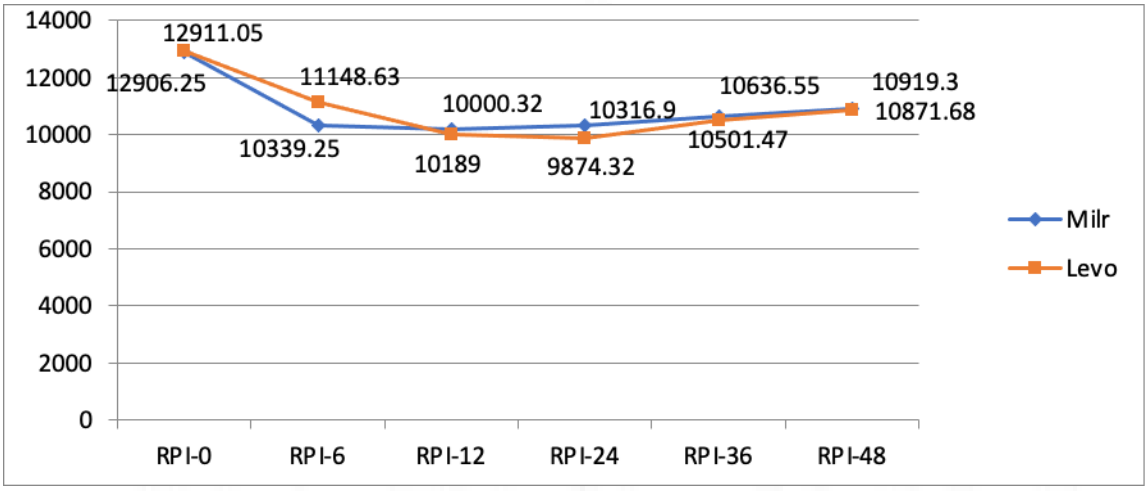



**Rate pressure index (RPI) :**There was no statistically significant difference in Mean Rate pressure index **(**RPI) at every time point between The study group with (P-value > 0.05) (Table 8 & Figure 7)

**Table 8: Comparison of mean of Rate pressure index (RPI) at different time points between the study group(N=39)**

| **Parameter** | **Study group (Mean± SD)** | | **P-value** |
|---|---|---|---|
| | **M(N=20)** | **L(N=19)** | |
| RPI-0 | 12906.25 ± 2806.49 | 12911.05 ± 1452.71 | 0.995 |
| RPI-6 | 10339.25 ± 1876.22 | 11148.63 ± 2168.31 | 0.220 |
| RPI-12 | 10189 ± 1027.35 | 10000.32 ± 1188.4 | 0.598 |
| RPI-24 | 10316.9 ± 1546.78 | 9874.32 ± 1523.9 | 0.374 |
| RPI-36 | 10636.55 ± 1605.91 | 10501.47 ± 1988.25 | 0.816 |
| RPI-48 | 10919.3 ± 1889.42 | 10871.68 ± 2136.46 | 0.942 |

**Figure 7: Line chart for comparison of mean temp(c-p) between The study group (N=39)**

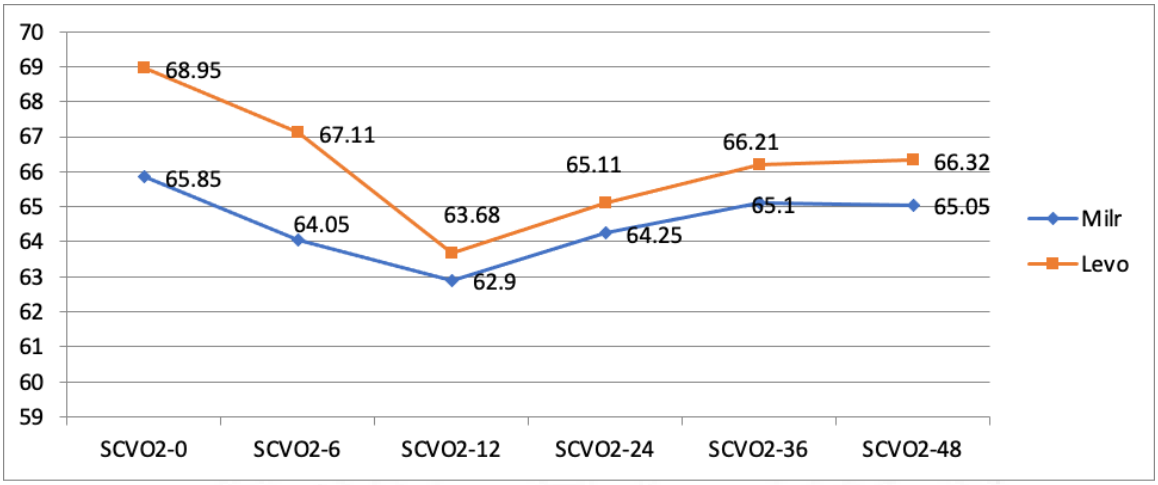



**Central venous oxygen saturation (SCVO2:** There was no statistically significant difference in Mean SCVO2at every time points between The study group with (P-value > 0.05) (Table 9& Figure 8)

**Table 9: Comparison of mean of Central venous oxygen saturation (SCVO2 )% at different time points between the study group(N=39)**

| **Parameter** | **Study group (Mean± SD)** | | **P-value** |
|---|---|---|---|
| | **M(N=20)** | **L(N=19)** | |
| SCVO2-0 | 65.85 ± 9.28 | 68.95 ± 7.55 | 0.261 |
| SCVO2-6 | 64.05 ± 7.81 | 67.11 ± 5.44 | 0.167 |
| SCVO2-12 | 62.9 ± 7.05 | 63.68 ± 5.64 | 0.704 |
| SCVO2-24 | 64.25 ± 4.24 | 65.11 ± 3.81 | 0.513 |
| SCVO2-36 | 65.1 ± 6.5 | 66.21 ± 4.16 | 0.531 |
| SCVO2-48 | 65.05 ± 5.12 | 66.32 ± 3.86 | 0.391 |

**Figure 8: Line chart for comparison of mean SCVO2 between The study group (N=39)**

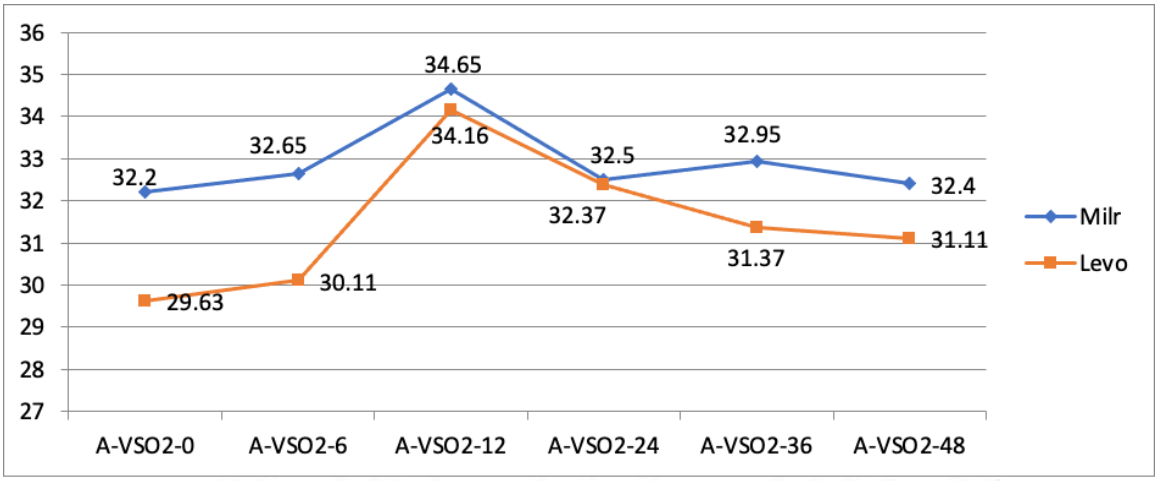



**Arterio-venous oxygen saturation difference (A-VSO2):** There was no statistically significant difference in Mean A-VSO2 at every time point between The study group with (P-value > 0.05) (Table 10 & Figure 9)

**Table 10: Comparison of mean of arterio-venous oxygen saturation % difference (A-VSO2) at different time points between the study group (N=39)**

| Parameter | Study group (Mean± SD) | | P-value |
|---|---|---|---|
| | M(N=20) | L(N=19) | |
| A-VSO2-0 | 32.2 ± 7.32 | 29.63 ± 7.57 | 0.289 |
| A-VSO2-6 | 32.65 ± 7.63 | 30.11 ± 5.65 | 0.246 |
| A-VSO2-12 | 34.65 ± 6.72 | 34.16 ± 4.91 | 0.796 |
| A-VSO2-24 | 32.5 ± 5.09 | 32.37 ± 3.56 | 0.926 |
| A-VSO2-36 | 32.95 ± 7.19 | 31.37 ± 3.92 | 0.403 |
| A-VSO2-48 | 32.4 ± 5.34 | 31.11 ± 4.37 | 0.414 |

**Figure 9: Line chart for comparison of mean A-VSO2 between The study group (N=39)**



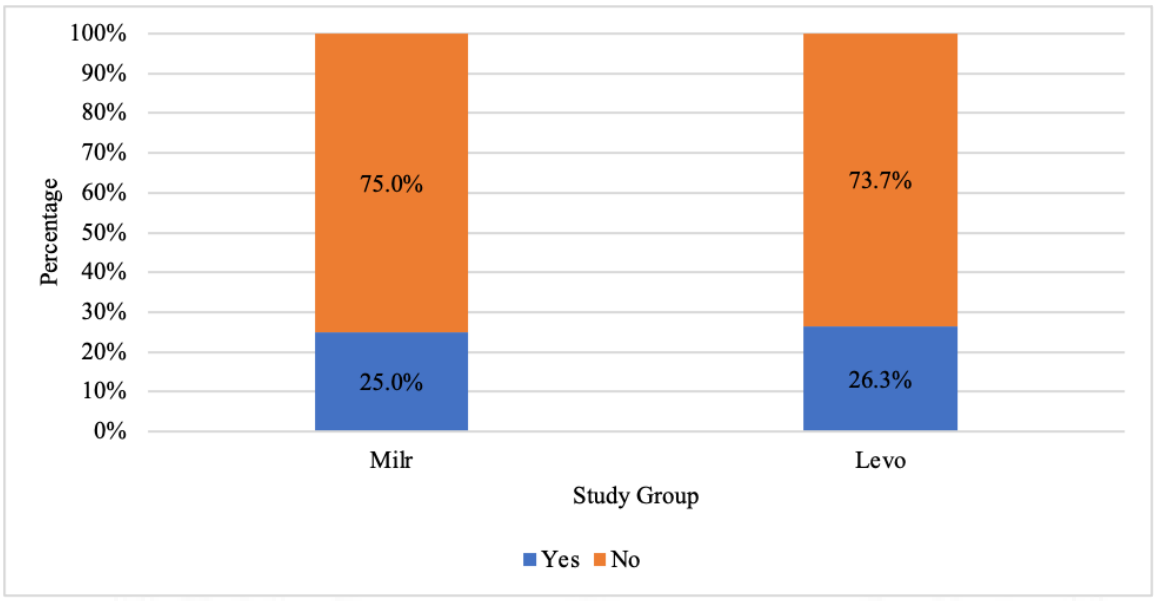

**Arrhythmias:** There was no statistically significant difference in Arrhythmias between the study group with P-value 1.00). (Table 11& Figure 10)

**Table 11: Comparison of arrhythmias between the study group (N=39)**

| **Arrhythmias** | **Study Group** | | **Chi-square** | **Fisher exact P-value** |
|---|---|---|---|---|
| | **M(N=20)** | **L(N=19)** | | |
| Yes | 5 (25%) | 5 (26.32%) | 0.009 | 1.000 |
| No | 15 (75%) | 14 (73.68%) | | |

There was no statistically significant difference in Arrhythmias between the study group with P-value 1.00). (Table 11& Figure 10)

**Figure Stacked bar chart of comparison of arrhythmias between the study group (N=39)**



## Secondary outcomes:

**Post repair diastolic forward flow in pulmonary artery:** Post repair diastolic forward flow in pulmonary artery represents right restrictive ventricular physiology in Tetralogy of Fallot. There was no statistically significant difference in Diastolic Forward Flow between the Study groups with P-value 0.605). (Table 12& Figure 11)

**Table 12: Comparison of Post repair diastolic forward flow in pulmonary artery between the study group (N=39)**

| **Dias Forward Flow** | **Study Group** | | **Chi square** | **Fisher exact P-value** |
|---|---|---|---|---|
| | **M (N=20)** | **L(N=19)** | | |
| Yes | 3 (15%) | 1 (5.26%) | 1.004 | 0.605 |
| No | 17 (85%) | 18 (94.74%) | | |

**Figure 11: Stacked bar chart of comparison Post repair diastolic forward flow in pulmonary artery between the study group (N=39)**


**Post CPB RV -PA Peak gradient:** There was no statistically significant difference in Mean RV -PA Peak gradient -POST CPB TEE between the study group with (P-value 0.371). There was no statistically significant difference in Mean RV -PA Peak gradient -POD1(TTE) between the study group with (P-value 0.293). There was no statistically significant difference in Mean RV -PA Peak gradient GD-POD2(TTE)between The study groups (P-value 0.314). There was no statistically significant difference in Mean RV -PA Peak gradient -POD3(TTE) between The study group with (P-value 0.181) (Table 13& Figure 12 to 15)

**Table 13: Comparison of Post CPB average RV -PA Peak gradient in mm of hg at a different POD (TEE) follow-ups between the study groups (N=39)**

| Parameter | Study group (Mean± SD) | | P-value |
|---|---|---|---|
| | M(N=20) | L(N=19) | |
| RVOT -PA PEAK GD-POST CPB TEE | 20.05 ± 8.84 | 17.26 ± 10.36 | 0.371 |
| RVOT PA GD-POD1(TTE) | 19.1 ± 10.16 | 15.47 ± 11.07 | 0.293 |
| RVOT PA GD-POD2(TTE) | 17.6 ± 9.81 | 14.16 ± 11.23 | 0.314 |
| RVOT PA GD-POD3(TTE) | 20.25 ± 12.88 | 14.84 ± 11.83 | 0.181 |

**Figure 12: Bar chart of comparison of mean RV -PA Peak gradient -POST CPB TEE between the study group (N=39)**

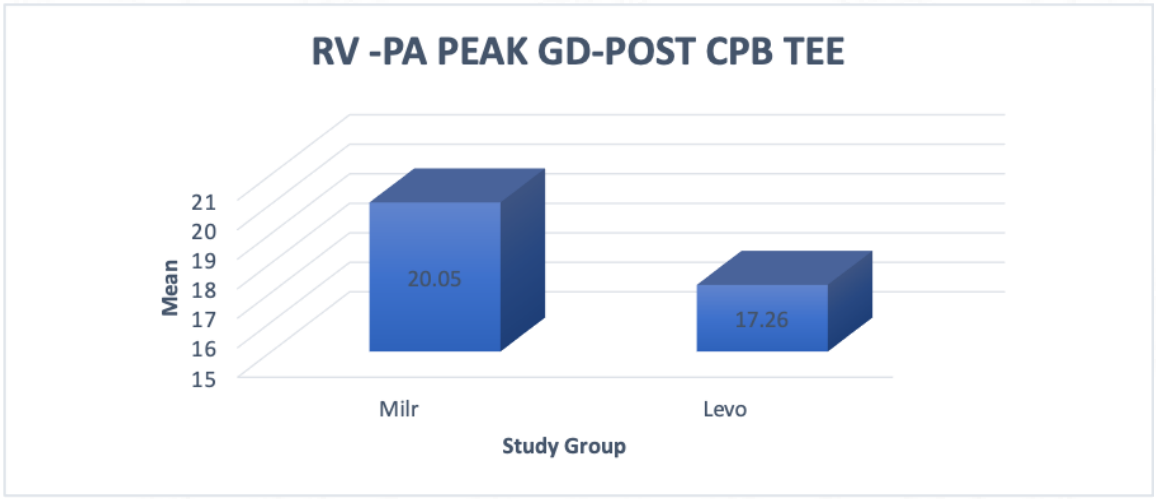


**Figure 13: Bar chart of comparison of** mean RV -PA Peak gradient **-POD 1 (TTE) between the study group (N=39)**

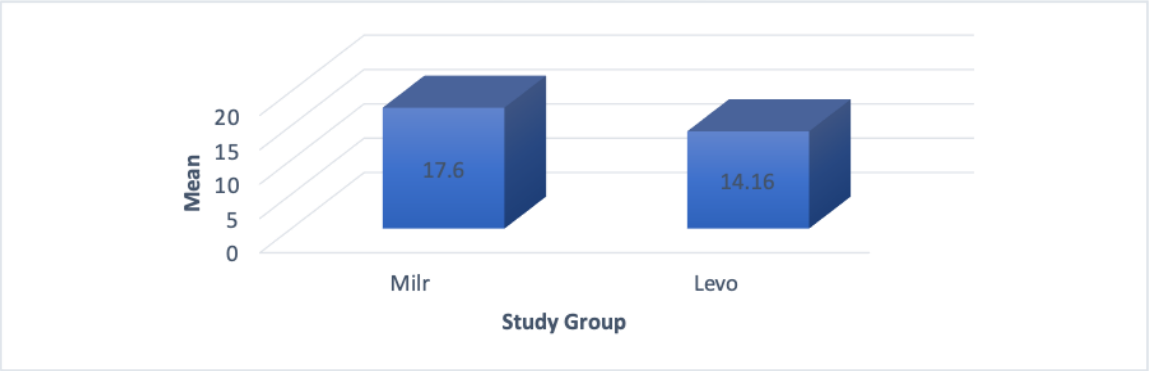



**Figure 14: Bar chart of comparison of mean RV -PA Peak gradient -POD2 (TTE) between the study group (N=39)**

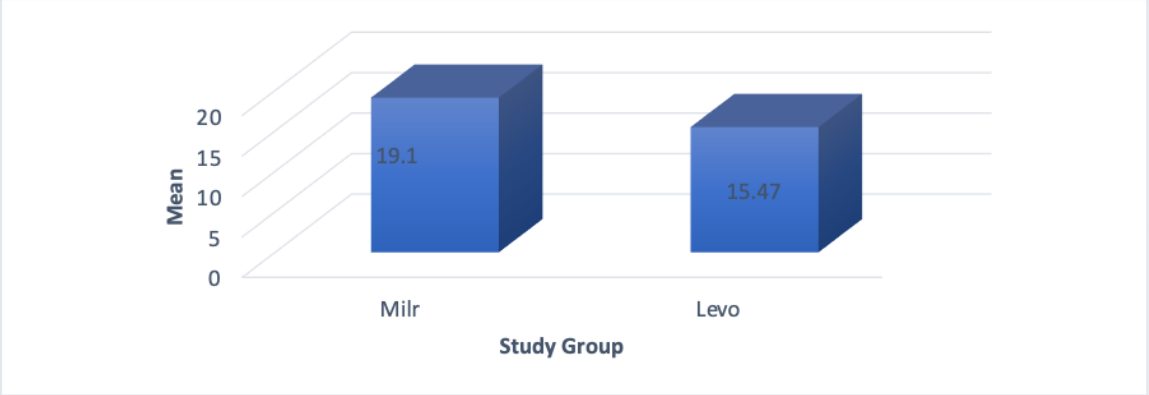
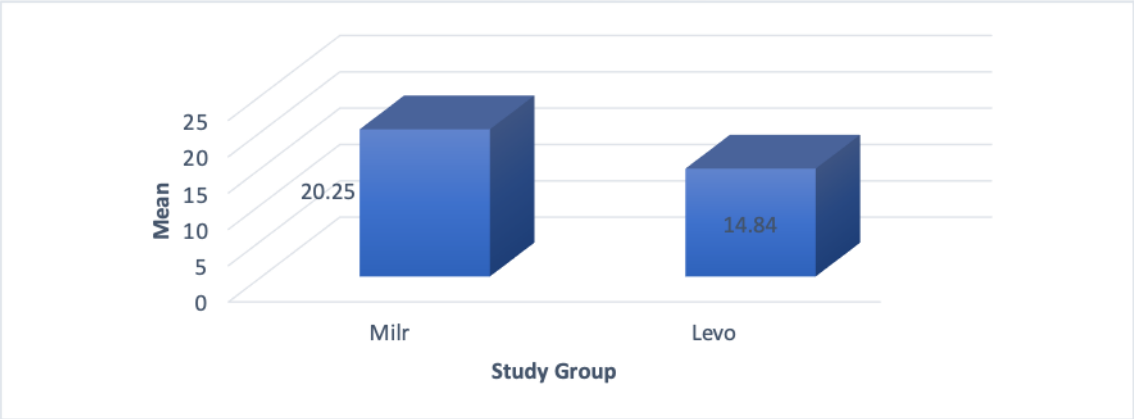


**Figure 15: Bar chart of comparison of mean RV -PA Peak gradient -POD 3(TTE) between the study group (N=39)**




**Patent foramen ovale (PFO) in post CPB TEE:** Among the study group with Milrinone, 6(30%) participants had L-R PFO and 1(5%) participants had R-L PFO and Among the study group with Levosimendan, 12(63.16%) participants had L-R PFO and no participant had R-L (Table 14 & Figure 16 )

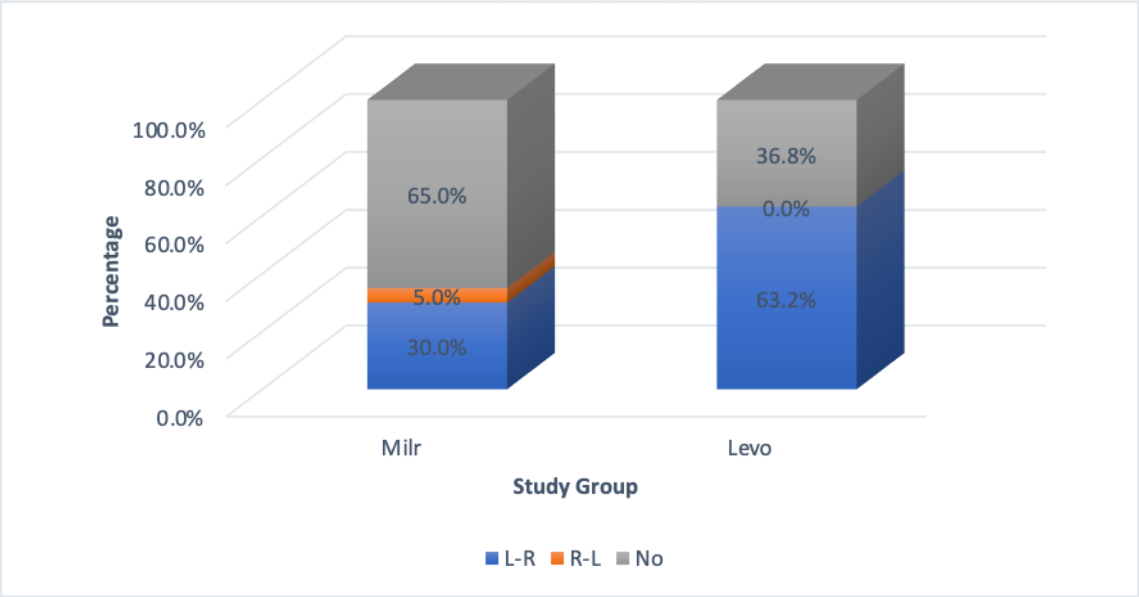
**Table 14: Comparison of Patent foramen ovale (PFO) in post CPB TEE between the study group (N=39)**

| **POST CPB(TEE) - PFO** | **Study Group** | |
|---|---|---|
| | **M(N=20)** | **L(N=19)** |
| L-R | 6 (30%) | 12 (63.16%) |
| R-L | 1 (5%) | 0 (0%) |
| No | 13 (65%) | 7 (36.84%) |

*No statistical test was applied- due to 0 subjects in the cells

L-R= Left to right shunt, R-L= Right to left shunt

**Figure 16: Stacked bar chart of comparison of PFO in post CPB TEE between the study group (N=39)**

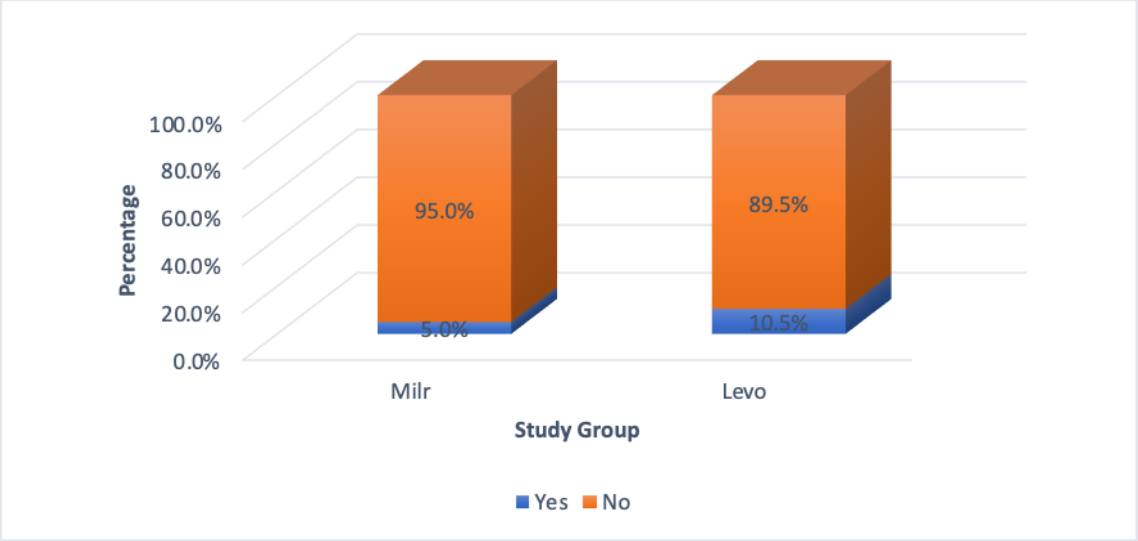



**Reintervention:** There was no statistically significant difference in Re Intervention Flow between the study group with (P-value 0.605). (Table 15 & Figure 17)

**Table 15: Comparison of reintervention between the study group (N=39)**

| **Re Intervention** | **Study Group** | | **Chi-square** | **Fisher exact P-value** |
|---|---|---|---|---|
| | **M (N=20)** | **L(N=19)** | | |
| Yes | 1 (5%) | 2 (10.53%) | 0.419 | 0.605 |
| No | 19 (95%) | 17 (89.47%) | | |

**Figure 17: Stacked bar chart of comparison of reintervention between the study group (N=39)**




**Postoperative outcomes:** There was no statistically significant difference in Mean LOS-ICU In Days between The study group with (P-value 0.167). There was no statistically significant difference in Mean LOS-Hospital In Days between The study group with (P-value 0.311). There was no statistically significant difference in Mean Duration Of Mech Ventilation between The study group with (P-value 0.181) (Table 16 & Figure 18 to 20)

**Table 16: Comparison of mean of Length of stay (LOS)- ICU in days, LOS-hospital in days & Duration Of Mech Ventilation between the study group(N=39)**

| Parameter | Study group (Mean± SD) | | P-value |
|---|---|---|---|
| | M (N=20) | L(N=19) | |
| LOS-ICU In Days | 4.75 ± 2 | 3.95 ± 1.51 | 0.167 |
| LOS-Hospital In Days | 7.05 ± 1.76 | 6.47 ± 1.74 | 0.311 |
| Duration Of Mech. Ventilation | 23.9 ± 20.71 | 16.68 ± 11.05 | 0.186 |

**Figure 18: Bar chart of comparison of mean Los-ICU in Days between the study group (N=39)**

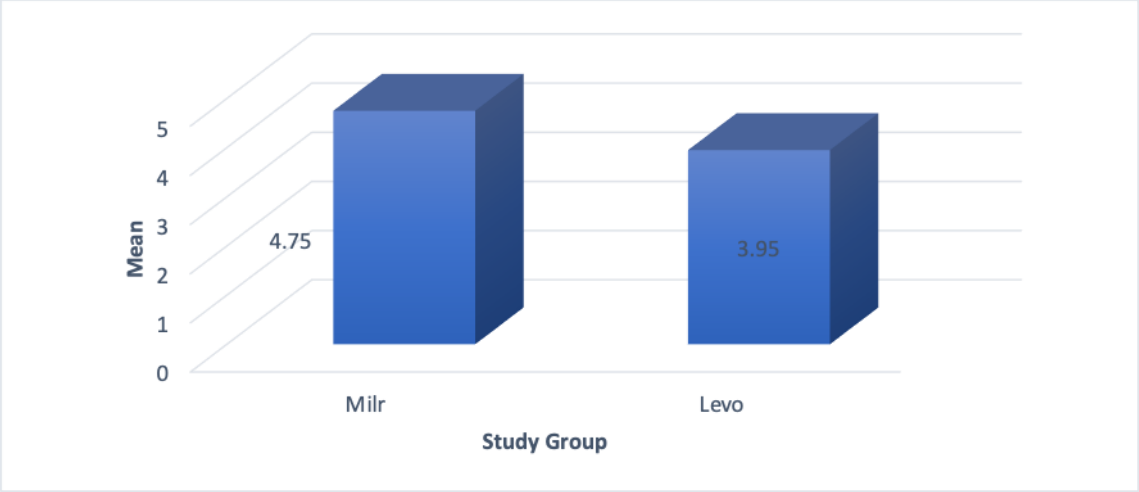



**Figure 19: Bar chart of comparison of mean LOS-hospital in days between the study group (N=39)**

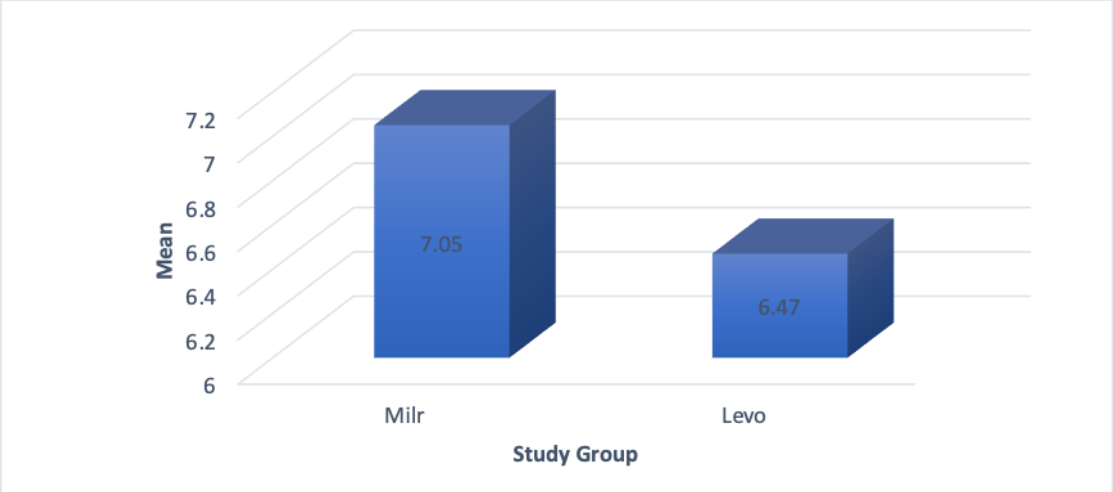
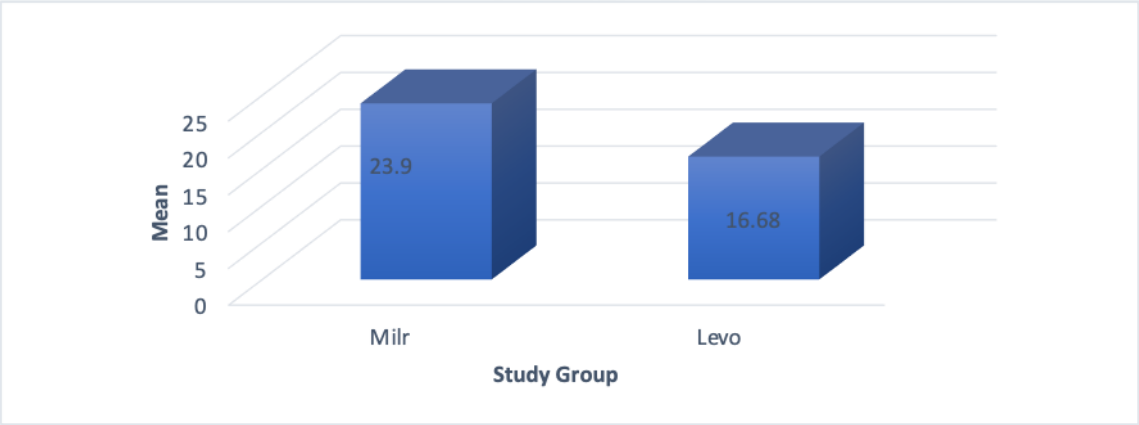


**Figure 20: Bar chart of comparison of mean duration of mech ventilation between the study group (N=39)**




**Chest Drain:** There was no statistically significant difference in Mean Duration Of Chest Drain (Hours) between The study group with (P-value 0.794). There was no statistically significant difference in Mean Chest Drain (ml/Kg) between The study group with (P-value 0.549). (Table 17 & Figure 21 & 22)

**Table 17: Comparison of mean of duration of Chest Drain ( Hrs) & Chest Drain (ml/Kg)between the study group(N=39)**

| **Parameter** | **Study Group (Mean± SD)** | | **P-value** |
|---|---|---|---|
| | **M(N=20)** | **L(N=20)** | |
| Duration Of Chest Drain( Hrs) | 40.65 ± 29.57 | 38.58 ± 17.72 | 0.794 |
| Chest Drain (Ml/Kg) | 33.3 ± 13.43 | 29.95 ± 20.61 | 0.549 |

**Figure 21: Bar chart of comparison of mean Duration Of Chest Drain( Hrs) between the study group (N=39)**

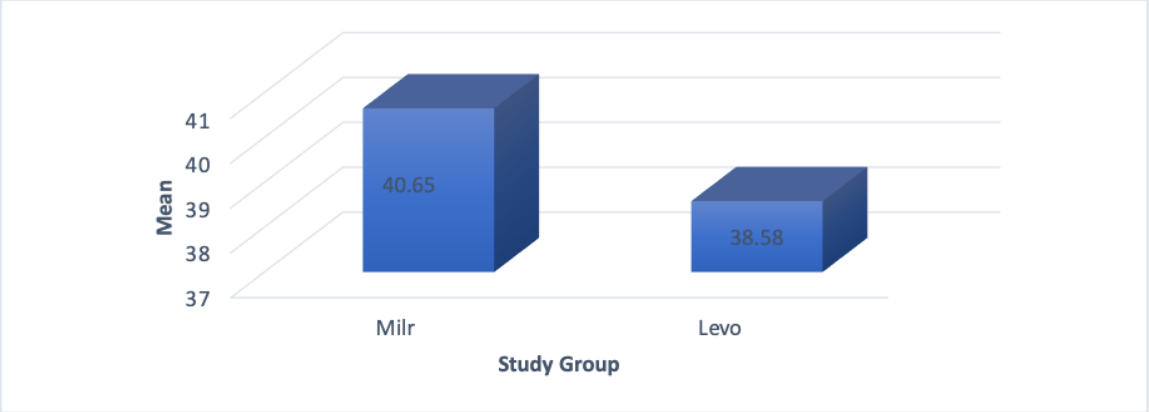
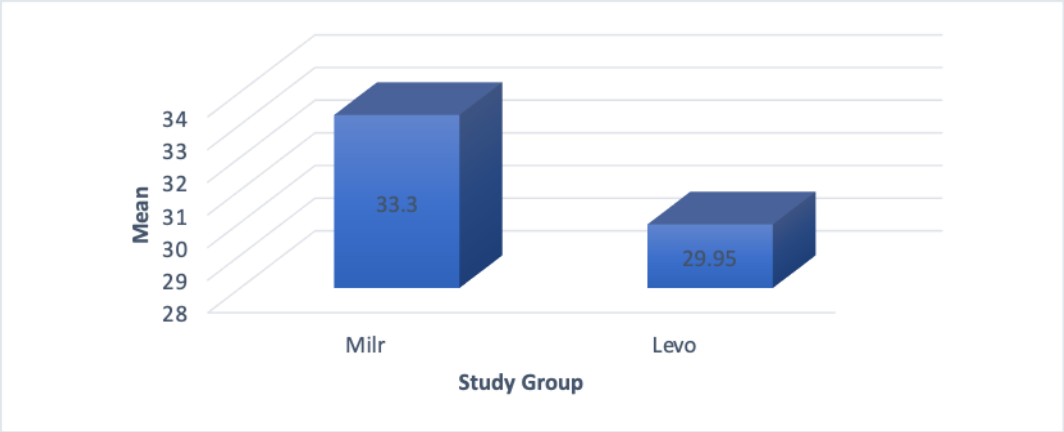



**Figure 22: Bar chart of comparison of mean Chest Drain (ml/Kg) between the study group (N=39)**



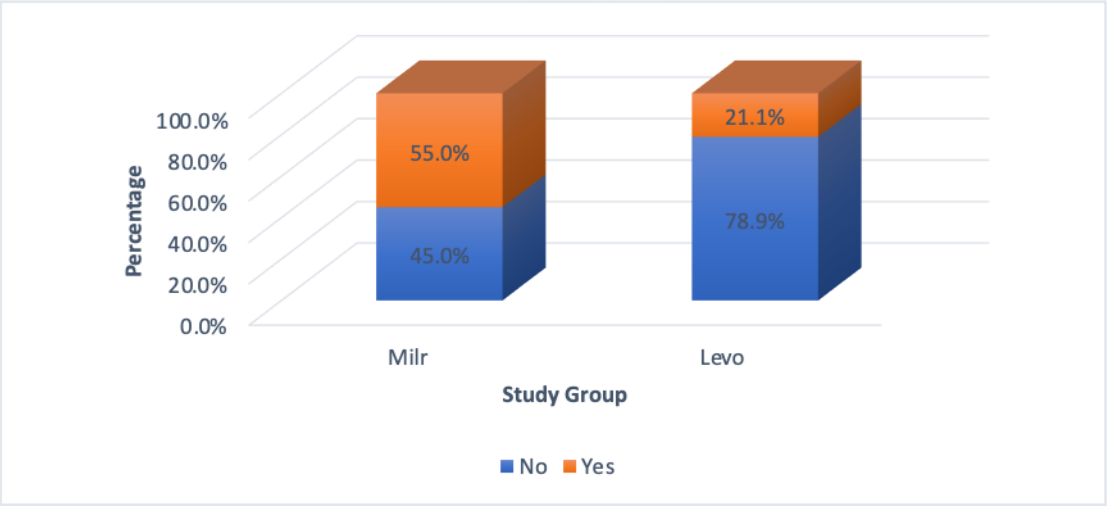
**Rescue Milrinone:** In the Milrinone group 55% of patients required rescue milrinone infusions after 48hr infusion of Milrinone compared with 21% in the Levosimendan group. There was a statistically significant difference in Rescue Milrinone requirement between the study group with **a** P-value of 0.029). (Table 18 & Figure 23)

**Table 18: Comparison of number of patient required Rescue Milrinone in between the study group (N=39)**

| **Rescue Milrinone** | **Study Group** | | **Chi square** | **P-value** |
|---|---|---|---|---|
| | **M(N=20)** | **L(N=19)** | | |
| No | 9 (45%) | 15 (78.95%) | 4.744 | 0.029 |
| Yes | 11 (55%) | 4 (21.05%) | | |

In the Milrinone group 55% of patients required rescue milrinone infusions after 48hr infusion of Milrinone compared with 21% in the Levosimendan group. There was a statistically significant difference in Rescue Milrinone requirement between the study group with **a** P-value of 0.029). (Table 18 & Figure 23)

**Figure 23: Stacked bar chart of comparison of the number of patients required Rescue Milrinone between the study group (N=39)**



**Vasoactive agents:** Levosimendan group required significantly less Total mean Noradrenaline 23.5 ± 2.68 µg compared with Milrinone group 72.15 ± 68.72 µg. with P-value 0.016 . There was no statistically significant difference in Total Mean Adrenaline between the study group with (P-value 0.18). There was no statistically significant difference in Mean Vasopressin between the study group with (P-value 0.562) (Table 19 & Figure 24 to 26)

**Table 19: Comparison of mean amount of Noradrenaline(NORADR), Adrenaline(ADR) and Vasopressin in between the study group (N=39)**

| Parameter | Study group (Mean± SD) | | P-value |
|---|---|---|---|
| | M (N=20) | L (N=20) | |
| Noradrenaline (µg) | 72.15 ± 68.72 | 23.5 ± 2.68 | 0.016 |
| Adrenaline(µg) | 16.35 ± 42.53 | 2.68 ± 11.70 | 0.185 |
| Vasopressin | 0.07 ± 0.21 | 0.0 ± 0.00 | 0.562 |

**Figure 24: Bar chart of comparison of mean NORADR between the study group (N=39)**

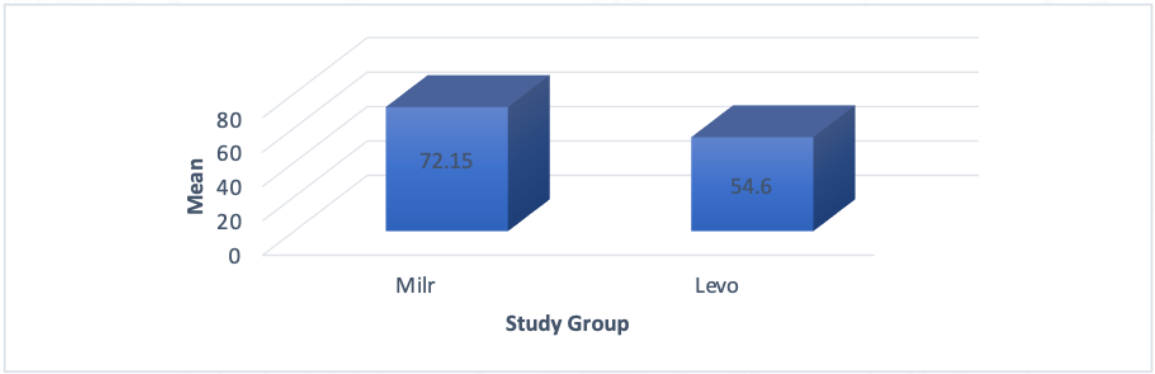


**Figure 25: Bar chart of comparison of mean ADR between the study group (N=39)**

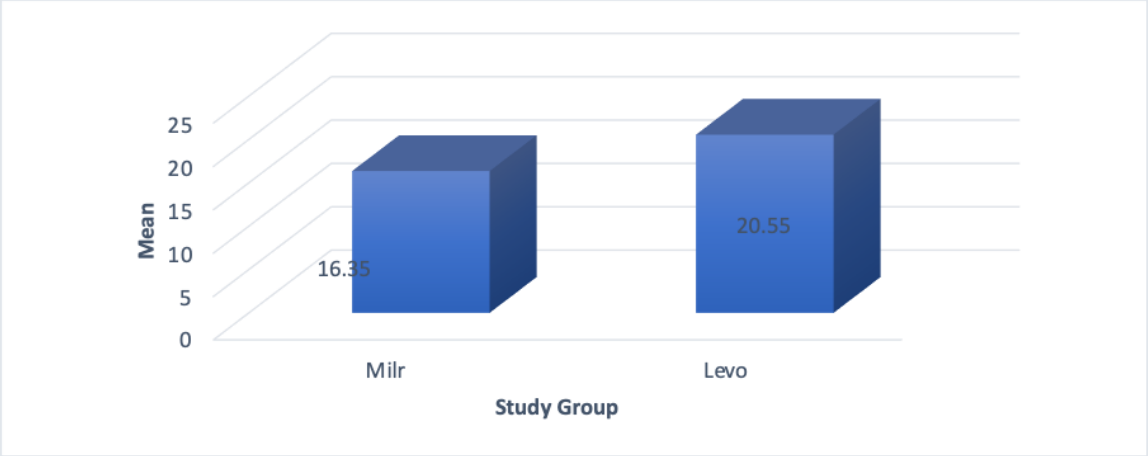
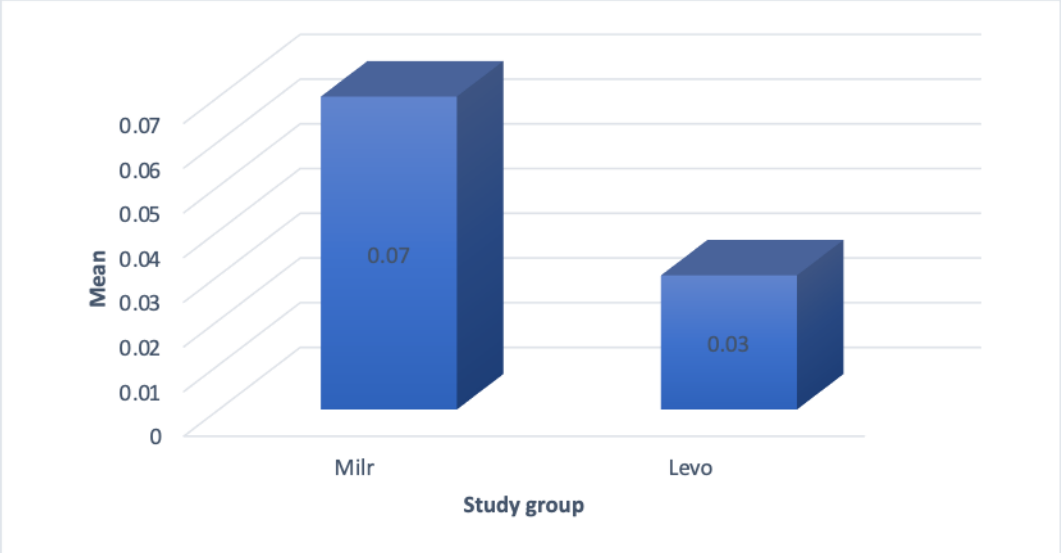



**Figure 26: Bar chart of comparison of mean Vasopressin between the study group (N=39)**

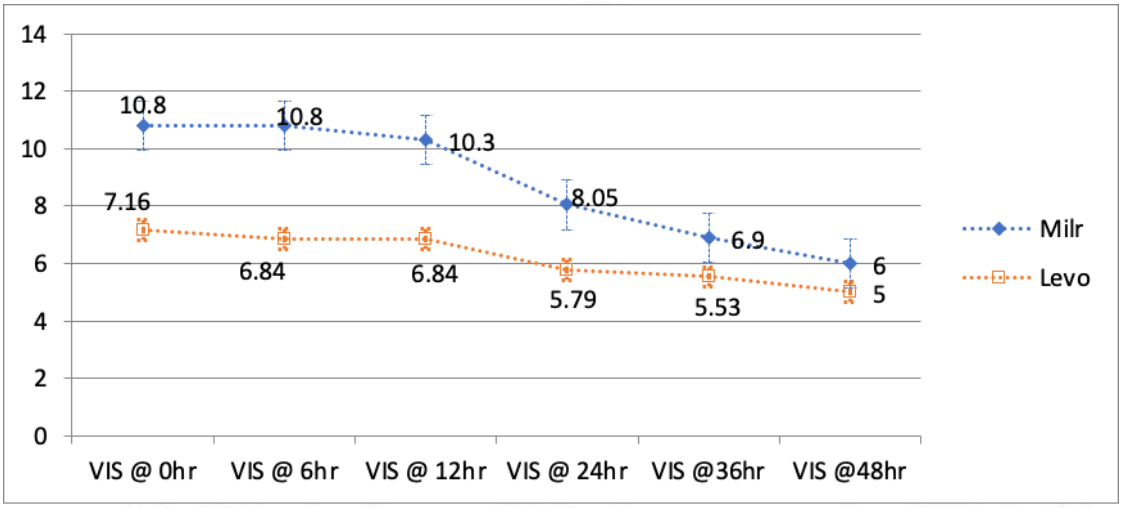


**Vasoactive inotrope score (VIS):** Patients in the Levosimendan group required statistically significant less amount of vasoactive agents requirement at 0 hr, 6 hr and 12hrs after surgery than the milrinone group. There was a statistically significant difference in Mean VIS at 0 hours, 6 hour and 12 hour between The study group with (P-value <0.05) (Table 20 & Figure 27)

**Table 20: Comparison of mean of Vasoactive inotrope score (VIS) at different time points between the study group(N=39)**

| **Parameter** | **Study group (Mean± SD)** | | **P-value** |
|---|---|---|---|
| | **M(N=20)** | **L (N=19)** | |
| VIS @ 0hr | 10.8 ± 4.2 | 7.16 ± 3 | 0.004 |
| VIS @ 6hr | 10.8 ± 4.2 | 6.84 ± 2.99 | 0.002 |
| VIS @ 12hr | 10.3 ± 3.95 | 6.84 ± 2.99 | 0.004 |
| VIS @ 24hr | 8.05 ± 3.95 | 5.79 ± 1.87 | 0.030 |
| VIS @36hr | 6.9 ± 3.57 | 5.53 ± 1.58 | 0.132 |
| VIS @48hr | 6 ± 2.62 | 5 ± 0 | 0.104 |

**Figure 27: Line chart of comparison of mean VIS between the study group (N=39)**




**Cardiopulmonary Bypass (CPB )time & Aortic Cross Clamp(ACC ) time:** There was no statistically significant difference in Mean CPB time between The study group with (P-value 0.115). There was no statistically significant difference in Mean ACC time between The study groups (P-value 0.257). (Table 21 & Figure 28& 29)

**Table 21: Comparison of Mean of Cardiopulmonary Bypass (CPB )time & Aortic Cross Clamp(ACC ) time in min between the study group(N=39)**

| **Parameter** | **Study group (Mean± SD)** | | **P-value** |
|---|---|---|---|
| | **M (N=20)** | **L(N=19)** | |
| CPB time In Minutes | 161.8 ± 32.1 | 144.32 ± 35.53 | 0.115 |
| ACC time In Minutes | 109.9 ± 23.93 | 100.47 ± 27.14 | 0.257 |

**Figure 28: Bar chart of comparison of mean CPB time in min between the study group (N=39)**

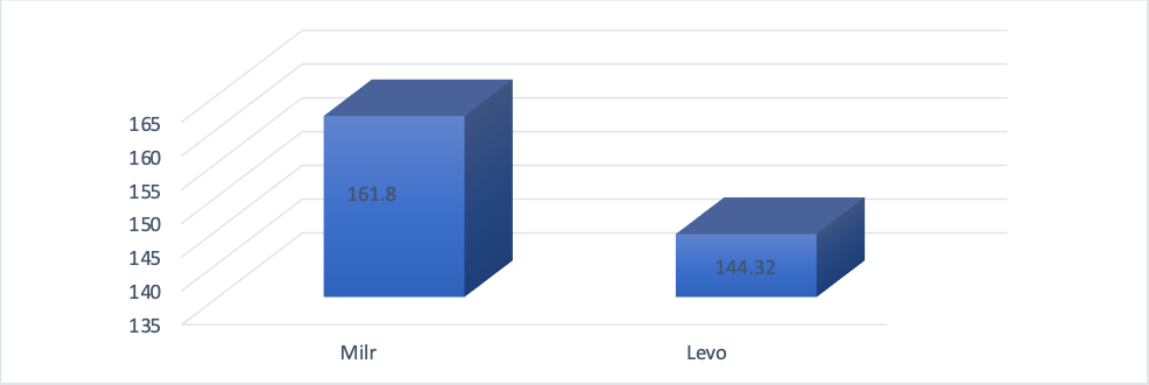
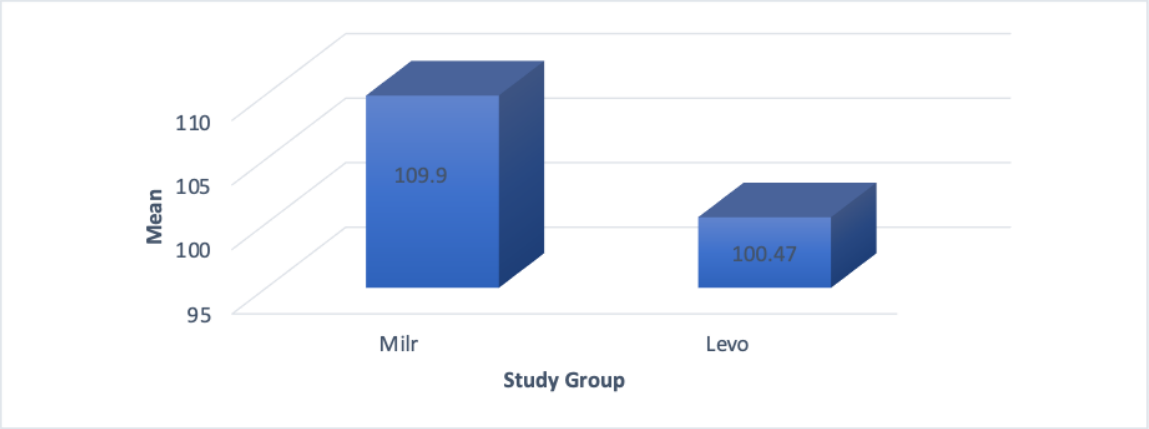



**Figure 29: Bar chart of comparison of mean ACC in min between the study group (N=39)**



## Repeated measures analysis of variance (RMANOVA):

### Table 22: Comparing Low cardiac output parameters at different time points for Milrinone over Levosimendan group

| Parameters | Group | @0 Mean (SD) | @6 Mean (SD) | @12 Mean (SD) | @24 Mean (SD) | @36 Mean (SD | @48 Mean (SD) | F statistics | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | F1 | F2 | F3 |
| Lactate mmol/L | M | 2(0.69) | 1.7(106) | 1.69(1.19) | 1.47(0.5) | 1.42(0.45) | 1.46(0.53) | 4.36** | 0.280 | 0.484 |
| | L | 2.14(0.67) | 1.59(0.73) | 1.5(0.48) | 1.61(0.66) | 1.58(0.61) | 1.49(0.59) | | | |
| Temperature(c-p) | M | 5.35(1.85) | 5.7(2.67) | 5.31(2.39) | 4.93(2.39) | 4.97(2.01) | 5(1.98) | 0.124 | 1.02 | 0.689 |
| | L | 5.08(2.07) | 5.62(1.97) | 5.55(1.50) | 5.84(2.09) | 5.57(1.76) | 5.81(1.94) | | | |
| RPI (SBP*HR) | M | 12906.3(2806.5) | 10339.3(1867.2) | 10189(1027.4) | 10316.9(1546.78) | 10636.6(1605.1) | 10919.3(1889.4) | 18.40*** | 0.016 | 0.495 |
| | L | 12911(1452.7) | 11148(2168.3) | 10000.3(1188.4) | 9874.3(1523.9) | 10501. (1988.25) | 10871.7(2136.5) | | | |
| SCVO2(%) | M | 65.85(9.3) | 64.05(7.81) | 62.9(7.1) | 64.25(4.24) | 65.1(6.5) | 65.05(5.1) | 2.30 | 1.75 | 0.392 |
| | L | 68.95(7.6) | 67.11(5.44) | 63.68(5.64) | 65.11(3.81) | 66.21(4.16) | 66.32(3.7) | | | |
| AVSO2 | M | 32.7(7.32) | 32.65(7.63) | 34.65(6.72) | 32.5(5.09) | 32.95(7.19) | 32.4(5.34) | 1.82 | 1.32 | 0.488 |
| | L | 29.63(7.6) | 30.11(5.65) | 34.16(4.91) | 32.37(3.56) | 31.37(3.92) | 31.11(4.7) | | | |
| VIS | M | 10.8(4.2) | 10.8(4.2) | 10.3(3.95) | 8.05(3.95) | 6.9(3.5) | 6(2.62) | 5.80*** | 0.0*** | 0.0*** |
| | L | 7.16(3) | 6.84(2.99) | 6.84(2.99) | 5.79(1.87) | 5.53(1.58) | 5(0) | | | |
| Urine Output(ml/kg) | M | | 24.95(23.24) | 20.15(16.11) | 25.3(19.22) | 32.5(17.7) | 30.7(17.1) | 2.83* | 1.41 | 0.558 |
| | L | | 29.32(15.51) | 30.68(20.97) | 27.5(20.7) | 34.1(21.9) | 34.1(24.7) | | | |

Two-Way Repeated measures analysis of variance by Huynh-Feldt epsilon F1= time effect, F2= the study group effect, F3 = the study group ×time interaction effect.

*****P-value <0.05

**P-value <0.01, ***P-value <0.001

**For Time Effect**, There was a statistically significant decrease in the Mean Lactate level between the time points from 0 hr to 48 hrs with F statistic 4.36 and P-value <0.05. There was a statistically significant decrease in Mean RPI between the time points from 0 hr to 48 hrs with F statistic 18.4 with P-value <0.001). There was a statistically significant decrease in Mean VIS between time points from 0 hr to 48 hrs with F statistic 5.80 with P-value <0.001.

There was statistically significant increase in Mean Urine output between time from 0 hr to 48 hrs with F statistic 2.83 with P-value <0.05.

**For the study group effect**, There was a statistically significant difference in Mean VIS between The study groups with F statistics 0 and P-value <0.001.which signifies there is a statistically significant low VIS in the Levosimendan group compared with the Milrinone group.

**For the study group × time interaction effect**, There was a statistically significant difference in group×interaction effect on mean VIS score with F factor 0 and P-value <0.001. (Table 22)

**SUBGROUP ANALYSIS**

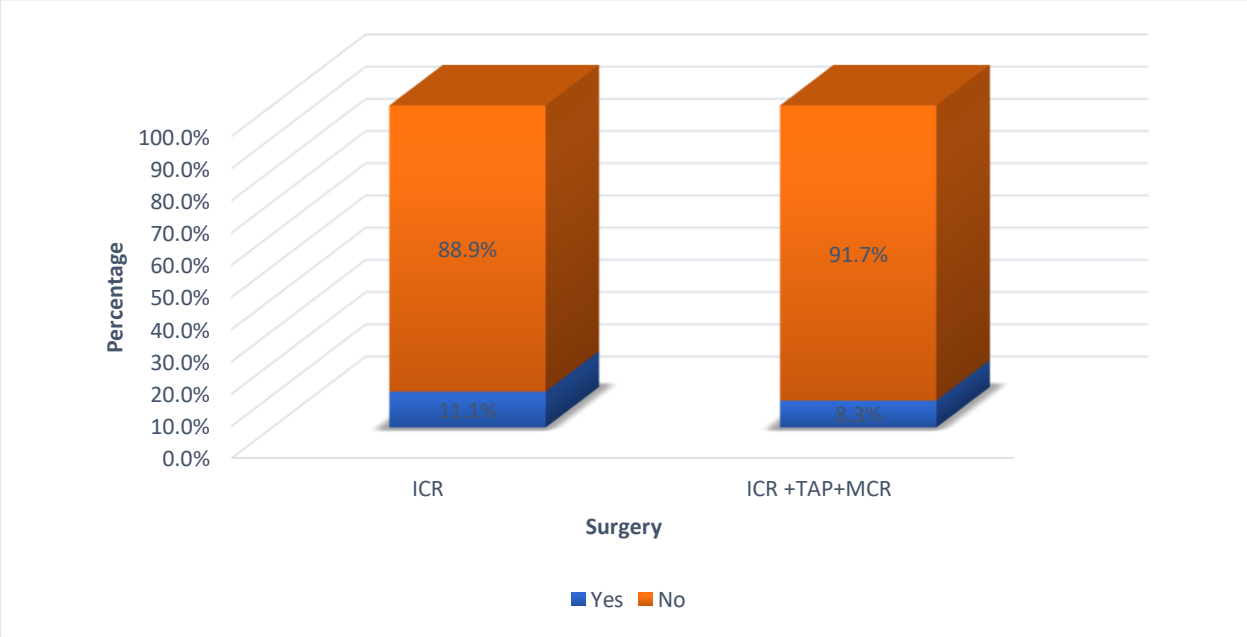
We performed subgroup analysis by using the type of surgeries as study groups (ICR (N=27) Vs ICR +TAP+MCR (N=12))to know the effect of Diastolic antegrade Flow in PA, Requirement of Rescue milrinone after 48 hours, CPB time, ACC time and requirement of the vasoactive agent. Out of 39 TOF patients, 27 patients underwent ICR and 12 patients underwent ICR +TAP+MCR.

**Diastolic Antegrade flow in pulmonary artery:** There was no statistically significant difference in Diastolic antegrade Flow in the pulmonary artery between Surgery (P-value <0.05). . (Table 23 & Figure 30)

**Table 23: Comparison of Diastolic Antegrade flow in pulmonary artery between Surgery (N=39)**

| Dias antegrade Flow | Surgery | | Chi-square | Fisher exact P-value |
|---|---|---|---|---|
| | ICR (N=27) | ICR +TAP+MCR (N=12 | | |
| Yes | 3 (11.11%) | 1 (8.33%) | 0.070 | 1.000 |
| No | 24 (88.89%) | 11 (91.67%) | | |

**Figure 30: Stacked bar chart of comparison of Dias antegrade flow between Surgery (N=39)**




**Comparison of Noradrenaline, CPB time, ACC time and requirement of Mean of Rescue Milrinone between Surgery:**

There was no statistically significant difference in Mean Rescue Milrinone in hrs. Between Surgery with P-value 0.791. A statistically significant difference was not there in the Mean NORADR requirement between Surgery (P-value 0.309). There was no statistically significant

difference in Mean CPB time and Mean ACC time between Surgery with P-value 0.703 and 0.512, respectively. (Table 24 & Figure 31 & 34)

**Table 24: Comparison of Noradrenaline, CPB time, ACC time and requirement of Mean of Rescue Milrinone between Surgery (N=39)**

| Parameter | SURGERY (Mean± SD) | | P-value |
|---|---|---|---|
| | ICR (N=27) | ICR +TAP+MCR (N=12) | |
| RESCUE MILRI IN HRS | 0.37 ± 0.49 | 0.42 ± 0.51 | 0.791 |
| NORADR | 42.89 ± 62.39 | 64.75 ± 58.04 | 0.309 |
| CPB IN MIN | 151.85 ± 35.37 | 156.5 ± 33.81 | 0.703 |
| ACC IN MIN | 103.48 ± 25.98 | 109.42 ± 25.51 | 0.512 |

**Figure 31: Bar chart of comparison of mean RESCUE MILRI IN HRS between study group (N=39)**

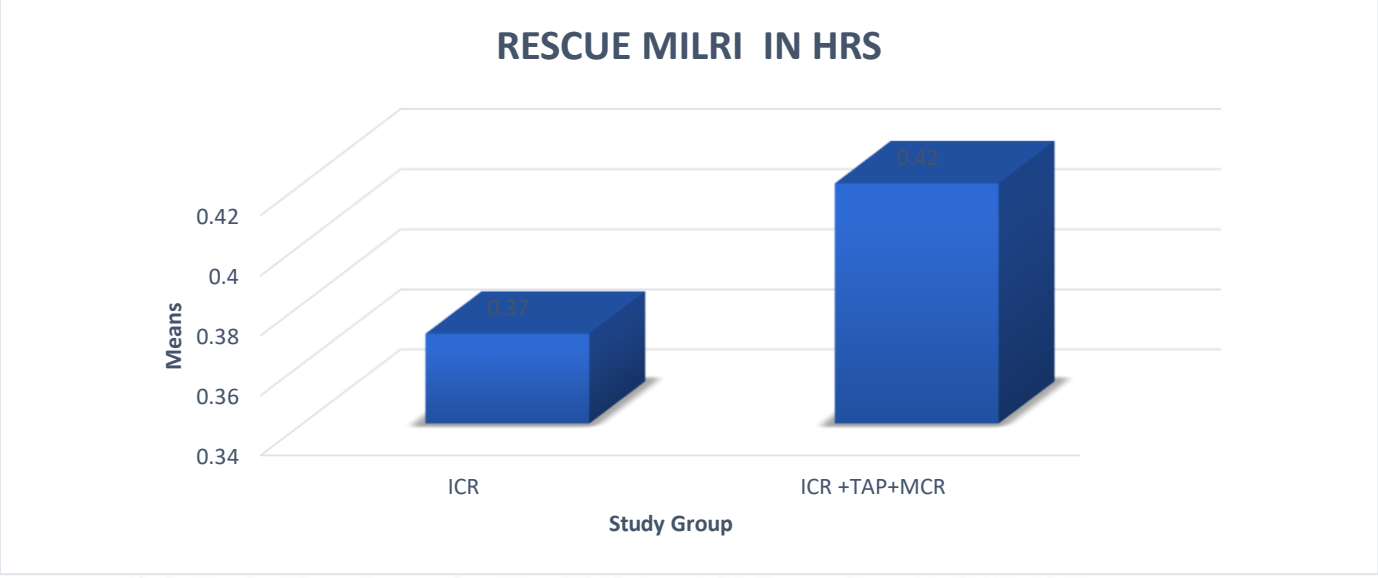


**Figure 32: Bar chart of comparison of mean** NORADR **between study group (N=39)**

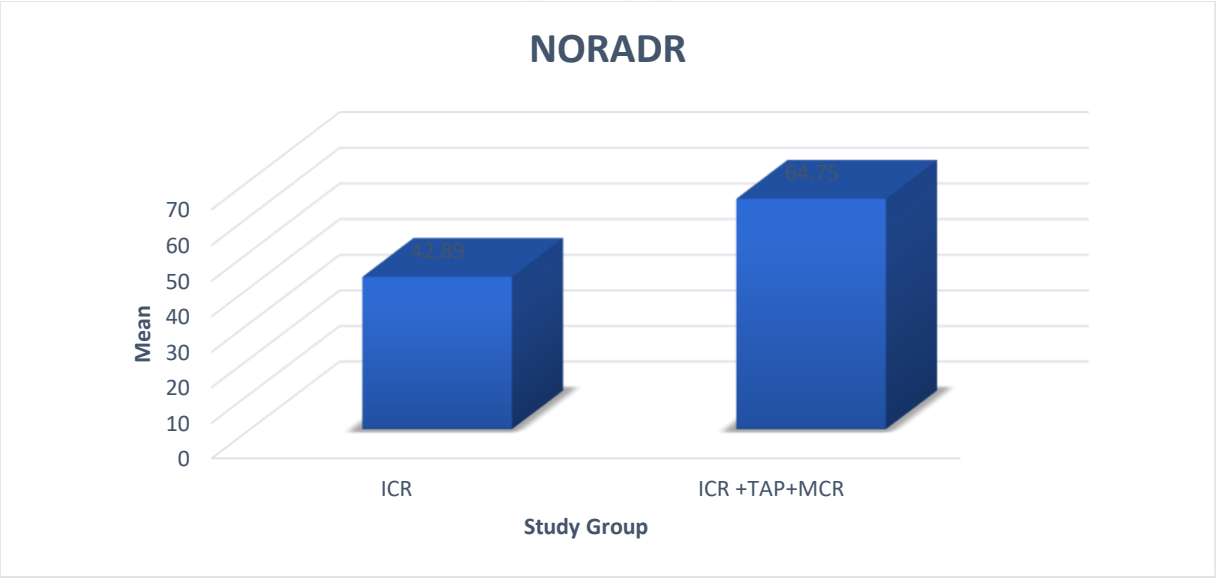



**Figure 33: Bar chart of comparison of mean CPB IN MIN between study group (N=39)**

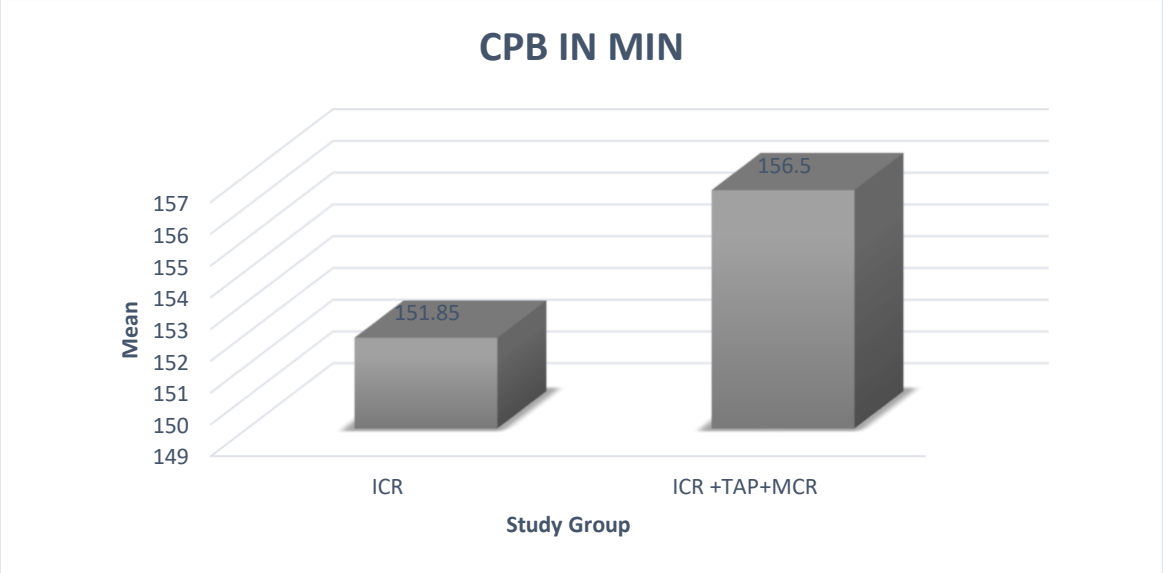
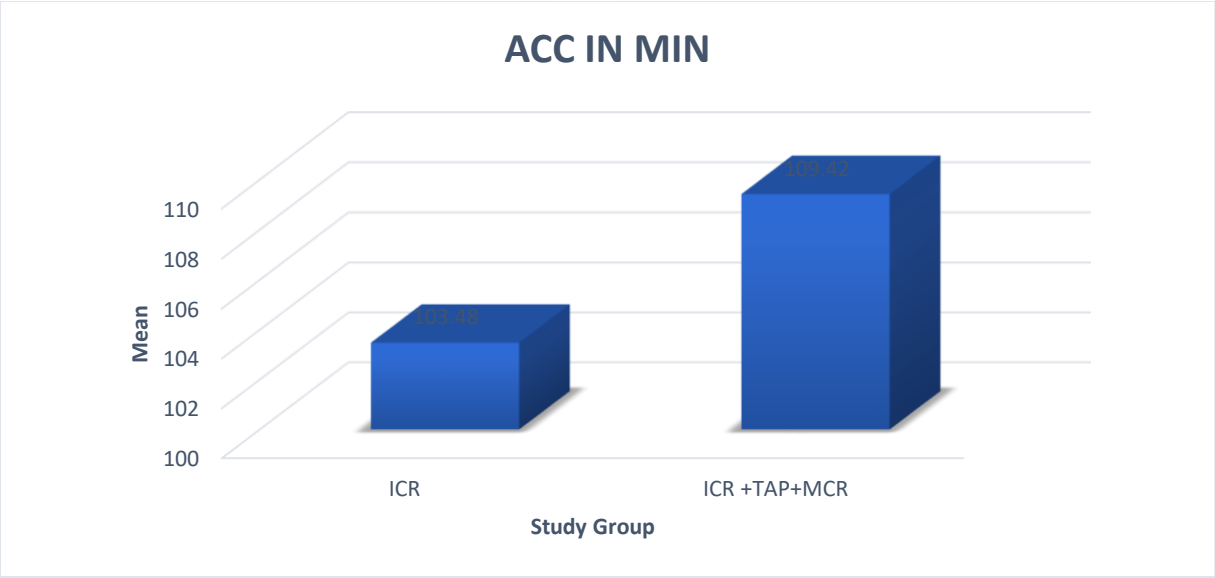


**Figure 34: Bar chart of comparison of mean ACC IN MIN between study group (N=39)**



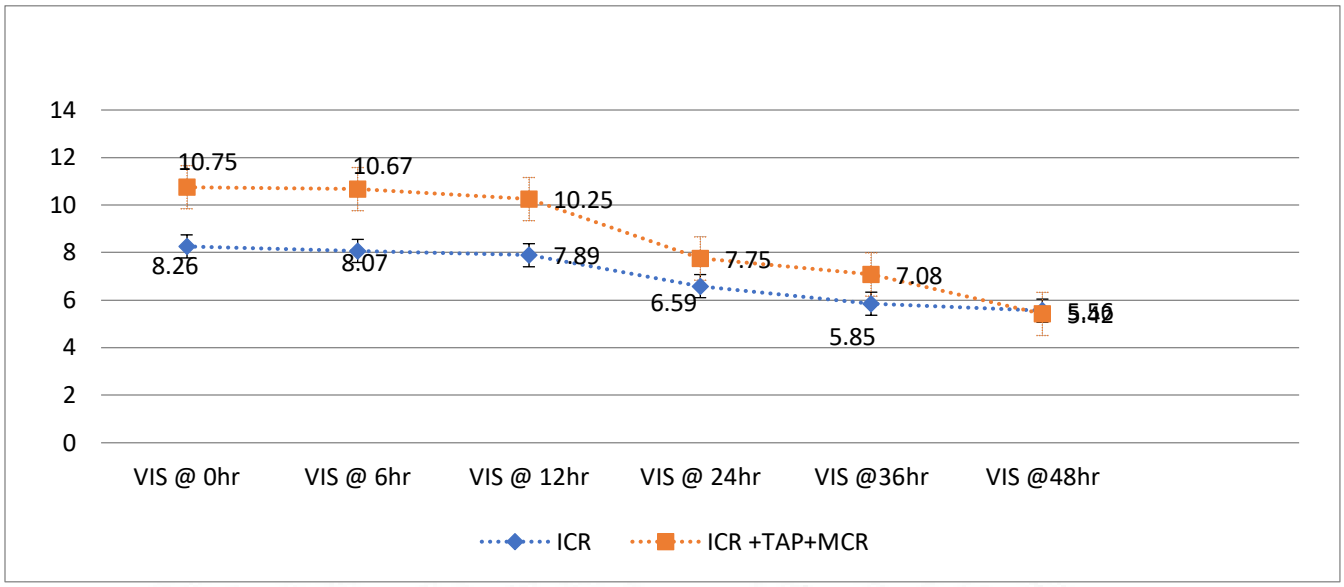

**Comparison of Mean VIS at different time points between Surgery:**

There was statistically no significant difference in Mean VIS at different time points between Surgery (P-value >0.05). ICR surgery had relatively less VIS at 0 hr. (8.26 ± 3.81 Vs 10.75 ± 4.25, P-value 0.077),6 hr. (8.07 ± 3.84 Vs 10.67 ± 4.36, P-value 0.07 TAP+MCR) and 12 hr. (7.89 ± 3.87 Vs 10.25 ± 3.55) compared with ICR+ TAP+MCR surgery

**Table 25: Comparison of Mean VIS at different time points between Surgery (N=39)**

| Parameter | SURGERY (Mean± SD) | | P-value |
|---|---|---|---|
| | ICR (N=27) | ICR +TAP+MCR (N=12) | |
| VIS @ 0hr | 8.26 ± 3.81 | 10.75 ± 4.25 | 0.077 |
| VIS @ 6hr | 8.07 ± 3.84 | 10.67 ± 4.36 | 0.070 |
| VIS @ 12hr | 7.89 ± 3.87 | 10.25 ± 3.55 | 0.079 |
| VIS @ 24hr | 6.59 ± 2.91 | 7.75 ± 4.03 | 0.316 |
| VIS @36hr | 5.85 ± 2.55 | 7.08 ± 3.34 | 0.215 |
| VIS @48hr | 5.56 ± 2.12 | 5.42 ± 1.44 | 0.838 |

**Figure 46: Line chart of comparison of mean VIS @ every point between study group (N=39)**


14
12
10
8
6
4
2
0
10.75
10.67
10.25
8.26
8.07
7.89
7.75
7.08
6.59
5.85
5.42
VIS @ 0hr
VIS @ 6hr
VIS @ 12hr
VIS @ 24hr
VIS @36hr
VIS @48hr
ICR
ICR +TAP+MCR

# DISCUSSION

We conducted a prospective observational open-label study comparing Levosimendan and milrinone in Tetralogy of Fallot in 39 children under 12 years of age who underwent intracardiac repair on cardiopulmonary bypass. To our knowledge, this is the first study that compared the two inodilators in a homogenous tetralogy of Fallot physiology patients. Previous studies compared above mentioned two drugs in heterogeneous congenital heart diseases with different pathophysiology

In our study, patients prophylactically received either a loading dose of Milrinone (Group M) or Levosimendan (Group L) followed by a maintenance dose, immediately after aortic cross-clamp removal to evaluate the effect of these inotropic agents on markers of LCOS such as lactate, mixed venous saturation, the difference between arterial and venous saturation, core body to peripheral skin temperature difference, urine output and postoperative arrhythmias and the effects on postoperative outcomes, duration of ventilation, ICU stay, morbidity (renal, cardiovascular and neurological) and mortality. The perioperative management was standardized across all patients as per our institutional protocol.

Levosimendan improves myocardial contractility without increasing myocardial oxygen consumption, impairing diastolic relaxation, or causing an increase in intracellular calcium concentration.[31,32]Levosimendan has been extensively evaluated in the adult population.[33,34] but has received little attention in the pediatric and has gained greater attention in the last few years. Due to its mechanism of action through calcium sensitization and its additional inotropic and vasodilator properties, Levosimendan might be considered superior to Milrinone in preventing

LCOS and arrhythmias after corrective cardiac surgery in Tetralogy of Fallot in children and infants.

**Effect on Low cardiac output syndrome:**

In our study, we found no statistical difference in the markers of LCOS in both groups. After surgery, the primary endpoints such as serum lactate concentrations, Central venous saturation (SCVO2), the difference between arterial and venous saturation (A-V SO2), core body to peripheral skin temperature difference (TEMP C-P) and urine output did not differ between the Levosimendan and Milrinone groups in first 48 hrs. after corrective cardiac surgery for Tetralogy of Fallot.

**Serum lactate concentrations:**

Among biochemical markers routinely used to support LCOS diagnosis, the serum lactate level is considered one of the important biochemical markers of early adverse outcomes after complex congenital cardiac surgery.

In our study, we didn't find a statistically significant difference in Mean Lactate level between M and L study groups (P-value > 0.05) for the first 48hrs.which is in agreement with the study conducted by Momeni et al., A randomized controlled trial in children after congenital heart surgery, [9] compared the prophylactic use of Milrinone against the prophylactic of Levosimendan. They didn't find a significant difference in Lactate 1±0.3 (L), 1±0.5 (M), between L and M groups,

**Rate pressure index (RPI)**

RPI reflects myocardial oxygen demand. It was significantly lowered over 48 hours postoperatively in both Levosimendan and milrinone group compared with RPI at 0 hr.but there was no significant difference between the groups at different time points in 48hrs postoperatively. Our results contrast with the memoni et al. [9] and Himanshu et al. [11] studies, where they observed significantly lower RPI in the Levosimendan group than milrinone. Our study got a lower RPI at 6,12,24,36 and 48 hrs, but it was not statistically significant.

Our study patients were possibly not sick enough to form a valid study population. One could speculate that in the study population with pre-existing congestive heart failure or more complex cardiac lesions, Levosimendan might have been more advantageous due to its inotropic properties and pharmacologic profile.

**Arrhythmias:**

Milrinone usually increases heart rate and oxygen consumption through its action on cAMP. In contrast to that, Levosimendan is a non-cAMP-dependent inodilator; it's a calcium sensitizer and potassium channel opener; hence we hypothesized to test its effect in postoperative arrhythmia. Our study found a similar incidence of arrhythmias in both groups (M,25% Vs L,26.32%, P-value 1.00). Therefore, it seems arrhythmias after intracardiac repair due to surgical insult of conduction system rather than inodilator.

**Rescue Milrinone:**

Levosimendan metabolize into OR-1896, an active metabolite, with a longer half-life of 75 to 80 hours.[21,22] Prolonged duration of action of Levosimendan led to a significant difference in the postoperative requirement of Milrinone after 48 hours compared with Milrinone group (P-value =

0.029). In the Milrinone group, 55% of patients required rescue milrinone infusions after 48hr infusion of Milrinone compared with 21% in the Levosimendan group. There was a statistically significant difference in Rescue Milrinone requirement between the study groups (**P-value** of 0.029).

An interesting finding of our study is that Levosimendan was very well tolerated and did not cause systemic hypotension, an excessive need of inotropes or vasoconstrictors not required when administered through a continuous infusion.

**Vasoactive inotropic score (VIS score):**

Patients in the Levosimendan group required statistically significant less vasoactive agents at 0 hr., 6 hr. and 12hrs after surgery compared with the milrinone group. There was a statistically significant difference in Mean VIS at 0-hour, 6 hours and 12 hours between the study group (P-value <0.05). In contrast to our results. Lecher et al.[10,] in their study, proposed no difference in the inotropic score (IS) in both the groups, but the study used the IS offered by Wernovsky et al.[35]Two significant drawbacks of the IS score proposed by Wernovsky et al.[35] was that it neither included Milrinone or Levosimendan and did not include vasopressin in the score, which was used in few cases in our study.

The vasoactive inotropic score (VIS score) proposed by Gaies et al.[36] was used in our study. The usual maintenance dose of Levosimendan (0.1 μg/kg/min) was given a score of 5 to match the inotropic score of the maintenance dose of Milrinone (0.5 μg /kg/min) which in the VIS score had a score of 5. The use of additional catecholamines did not differ between the groups.

Another reason for the high VIS score in the milrinone group could be the type of surgery received. In the Milrinone group, 40% of patients underwent a Transannular patch with monocuspid valve reconstruction, compared to 21% in the Levosimendan group. The Transannular patch with monocuspid valve reconstruction requires more operation time and extensive ventricular incision than simple intracardiac repair surgery. Our subgroup analysis found that the patient who underwent intracardiac repair with transannular patch and monocuspid valve reconstruction had more (even though statistically not significant )VIS scores for 24hrs after surgery than intracardiac repair alone irrespective of inodilator received. Therefore, patients receiving ICR + TAP + MCR are expected to have more myocardial dysfunction, so this subgroup needs more inotropic drugs immediately after surgery to prevent LCOS than intracardiac repair alone.

## LIMITATIONS

1. Overall, this the study and its observations were limited by its small number and the study population even though it is the first the study confined to Tetralogy of Fallot
2. One limitation of our study was the fact that we could not be able to perform complete right ventricular diastolic function parameters such as tricuspid inflow E/A, tricuspid annulus e' by transesophageal echocardiography due to doppler alignment issues and could not able differentiate between E and A due to effect of preload on tricuspid inflow doppler spectrum
3. We could not include patients with preoperative ventricular dysfunction where the expected effect of Levosimendan seems to have a better outcome, as stated in several adult studies and one paediatric retrospective the study.
4. However, the study demonstrates that Levosimendan can be safely used in children. Its use is associated with an overall trend toward hemodynamic benefit in a critically ill paediatric patient population.
5. To evaluate incidence of post-operative arrhythmias, chest drain, duration of mechanical ventilation, which are major contributing factors for the ICU stay, required a larger the study population.
6. Several subsets like premature infants, low-birth-weight children, infants with preoperative ventricular dysfunction and infants with preoperative altered renal parameters have to be evaluated to confirm the superiority of this drug over various available inotropic and indicator agents.

# CONCLUSIONS

1. In our prospective observational the study of 39 infants undergoing surgery for complex congenital cardiac condition, postoperative hemodynamic parameters and markers of tissue perfusion over time were similar in infants with the administration of either Levosimendan or Milrinone.
2. There was no statistically significant difference in post-operative arrhythmia incidences in both groups. The present study found that no drug superior over other in preventing post-operative arrythmias
3. We observed a low VIS score in the Levosimendan group in the first 24 hrs. Which was a direct result of less requirement of vasopressors to maintain systemic arterial blood pressure in Levosimendan. It could be due to less inadvertent peripheral vasodilatation with Levosimendan compared with Milrinone
4. In our study, utilization of Milrinone as a rescue drug after 48hrs of surgery to maintain stable hemodynamics was significantly less in the Levosimendan group, Due to the prolonged action of Levosimendan active metabolites compared to Milrinone.
5. Levosimendan drug cost is approximately 1/3 of milrinone cost, so it adds cost-effectiveness in patient management
6. Thus, Levosimendan offers a cheaper, unique, timely, attractive, and equipotent alternative to Milrinone in use today to prevent LCOS following corrective cardiac surgery in Tetralogy of Fallot.
7. Our results might be the basis of future controlled trials of Levosimendan in children with a particular focus on Post-operative outcomes such as Low cardiac output syndrome,

arrythmias, the duration of mechanical ventilation, length of ICU stay, and length of hospital stay

8. This prospective observational study has primarily served experience using the relatively new drug Levosimendan in Tetralogy of Fallot children and to initiate further multicenter trials in pediatric patients.

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# ANNEXURES

## Annexure 1: IEC Approval Letter

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
*(An Institute of National Importance under Govt. of India)*
Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

**Institutional Ethics Committee**
(IEC Regn No. ECR/189/Inst/KL/2013/RR-16)

SCT/IEC/1395 /AUGUST-2019 — 20.09.2019

**Dr. Aspari Mahammad Azeez**
Resident, Department of Anaesthesiology
SCTIMST, Thiruvananthapuram

Dear Dr. Aspari Mahammad Azeez,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled "THE EFFICACY AND SAFETY OF INTRAVENOUS LEVOSIMENDAN COMPARED WITH MILRINONE IN PREVENTING LOW CARDIAC OUTPUT AFTER CORRECTIVE CARDIAC SURGERY IN TETRALOGY OF FALLOT (IEC/1395)" on 17th August, 2019.

**The following documents were reviewed:**

*Original documents*
1. *Covering Letter addressed to the Chairman, IEC, SCTIMST with checklist*
2. *TAC Approval Letter*
3. *IEC Application Form*
4. *Project Proposal*
5. *Proforma*
6. *Patient Information Sheet and Informed Consent Form in English and Malayalam*
7. *Forwarding Letter from the HOD*
8. *CV of Principal Investigator and Co-Principal Investigators*

*Revised documents*
1. *Covering Letter addressed to the Chairman, IEC, SCTIMST dated 20.09.2019 with checklist*
2. *TAC Approval Letter*
3. *Copy of IEC Recommendations Letter dated 19.08.2019*
4. *IEC Application Form*
5. *Project Proposal*
6. *Proforma*
7. *Patient Information Sheet and Informed Consent Form in English and Malayalam*
8. *Patient Information Sheet and Informed Consent Form for 10-12 years children in English and Malayalam*
9. *Forwarding Letter from the HOD*
10. *CV of Principal Investigator and Co-Principal Investigators*

**The following members of the Ethics Committee were present at the meeting held on 17th August, 2019 at G. Parthasarathi Board Room, AMCHSS, SCTIMST**

| SL. No. | Member Name | Highest Degree | Gender | Scientific /Non Scientific | Affiliation with Institution(s) |
|---|---|---|---|---|---|
| 1. | Dr. R V G Menon | M Tech, PhD | Male | Lay Person (Chairman) | No |
| 2. | Dr. Rema M. N | MD | Female | Basic Medical Scientist | No |
| 3. | Dr. Kala Kesavan. P | MBBS, MD | Female | Basic Medical Scientist | No |
| 4. | Dr. K R S Krishnan | M.E., Ph.D. | Male | Medical Technology | Yes |
| 5. | Dr. Harikrishna Varma PR | Ph.D( Materials Science) | Male | Medical Technology | Yes |
| 6. | Dr. S S Giri Sankar | LL.M. Ph.D. | Male | Legal Expert | No |
| 7. | Dr. Anand Kumar A | MD, DM | Male | Clinician | No |
| 8. | Dr. V. Raman Kutty | M D, M Phil, M P H | Male | Health Sciences Expert/Clinician | Yes |
| 9. | Dr. Aneesh V Pillai | BA. LLB (Hons.), LLM, Ph. D, SET (Law) | Male | Legal Expert | No |
| 10. | Smt. Sathi Nair | MA (English Literature) | Female | Lay Person | No |
| 11. | Dr. P. Manickam | BSMS, MSc (Epid) ,PhD | Male | Health Science Expert/ Social Scientist | No |
| 12. | Dr. Harikrishnan S | MD, DM (Cardiology) DNB (Cardiology) | Male | Clinician | Yes |
| 13. | Mr. Satheesh Chandran | MSW, PGDPM | Male | Lay person/ NGO/ Social Scientist | No |
| 14. | Dr. Mala Ramanathan | PhD | Female | Social Scientist (Member Secretary) | Yes |

**IEC Decision**

The IEC approved the conduct of the study in the present form.

**Remarks:**
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

**Mala Ramanathan**
Member Secretary, IEC

## Annexure 2: Patient Information Sheet

**TITLE:** The Efficacy and safety of intravenous Levosimendan compared with Milrinone in preventing low cardiac output after corrective cardiac surgery in Tetralogy of Fallot.

- **Aim of the study (Why are we doing this study?)**

  Children with cyanotic congenital heart disease have a high incidence of going into low cardiac output after the corrective cardiac surgery. In tetralogy of Fallot (blue babies with the hole in the septum which separates the ventricles along with thickening of right ventricle) this problem is even more in immediate post-operative period. Prevention and treatment of low cardiac output can be done by few drugs known as inodilators in that Milrinone and Levosimendan are the drugs which are using as a routine clinical practice in our institute and as well as all over the world. There are very few studies comparing the efficacy and safety of these two drugs in Tetralogy of Fallot patients, hence we intended to do this study for better patient care in preventing and treating the low cardiac output in tetralogy of Fallot patients.

- **Risks and side-effects for your child for participating in this study:**

  Milrinone and Levosimendan as inodilators is safe and recommended for preventing and treating low cardiac output in children and adult cardiac surgery. In your child also, as routine, irrespective of whether your child is included in the study or not the above-mentioned drugs will be given and is an essential part of the management of your child. These drugs are safe and the benefits related to the use of these drugs out weights the risks. However, minor side effects can be managed if it happens and should not cause any harm to your child.

- **Can you withdraw your child from this study after it starts?**

  Your consent for allowing the participation of your child in this study is entirely voluntary and you will be free to decide to withdraw permission for your child to participate in this study, should you feel so. If you do so, this will not affect your child's usual treatment in this hospital in any way.

- **What will happen if your child develops any study related injury?**

  We do not expect any injury to happen to your child but if he/she develops any side effects or problems due to the study, these will be treated at no extra cost to you. We are unable to provide any monetary compensation, however.

- **Will do you have to pay for the study?**

  This study does not require you to pay any additional charges over and above what you will have to bear for the routine expenditure for the operation for your child.

- **Will your child's personal details are kept confidential?**

Your child's personal details will be kept confidential. The result of this study will be sent for publication in a medical journal upon its completion, but your child will not be identified by name or any other form of identification in such a publication or any presentation anywhere.

If you have any further questions, please ask any of the study investigators listed below:

i) Dr . Aspari Mahammad Azeez , DM Senior resident, Cardiothoracic & Vascular Anaesthesia, Division of Cardiac Anaesthesia (Phone:8427693477 ; email - aspariazeez@gmail.com)

ii) Dr .Unnikrishnan K.P, Professor, Division of Cardiac Anaesthesia (Phone: 9446177521; email – unnikp@gmail.com)

iii) Dr .Sabarinath Menon, Associate professor, paediatric cardiac surgery, Department of CVTS; email.com-sabarinath.menon@gmail.com

iv) Dr .Baiju S Dharan, Professor and Head ,Department of Cardio Vascular and Thoracic Surgery ,email : baijusd@sctimst.ac.in Phone: +91 9995019925

v) Dr .Mala Ramanathan, Member Secretary, IEC & Additional Professor(study independent contact person, tel:04712524-234)

## Annexure 3: Informed Consent Form

I, _____,F/O,M/O,R/O _____[**Participant's name: Date of Birth / Age (in years)**] declare that I have read the patient information sheet provided to me regarding the study.

**The Efficacy and safety of intravenous Levosimendan compared with milrinone in Preventing low cardiac output after corrective cardiac surgery in Tetralogy of Fallot**

- I have clarified any doubts that I had. [ ]

- I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting my usual treatment or my legal rights [ ]

- I understand that the study staff and institutional ethics committee members will not need my permission to look at my health records even if I withdraw from the trial. I agree to this access [ ]

- I understand that my identity will not be revealed in any information released to third parties or published [ ]

- I understand that I have to Undergo Transoesophageal echocardiography and Levosimendan/milrinone will be administered, which is routinely done for all open heart surgery patients

- I voluntarily agree to take part in this study [ ]

- I received a copy of this signed consent form [ ]

Name:

Signature:

Date:

Name Of Witness

Relation To Participant

Study Independent contact person- Dr . Mala Ramanathan, AMCHSS & IEC Member Secretary, SCTIMST (0471-2446234) Email: iec.mem.sec@sctimst.ac.in

## Declaration by Person Obtaining Consent

I attest that the requirements for informed consent for the medical research project described in this form have been satisfied. I have discussed the research project with the participant and explained to him or her in nontechnical terms all of the information contained in this informed consent form, including any risks and adverse reactions that may reasonably be expected to occur. I further certify that I encouraged the participant to ask questions and that all questions asked were answered.

Signature:

Date:

Dr . Aspari Mahammad Azeez Senior Resident, CVTA, SCTIMST

Email : aspariazeez@gmail.com

## Annexure 4: Observation Chart

The observations will be noted by the principal investigator and confidentiality will be maintained regarding patient identification. Data will be stored by the principal investigator in his personal computer for three years.

### I. Demographic data:

a) Patient's name:
b) Age:
c) Weight:
d) Height:
e) Body surface area:

- Diagnosis:
- Surgical procedure:
- Date of surgery:
- Pre op ECHO findings:
- Baseline saturation:
- Pre-operative haemogram:

Hb-

TLC-

Platelet counts -

### II. Primary outcomes:

i. **LCOS**

| Time points | 0 hr | 6 hr | 12 hrs | 24 hrs | 36hrs | 48hrs |
|---|---|---|---|---|---|---|
| Blood lactate | | | | | | |
| ScVO2 | | | | | | |
| A-VSo2 | | | | | | |
| U/O | | | | | | |
| Temp(c-p) | | | | | | |
| Rate pressure index | | | | | | |

ii. Arrhythmias in both milrinone and Levosimendan: SVT, Ectopic atreial tachycardias, AF, accelerated junctional rhythms, JET, VT and VF

## III. Secondary outcomes

**Echocardiography:**

**#Post repair End-diastolic forward flow in the pulmonary artery (PA):**

| Time points | Immediate<br>Post CPB(TEE) | POD 1(TTE) | POD 2(TTE) | POD 3 (TTE) |
|---|---|---|---|---|
| Tricuspid inflow E/A | | | | |
| Mitral inflow E/A | | | | |
| RVOT to PA Pre Grad | | | | |
| PFO shunt direction | | | | |

1) **Adverse events** due to inodilator infusions:

   Hypotension, hypokalemia, and thrombocytopenia

2) Re-Interventions:
3) Length of intensive care unit (ICU) stay:
4) Length of hospital stay:
5) Duration of mechanical ventilation:
6) Duration of chest drain:
7) Vasoactive-Inotrope score:
8) Requiring mechanical circulatory support –ECMO:

# Annexure 5:Plagiarism

Curiginal

## Document Information

| | |
|---|---|
| Analyzed document | Dr Azeez Thesis.docx (D110939754) |
| Submitted | 8/2/2021 4:45:00 PM |
| Submitted by | Dr P K Dash |
| Submitter email | dash@sctimst.ac.in |
| Similarity | 12% |
| Analysis address | sadh.sctims@analysis.urkund.com |

## Sources included in the report

| | | |
|---|---|---|
| W | URL: https://www.researchgate.net/publication/284279167_Management_of_the_Low_Cardiac_Output_Syndrome_Following_Surgery_for_Congenital_Heart_Disease<br>Fetched: 3/9/2020 1:58:04 PM | 1 |
| W | URL: https://www.researchgate.net/publication/274090149_Prophylactic_milrinone_for_the_prevention_of_low_cardiac_output_syndrome_and_mortality_in_children_undergoing_surgery_for_congenital_heart_disease<br>Fetched: 3/9/2020 3:08:24 PM | 14 |
| SA | joe thesis (3) final.docx<br>Document joe thesis (3) final.docx (D58638273) | 1 |
| W | URL: https://www.sciencedirect.com/topics/nursing-and-health-professions/milrinone<br>Fetched: 5/1/2020 5:39:12 PM | 2 |
| W | URL: https://www.researchgate.net/publication/6665814_Mechanisms_of_a_reduced_cardiac_output_and_the_effects_of_Milrinone_and_Levosimendan_in_a_model_of_infant_cardiopulmonary_bypass<br>Fetched: 2/25/2021 2:33:44 PM | 3 |
| W | URL: https://www.researchgate.net/publication/257476851_Efficacy_and_safety_of_Milrinone_in_preventing_low_cardiac_output_syndrome_in_infants_and_children_after_corrective_surgery_for_congenital_heart_disease<br>Fetched: 11/29/2020 11:35:54 AM | 3 |
| W | URL: https://www.zora.uzh.ch/id/eprint/151479/1/00130478-900000000-98471.pdf<br>Fetched: 3/8/2021 3:29:42 PM | 1 |
| W | URL: https://www.researchgate.net/publication/317118007_Question_2_Is_levosimendan_better_than_milrinone_in_preventing_post_operative_low_cardiac_output_syndrome_and_improving_cardiac_function_in_children_with_congenital_heart_disease<br>Fetched: 8/2/2021 4:46:00 PM | 1 |
| W | URL: https://www.semanticscholar.org/paper/Comparative-study-of-levosimendan-versus-milrinone-Shah-Bhavsar/891db708c4aa0cb46cdc2102b85d4da41a47f0c7<br>Fetched: 8/2/2021 4:46:00 PM | 3 |
| SA | Sree Chitra Tirunal Institute, Thiruvananthapuram / New Microsoft Word Document.docx<br>Document New Microsoft Word Document.docx (D110761874)<br>Submitted by: dash@sctimst.ac.in | 4 |

# Annexure 6:Master chart

| S.NO | GROUP MILRI-1,LEVO-2 | AGE IN MN | GENDER,F-1,M-2 | WT KG | HEIGHT CM | BSA KG/M2 | ADD VSD Y-1,N-0 | DIAGNOSIS | SURGERY | DSC N-0,Y-1 | BASELINE SAT% | PRE OP HB | TLC | PLATELETS | LACTATE-0 | LACTATE-6 | LACTATE-12 | LACTATE-24 | LACTATE-36 | LACTATE-48 | URINE OUTPUT-6 | URINE OUTPUT-12 | URINE OUTPUT-24 | URINE OUTPUT-36 | URINE OUTPUT-48 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 24 | 2 | 9 | 82 | 0.46 | 1 | TOF VAL+SUB | ICR+TAP | 0 | 84 | 14 | 14500 | 4.9 | 2.8 | 1.1 | 1 | 1 | 1.4 | 1.1 | 10 | 15 | 10 | 15 | 12 |
| 2 | 1 | 9 | 2 | 7 | 70 | 0.36 | 0 | TOF ,SUB VAL | ICR | 0 | 87 | 15 | 15980 | 7.0 | 1.6 | 1.2 | 1.2 | 1.3 | 1.8 | 1.9 | 16 | 12 | 14 | 23 | 20 |
| 3 | 1 | 4 | 1 | 5.2 | 59 | 0.28 | 0 | TOF VAL PS | ICR+TAP+MCF | 0 | 52 | 17.4 | 7500 | 1.9 | 2.1 | 1.5 | 1.4 | 2.6 | 2 | 1.5 | 10 | 10 | 15 | 10 | 15 |
| 4 | 1 | 32 | 1 | 8.6 | 78 | 0.43 | 0 | TOF VAL PS | ICR+TAP+MCF | 0 | 94 | 16.5 | 8390 | 4.5 | 1 | 1.1 | 1 | 1 | 1.6 | 2 | 30 | 15 | 10 | 50 | 50 |
| 5 | 1 | 22 | 2 | 9 | 80 | 0.45 | 0 | TOF VAL+SUB | ICR+TAP+MCF | 0 | 90 | 15 | 14000 | 4.3 | 1.4 | 0.8 | 0.7 | 0.9 | 1 | 1 | 16 | 44 | 23 | 50 | 32 |
| 6 | 1 | 6 | 2 | 14 | 78 | 0.53 | 0 | TOF VAL+SUB | ICR+TAP+MCF | 0 | 81 | 13.8 | 9360 | 3.0 | 1.8 | 3.4 | 1.8 | 1.5 | 1.3 | 2.2 | 90 | 20 | 20 | 42 | 25 |
| 7 | 1 | 4 | 2 | 6.2 | 56 | 0.3 | 0 | TOF ,SUB VAL | ICR | 0 | 94 | 10.7 | 9500 | 5.5 | 3.1 | 1.6 | 1.6 | 1.2 | 0.8 | 0.6 | 10 | 12 | 11 | 20 | 22 |
| 8 | 1 | 13 | 1 | 7.5 | 72 | 0.38 | 0 | TOF ,SUB VAL | ICR+TAP+MCF | 0 | 80 | 17.3 | 9980 | 4.2 | 1.6 | 1.3 | 1.2 | 1.8 | 1.2 | 1.3 | 16 | 8 | 22 | 30 | 30 |
| 9 | 1 | 85 | 1 | 18 | 118 | 0.78 | 0 | TOF ,SUB VAL | ICR | 0 | 74 | 16.4 | 12000 | 3.9 | 1.7 | 1.4 | 1.3 | 0.7 | 0.9 | 1.1 | 30 | 25 | 90 | 67 | 65 |
| 10 | 1 | 13 | 2 | 10 | 77 | 0.42 | 0 | TOF-PA | ICR+REV | 1 | 74 | 18 | 11700 | 3.0 | 1.6 | 3.2 | 4.5 | 1.8 | 1.5 | 1.7 | 8 | 18 | 25 | 27 | 28 |
| 11 | 1 | 8 | 2 | 8 | 69 | 0.39 | 0 | TOF ,SUB VAL | ICR+LPA PLAT | 0 | 90 | 12.7 | 9900 | 5.0 | 2.1 | 1.1 | 1.1 | 1.4 | 2.2 | 2.2 | 10 | 15 | 15 | 15 | 15 |
| 12 | 1 | 23 | 1 | 10 | 81 | 0.48 | 0 | TOF VAL+SUB | ICR | 0 | 82 | 16 | 9800 | 2.4 | 1.6 | 0.7 | 1.5 | 1.8 | 1.5 | 1.2 | 12 | 40 | 46 | 40 | 40 |
| 13 | 1 | 96 | 1 | 29 | 125 | 1 | 0 | TOF VAL+SUB | ICR+TAP+MCF | 0 | 83 | 18.5 | 7600 | 1.1 | 4.1 | 5 | 5.5 | 2.4 | 1.5 | 1.1 | 76 | 74 | 54 | 75 | 68 |
| 14 | 1 | 10 | 2 | 6.25 | 64 | 0.33 | 0 | TOF ,SUB VAL | ICR | 0 | 85 | 13 | 9300 | 3.6 | 1.7 | 1.7 | 1.1 | 1 | 2 | 1.4 | 14 | 10 | 14 | 25 | 20 |
| 15 | 1 | 5 | 1 | 4.8 | 56 | 0.27 | 0 | TOF VAL PS | ICR+TAP | 0 | 86 | 13.5 | 10900 | 1.9 | 2.2 | 1.3 | 1.7 | 1.5 | 1.3 | 1.5 | 14 | 7 | 13 | 18 | 13 |
| 16 | 1 | 60 | 1 | 17 | 105 | 0.69 | 0 | TOF VAL+SUB | ICR+TAP+MCF | 0 | 94 | 15.2 | 8500 | 2.5 | 2 | 1.4 | 1.1 | 1.3 | 1.1 | 1 | 30 | 25 | 38 | 35 | 30 |
| 17 | 1 | 20 | 2 | 9 | 80 | 0.44 | 0 | TOF VAL PS | ICR+LPA PLAT | 0 | 95 | 12.1 | 10900 | 3.3 | 1.9 | 0.9 | 1.5 | 1.1 | 0.9 | 0.7 | 15 | 20 | 26 | 20 | 22 |
| 18 | 1 | 50 | 2 | 14.6 | 101 | 0.64 | 0 | TOF VAL+SUB | ICR+TAP+MCF | 0 | 98 | 13.7 | 7200 | 3.3 | 2.1 | 1.4 | 1 | 2 | 1.3 | 1.2 | 60 | 15 | 20 | 15 | 25 |
| 19 | 1 | 17 | 1 | 8 | 74 | 0.4 | 0 | TOF VAL PS | ICR+TAP | 0 | 86 | 17.9 | 9000 | 3.8 | 1.3 | 1.2 | 1.4 | 1.2 | 0.8 | 2 | 20 | 10 | 20 | 41 | 60 |
| 20 | 1 | 9 | 1 | 5.4 | 67 | 0.32 | 1 | TOF VAL+SUB | ICR+TAP | 0 | 70 | 14.6 | 9500 | 1.6 | 2.3 | 2.6 | 2.2 | 1.8 | 2.3 | 2.5 | 12 | 8 | 20 | 32 | 23 |

| S.NO | GROUP MILRI-1,LEVO-2 | AGE IN MN | GENDER,F-1,M-2 | WT KG | HEIGHT CM | BSA KG/M2 | ADD VSD Y-1,N-0 | DIAGNOSIS | SURGERY | DSC N-0,Y-1 | BASELINE SAT% | PRE OP HB | TLC | PLATELETS | LACTATE-0 | LACTATE-6 | LACTATE-12 | LACTATE-24 | LACTATE-36 | LACTATE-48 | URINE OUTPUT-6 | URINE OUTPUT-12 | URINE OUTPUT-24 | URINE OUTPUT-36 | URINE OUTPUT-48 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 17 | 2 | 8 | 78 | 0.42 | 0 | TOF SUB VAL | ICR+RVOT PAT | 0 | 82 | 14.7 | 19400 | 2.7 | 1.7 | 0.9 | 1.2 | 1 | 2.5 | 2.2 | 28 | 12 | 20 | 15 | 22 |
| 2 | 2 | 7 | 2 | 4.7 | 67 | 0.3 | 1 | TOF SUB VAL | ICR+TAP | 0 | 78 | 15.3 | 11600 | 3.7 | 2.9 | 1.7 | 1.6 | 1.6 | 1.7 | 1.5 | 10 | 20 | 30 | 5 | 50 |
| 3 | 2 | 24 | 1 | 8.6 | 79 | 0.43 | 0 | TOF VAL PS | ICR+RVOT PAT | 0 | 78 | 11.6 | 8400 | 3.3 | 1.8 | 1.4 | 1.2 | 1.3 | 2.2 | 1.4 | 25 | 5 | 10 | 10 | 10 |
| 4 | 2 | 31 | 1 | 12 | 91 | 0.52 | 0 | TOF VAL+SUB | ICR+LPA PLAT | 0 | 82 | 14.9 | 9800 | 3.3 | 1.6 | 1.2 | 1.5 | 1.1 | 1.2 | 1 | 10 | 15 | 20 | 15 | 20 |
| 5 | 2 | 13 | 2 | 9 | 78 | 0.44 | 0 | TOF ,SUB VAL | ICR+RVOT PAT | 0 | 75 | 16 | 14200 | 3.8 | 1.1 | 1.3 | 1.1 | 2.6 | 0.9 | 1.1 | 12 | 12 | 20 | 36 | 38 |
| 6 | 2 | 8 | 1 | 5.5 | 62 | 0.3 | 0 | TOF ,SUB VAL | ICR+RVOT PAT | 0 | 88 | 14.2 | 9330 | 4.6 | 2.8 | 3 | 1.5 | 1.9 | 1.4 | 1.2 | 30 | 25 | 15 | 30 | 45 |
| 7 | 2 | 57 | 2 | 12 | 95 | 0.55 | 0 | TOF VAL PS | ICR+LPA PLAT | 0 | 82 | 18.6 | 5600 | 1.9 | 3.1 | 2.2 | 1.4 | 1.5 | 1 | 0.7 | 40 | 72 | 42 | 53 | 82 |
| 8 | 2 | 16 | 2 | 9 | 75 | 0.43 | 0 | TOF VAL+SUB | ICR+TAP+MCF | 0 | 90 | 14 | 11700 | 3.8 | 1.9 | 2.4 | 1.5 | 1.2 | 1.2 | 1.3 | 16 | 47 | 12 | 30 | 26 |
| 9 | 2 | 27 | 1 | 9.5 | 78 | 0.45 | 0 | TOF VAL+SUB | ICR+TAP+MCF | 0 | 79 | 15.6 | 9400 | 2.9 | 1.9 | 1.8 | 2.4 | 1.3 | 1.1 | 1.1 | 52 | 16 | 20 | 80 | 32 |
| 10 | 2 | 12 | 2 | 9.5 | 72 | 0.42 | 0 | TOF VAL+SUB | ICR+RVOT PAT | 0 | 98 | 11.4 | 7500 | 3.3 | 1.9 | 1 | 0.8 | 1.3 | 3.1 | 1.8 | 46 | 68 | 23 | 32 | 30 |
| 11 | 2 | 24 | 1 | 12 | 84 | 0.53 | 0 | TOF VAL+SUB | ICR+LPA PLAT | 0 | 72 | 20.2 | 6400 | 2.7 | 2.6 | 1 | 2.2 | 2 | 1.8 | 2.8 | 30 | 46 | 25 | 56 | 23 |
| 12 | 2 | 10 | 2 | 8.5 | 75 | 0.42 | 0 | TOF VAL PS | ICR+TAP+MCF | 0 | 75 | 10 | 8190 | 2.8 | 2.1 | 1.4 | 1.3 | 3 | 1.8 | 1.9 | 26 | 25 | 17 | 16 | 14 |
| 13 | 2 | 144 | 1 | 33 | 141 | 1.1 | 0 | TOF-PA+LPAS | ICR+TAP+MCF | 0 | 76 | 20.2 | 6030 | 2.3 | 1.5 | 1 | 2.4 | 1.6 | 2.1 | 1.6 | 68 | 66 | 100 | 80 | 110 |
| 14 | 2 | 3 | 1 | 4.2 | 55 | 0.25 | 0 | TOF-APV | ICR+TAP+MCF | 0 | 84 | 10.3 | 9780 | 1.1 | 1.7 | 0.7 | 0.8 | 0.8 | 0.9 | 0.8 | 12 | 9 | 11 | 20 | 16 |
| 15 | 2 | 21 | 2 | 12 | 79 | 0.5 | 0 | TOF VAL PS | ICR+TAP | 0 | 86 | 15.2 | 16600 | 3.6 | 3.6 | 2.9 | 1.3 | 1 | 0.9 | 1.1 | 40 | 30 | 20 | 18 | 20 |
| 16 | 2 | 31 | 2 | 8.8 | 83 | 0.45 | 0 | TOF SUB VAL | ICR+RVOT PAT | 0 | 83 | 17.6 | 9300 | 2.6 | 2.6 | 2.7 | 1.5 | 1 | 0.9 | 1.4 | 22 | 27 | 52 | 40 | 42 |
| 17 | 2 | 16 | 2 | 8 | 73 | 0.4 | 0 | TOF SUB VAL | ICR+RVOT PAT | 0 | 96 | 13.9 | 13500 | 4.2 | 2 | 1.8 | 1.5 | 3 | 1.7 | 1.5 | 20 | 12 | 40 | 25 | 20 |
| 18 | 2 | 7 | 2 | 5.2 | 59 | 0.3 | 0 | TOF SUB VAL | ICR+RVOT PAT | 0 | 85 | 15.6 | 11220 | 3.0 | 1.2 | 0.8 | 1.1 | 1.3 | 1.8 | 1.2 | 40 | 30 | 20 | 30 | 25 |
| 19 | 2 | 24 | 1 | 12 | 84 | 0.53 | 0 | TOF VAL+SUB | ICR+LPA PLAT | 0 | 72 | 20.2 | 6400 | 2.7 | 2.6 | 1 | 2.2 | 2 | 1.8 | 2.8 | 30 | 46 | 25 | 56 | 23 |

| TEMP(C-P)-0 | TEMP(C-P)-6 | TEMP(C-P)-12 | TEMP(C-P)-24 | TEMP(C-P)-36 | TEMP(C-P)-48 | RPI-0 | RPI-6 | RPI-12 | RPI-24 | RPI-36 | RPI-48 | SCVO2-0 | SCVO2-6 | SCVO2-12 | SCVO2-24 | SCVO2-36 | SCVO2-48 | A-VSO2-0 | A-VSO2-6 | A-VSO2-12 | A-VSO2-24 | A-VSO2-36 | A-VSO2-48 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 5.8 | 6.5 | 9.2 | 1.8 | 2.4 | 2.6 | 12600 | 10164 | 9828 | 11466 | 9408 | 9350 | 69 | 66 | 67 | 66 | 67 | 66 | 30 | 33 | 32 | 33 | 32 | 34 |
| 3 | 2 | 1 | 9 | 2 | 4 | 11550 | 9248 | 11520 | 12480 | 12150 | 11340 | 58 | 62 | 64 | 62 | 60 | 62 | 40 | 37 | 34 | 36 | 38 | 37 |
| 4 | 5 | 5 | 3 | 9 | 8 | 14628 | 10880 | 10318 | 8094 | 9840 | 10624 | 72 | 67 | 74 | 72 | 73 | 72 | 18 | 15 | 17 | 16 | 26 | 22 |
| 3 | 3.7 | 7 | 3.6 | 5.2 | 1.9 | 10452 | 9984 | 10353 | 8784 | 12272 | 8670 | 73 | 67 | 66 | 66 | 55 | 53 | 17 | 30 | 30 | 31 | 44 | 46 |
| 7 | 8 | 4 | 4 | 4.2 | 6 | 14400 | 12474 | 8700 | 7140 | 9344 | 10530 | 70 | 66 | 69 | 66 | 64 | 64 | 29 | 33 | 30 | 32 | 50 | 32 |
| 5 | 5.6 | 9 | 4 | 5 | 4 | 12220 | 9520 | 10650 | 10764 | 10824 | 9322 | 55 | 64 | 53 | 67 | 68 | 70 | 43 | 35 | 42 | 28 | 30 | 26 |
| 6 | 3.2 | 7.5 | 5.2 | 9 | 5 | 17658 | 11016 | 10701 | 12730 | 11280 | 10980 | 48 | 50 | 42 | 54 | 58 | 62 | 43 | 44 | 51 | 42 | 40 | 36 |
| 3.2 | 4 | 3.4 | 3.2 | 6 | 3 | 11424 | 10680 | 8308 | 9430 | 10560 | 8680 | 74 | 67 | 69 | 67 | 69 | 66 | 26 | 32 | 31 | 30 | 21 | 33 |
| 6 | 12 | 4 | 9 | 7 | 6 | 14400 | 12700 | 11663 | 10440 | 10032 | 9540 | 64 | 65 | 57 | 61 | 70 | 61 | 36 | 34 | 42 | 32 | 27 | 36 |
| 3.3 | 2.5 | 5.2 | 6.3 | 5 | 5 | 14378 | 12000 | 9875 | 8978 | 10336 | 12936 | 68 | 88 | 58 | 67 | 68 | 68 | 31 | 11 | 40 | 30 | 31 | 30 |
| 3 | 4.8 | 2.8 | 3 | 2.8 | 2.4 | 14259 | 12496 | 10912 | 10004 | 10800 | 11468 | 90 | 60 | 64 | 62 | 64 | 70 | 37 | 35 | 38 | 34 | 30 | 26 |
| 8 | 7 | 4 | 3 | 2 | 6 | 13674 | 10360 | 9100 | 10384 | 10492 | 10164 | 77 | 70 | 66 | 68 | 68 | 67 | 22 | 30 | 33 | 30 | 31 | 32 |
| 8.5 | 4 | 6.5 | 4.7 | 4.2 | 4 | 14396 | 9009 | 10353 | 9694 | 8850 | 9009 | 55 | 52 | 66 | 66 | 65 | 68 | 34 | 36 | 33 | 33 | 33 | 30 |
| 4.4 | 8 | 3.2 | 4.4 | 7 | 6 | 16128 | 11676 | 9184 | 9440 | 13328 | 12600 | 62 | 63 | 65 | 67 | 56 | 58 | 38 | 37 | 34 | 32 | 39 | 37 |
| 6.2 | 8.9 | 10 | 11 | 3.7 | 9 | 4200 | 4260 | 10880 | 12028 | 12350 | 12441 | 65 | 61 | 61 | 62 | 64 | 60 | 33 | 37 | 36 | 35 | 34 | 38 |
| 7 | 4 | 6 | 6 | 6 | 6 | 14632 | 10716 | 11020 | 10148 | 8892 | 12804 | 68 | 66 | 69 | 65 | 68 | 70 | 30 | 33 | 30 | 34 | 30 | 28 |
| 8 | 5 | 6.4 | 3.3 | 4 | 8 | 13736 | 11224 | 11252 | 8856 | 6840 | 11340 | 60 | 68 | 62 | 60 | 67 | 68 | 38 | 30 | 37 | 38 | 32 | 30 |
| 7 | 5 | 5.4 | 5 | 5.5 | 6 | 11440 | 10044 | 11115 | 11858 | 10266 | 9348 | 68 | 66 | 68 | 67 | 80 | 71 | 30 | 32 | 30 | 31 | 20 | 28 |
| 5 | 4 | 3.5 | 3 | 5.4 | 4 | 12150 | 8122 | 8320 | 11440 | 13392 | 10800 | 59 | 55 | 58 | 56 | 52 | 58 | 33 | 39 | 35 | 37 | 38 | 35 |
| 3.6 | 10.7 | 3 | 6 | 4 | 3 | 9800 | 10212 | 9728 | 12180 | 11475 | 16440 | 62 | 58 | 60 | 64 | 66 | 67 | 36 | 40 | 38 | 36 | 33 | 32 |

| TEMP(C-P)-0 | TEMP(C-P)-6 | TEMP(C-P)-12 | TEMP(C-P)-24 | TEMP(C-P)-36 | TEMP(C-P)-48 | RPI-0 | RPI-6 | RPI-12 | RPI-24 | RPI-36 | RPI-48 | SCVO2-0 | SCVO2-6 | SCVO2-12 | SCVO2-24 | SCVO2-36 | SCVO2-48 | A-VSO2-0 | A-VSO2-6 | A-VSO2-12 | A-VSO2-24 | A-VSO2-36 | A-VSO2-48 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 5.4 | 5.4 | 5.6 | 5.4 | 5.6 | 5 | 11925 | 9240 | 8142 | 8946 | 9315 | 15252 | 78 | 67 | 58 | 62 | 65 | 69 | 21 | 33 | 41 | 36 | 34 | 30 |
| 4.6 | 4.8 | 3.3 | 6.6 | 5 | 5 | 12717 | 10439 | 10920 | 11620 | 9100 | 9398 | 65 | 62 | 66 | 65 | 65 | 68 | 33 | 32 | 30 | 32 | 30 | 29 |
| 7.7 | 5.3 | 5.4 | 5.2 | 5 | 4.8 | 11088 | 9234 | 8855 | 10080 | 13064 | 12496 | 78 | 71 | 63 | 68 | 66 | 66 | 20 | 20 | 35 | 30 | 33 | 33 |
| 6.4 | 4.3 | 4.1 | 8.9 | 4.5 | 4.2 | 14040 | 9075 | 8496 | 8690 | 10192 | 11176 | 83 | 70 | 68 | 68 | 65 | 67 | 15 | 28 | 32 | 32 | 33 | 32 |
| 3.3 | 3.7 | 4.3 | 5 | 9 | 6 | 12328 | 14014 | 9204 | 11310 | 9052 | 8468 | 72 | 67 | 67 | 57 | 66 | 71 | 27 | 29 | 32 | 42 | 33 | 28 |
| 2 | 7.4 | 7.7 | 7.6 | 8.6 | 4.7 | 12288 | 11100 | 11544 | 12054 | 11760 | 11325 | 59 | 55 | 53 | 64 | 63 | 61 | 38 | 40 | 40 | 31 | 34 | 36 |
| 4 | 3.1 | 3 | 3 | 6 | 3.4 | 11040 | 8066 | 8066 | 7150 | 8580 | 7344 | 58 | 62 | 64 | 74 | 72 | 69 | 40 | 36 | 34 | 25 | 27 | 26 |
| 6.4 | 8 | 7.7 | 7.8 | 7.6 | 7.6 | 12920 | 13959 | 11058 | 9840 | 9600 | 12032 | 72 | 69 | 65 | 65 | 61 | 68 | 27 | 26 | 33 | 32 | 29 | 20 |
| 6.5 | 3.4 | 6.1 | 4 | 4.4 | 7.6 | 12549 | 10350 | 10080 | 9170 | 10530 | 11960 | 75 | 76 | 74 | 66 | 65 | 64 | 25 | 22 | 24 | 33 | 34 | 33 |
| 4.3 | 5 | 6 | 9 | 8.6 | 7.6 | 14338 | 10500 | 9856 | 11524 | 14960 | 12288 | 70 | 73 | 65 | 70 | 64 | 68 | 30 | 26 | 34 | 28 | 36 | 32 |
| 4.5 | 5.2 | 6.1 | 3.4 | 4.2 | 4 | 14832 | 8911 | 11424 | 7722 | 9198 | 8260 | 64 | 71 | 60 | 63 | 69 | 67 | 35 | 26 | 38 | 34 | 29 | 33 |
| 7.4 | 5.1 | 4.2 | 4.6 | 4.4 | 5.4 | 12825 | 10080 | 10320 | 11440 | 12126 | 13800 | 62 | 63 | 63 | 68 | 67 | 69 | 38 | 37 | 36 | 31 | 32 | 30 |
| 3.7 | 6.5 | 3.3 | 2.6 | 3.5 | 3 | 11660 | 12240 | 8160 | 8880 | 10560 | 10440 | 74 | 69 | 71 | 60 | 62 | 60 | 25 | 29 | 27 | 30 | 28 | 30 |
| 7.4 | 9.8 | 7.6 | 8.2 | 5.3 | 10 | 14784 | 14852 | 10500 | 9360 | 14980 | 12672 | 65 | 66 | 65 | 67 | 62 | 64 | 32 | 32 | 34 | 30 | 36 | 34 |
| 9 | 9 | 5.2 | 7.6 | 3.5 | 9 | 15930 | 15190 | 10080 | 10564 | 8520 | 10611 | 61 | 62 | 61 | 62 | 63 | 65 | 38 | 37 | 37 | 36 | 37 | 34 |
| 5.5 | 8 | 6.8 | 8 | 4 | 7 | 11310 | 10790 | 10010 | 11050 | 9750 | 12220 | 72 | 60 | 52 | 65 | 64 | 62 | 25 | 37 | 43 | 33 | 34 | 37 |
| 1 | 3.5 | 7 | 6 | 5.5 | 5 | 12000 | 12480 | 11160 | 11640 | 9000 | 10400 | 60 | 75 | 71 | 67 | 77 | 75 | 39 | 24 | 27 | 31 | 22 | 24 |
| 3 | 4 | 6 | 4.6 | 7 | 7 | 11904 | 12393 | 10707 | 8850 | 10043 | 8160 | 78 | 66 | 64 | 63 | 73 | 60 | 20 | 32 | 34 | 35 | 26 | 37 |
| 4.5 | 5.2 | 6.1 | 3.4 | 4.2 | 4 | 14832 | 8911 | 11424 | 7722 | 9198 | 8260 | 64 | 71 | 60 | 63 | 69 | 67 | 35 | 26 | 38 | 34 | 29 | 33 |

| ARRHYTHMIAS NO-0,YES-1 | DIASFORWARD FLOW NO-0,YES-1 | RVOT -PA PEAK GD-POST CPB TEE | RVOT PA GD POD1(TTE) | RVOT PA GD POD2(TTE) | RVOT PA GD POD3(TTE) | PFO NO-0,L-R 1,R-L 2,- POST CPB TEE | PFO L-R 1,R-L 2,- POD1(TTE) | PFO L-R 1,R-L 2,- POD2(TTE) | PFO L-R 1,R-L 2,- POD3(TTE) | RE INTERVENTION N-0,Y-1 | LOS-ICU IN DAYS | LOS-HOSPITAL IN DAYS | DURATION OF MECH VENTILATION | DURATION OF CHEST DRAIN( HRS) | CHEST DRAIN (ML/KG) | MILRINONE MCG/KG | RESCUE MILRI IN HRS | NORADR | ADR | VASOPRESSIN | NTG | VIS @ 0hr | VIS @ 6hr | VIS @ 12hr | VIS @ 24hr | VIS @36hr | VIS @48hr | CPB IN MIN | ACC IN MIN |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 15 | 12 | 5 | 5 | 0 | 0 | 0 | 0 | 0 | 5 | 7 | 18 | 28 | 24 | 1440 | 0 | 54 | 0 | 0 | 0 | 10 | 10 | 10 | 5 | 5 | 5 | 144 | 95 |
| 0 | 1 | 35 | 45 | 45 | 60 | 0 | 0 | 0 | 0 | 0 | 6 | 8 | 14 | 24 | 46 | 2160 | 24 | 39 | 0 | 0 | 0 | 10 | 10 | 10 | 5 | 5 | 5 | 153 | 84 |
| 1 | 1 | 18 | 24 | 26 | 29 | 2 | 1 | 1 | 1 | 0 | 11 | 13 | 96 | 144 | 48 | 2880 | 48 | 0 | 138 | 0.612 | 0 | 18 | 18 | 18 | 18 | 15 | 5 | 141 | 96 |
| 0 | 0 | 28 | 34 | 20 | 20 | 0 | 0 | 0 | 0 | 0 | 3 | 7 | 20 | 4 | 50 | 2160 | 24 | 135 | 0 | 0 | 0 | 10 | 10 | 10 | 10 | 10 | 5 | 145 | 117 |
| 0 | 0 | 20 | 18 | 22 | 28 | 1 | 1 | 1 | 1 | 0 | 4 | 7 | 18 | 36 | 40 | 1440 | 0 | 75 | 0 | 0 | 0 | 10 | 10 | 10 | 10 | 5 | 5 | 155 | 117 |
| 1 | 0 | 16 | 15 | 18 | 20 | 1 | 1 | 1 | 1 | 0 | 5 | 7 | 18 | 72 | 34 | 1620 | 12 | 63 | 0 | 0 | 0 | 10 | 10 | 10 | 5 | 5 | 5 | 145 | 105 |
| 1 | 0 | 22 | 18 | 14 | 12 | 1 | 1 | 1 | 1 | 0 | 4 | 7 | 18 | 36 | 23 | 1440 | 0 | 0 | 0 | 0 | 0 | 5 | 5 | 5 | 5 | 5 | 5 | 138 | 90 |
| 0 | 0 | 3 | 2 | 2 | 3 | 1 | 1 | 1 | 1 | 0 | 6 | 8 | 17 | 36 | 17 | 1440 | 0 | 36 | 0 | 0 | 0 | 10 | 10 | 10 | 5 | 5 | 5 | 147 | 109 |
| 1 | 0 | 14 | 15 | 12 | 15 | 0 | 0 | 0 | 0 | 0 | 2 | 5 | 8 | 41 | 20 | 1440 | 0 | 0 | 0 | 0 | 0 | 5 | 5 | 5 | 5 | 5 | 5 | 126 | 79 |
| 0 | 1 | 7 | 10 | 12 | 14 | 0 | 0 | 0 | 0 | 1 | 6 | 8 | 69 | 72 | 45 | 2970 | 51 | 240 | 0 | 0.756 | 0 | 13 | 13 | 13 | 13 | 13 | 10 | 222 | 143 |
| 0 | 0 | 22 | 18 | 18 | 12 | 0 | 0 | 0 | 0 | 0 | 3 | 5 | 18 | 8 | 18 | 1440 | 0 | 0 | 0 | 0 | 0 | 5 | 5 | 5 | 5 | 5 | 5 | 138 | 88 |
| 0 | 0 | 12 | 18 | 20 | 18 | 0 | 0 | 0 | 0 | 0 | 4 | 7 | 21 | 32 | 27 | 1860 | 14 | 48 | 0 | 0 | 0 | 10 | 10 | 10 | 5 | 5 | 5 | 146 | 97 |
| 0 | 0 | 35 | 30 | 30 | 26 | 0 | 0 | 0 | 0 | 0 | 3 | 6 | 18 | 36 | 45 | 1680 | 12 | 186 | 57 | 0 | 0 | 20 | 20 | 15 | 10 | 10 | 10 | 221 | 168 |
| 0 | 0 | 23 | 35 | 28 | 26 | 0 | 0 | 0 | 0 | 0 | 7 | 8 | 19 | 36 | 36 | 1680 | 8 | 78 | 0 | 0 | 0 | 10 | 10 | 10 | 10 | 5 | 5 | 138 | 92 |
| 0 | 0 | 17 | 8 | 5 | 5 | 1 | 1 | 1 | 1 | 0 | 5 | 7 | 20 | 38 | 38 | 2100 | 22 | 84 | 0 | 0 | 0 | 10 | 10 | 10 | 10 | 5 | 5 | 132 | 92 |
| 0 | 0 | 18 | 12 | 14 | 32 | 0 | 0 | 0 | 0 | 0 | 3 | 5 | 18 | 14 | 6 | 1440 | 0 | 60 | 0 | 0 | 0 | 10 | 10 | 10 | 5 | 5 | 5 | 203 | 112 |
| 0 | 0 | 19 | 18 | 15 | 15 | 0 | 0 | 0 | 0 | 0 | 5 | 6 | 18 | 50 | 58 | 1440 | 0 | 21 | 0 | 0 | 0 | 10 | 10 | 5 | 5 | 5 | 5 | 196 | 153 |
| 0 | 0 | 22 | 20 | 18 | 20 | 0 | 0 | 0 | 0 | 0 | 4 | 5 | 16 | 30 | 21 | 1440 | 0 | 36 | 0 | 0 | 0 | 10 | 10 | 10 | 5 | 5 | 5 | 197 | 122 |
| 1 | 0 | 38 | 15 | 18 | 33 | 1 | 1 | 1 | 1 | 0 | 6 | 8 | 20 | 40 | 35 | 3450 | 67 | 198 | 132 | 0 | 0 | 20 | 20 | 20 | 15 | 15 | 15 | 208 | 133 |
| 0 | 0 | 17 | 15 | 10 | 12 | 0 | 0 | 0 | 0 | 0 | 3 | 7 | 14 | 36 | 35 | 1980 | 18 | 90 | 0 | 0 | 0 | 10 | 10 | 10 | 10 | 5 | 5 | 141 | 106 |

| ARRHYTHMIAS NO-0,YES-1 | DIASFORWARD FLOW NO-0,YES-1 | RVOT -PA PEAK GD-POST CPB TEE | RVOT PA GD POD1(TTE) | RVOT PA GD POD2(TTE) | RVOT PA GD POD3(TTE) | PFO NO-0,L-R 1,R-L 2,- POST CPB TEE | PFO L-R 1,R-L 2,- POD1(TTE) | PFO L-R 1,R-L 2,- POD2(TTE) | PFO L-R 1,R-L 2,- POD3(TTE) | RE INTERVENTION N-0,Y-1 | LOS-ICU IN DAYS | LOS-HOSPITAL IN DAYS | DURATION OF MECH VENTILATION | DURATION OF CHEST DRAIN( HRS) | CHEST DRAIN (ML/KG) | LEVOSIMENDAN MCG/KG | RESCUE MILRI IN HRS | NORADR | ADR | VASOPRESSIN | NTG | VIS @ 0hr | VIS @ 6hr | VIS @ 12hr | VIS @ 24hr | VIS @36hr | VIS @48hr | CPB IN MIN | ACC IN MIN |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 0 | 3 | 2 | 3 | 3 | 0 | | 0 | 0 | 0 | 2 | 4 | 3 | 24 | 25 | 288 | 0 | 36 | 0 | 0 | 0 | 10 | 10 | 10 | 5 | 5 | 5 | 129 | 99 |
| 0 | 0 | 8 | 6 | 6 | 6 | 1 | 2 | 2 | 2 | 1 | 8 | 10 | 18 | 16 | 62 | 288 | 66 | 123 | 0 | 0 | 0 | 10 | 10 | 10 | 10 | 10 | 5 | 142 | 94 |
| 0 | 0 | 20 | 22 | 24 | 24 | 1 | 1 | 1 | 1 | 0 | 3 | 7 | 6 | 16 | 22 | 288 | 0 | 0 | 0 | 0 | 0 | 5 | 5 | 5 | 5 | 5 | 5 | 112 | 85 |
| 0 | 0 | 32 | 30 | 22 | 20 | 1 | 1 | 1 | 1 | 0 | 2 | 4 | 20 | 15 | 15 | 288 | 0 | 0 | 0 | 0 | 0 | 10 | 10 | 10 | 5 | 5 | 5 | 185 | 149 |
| 0 | 0 | 32 | 30 | 32 | 28 | 1 | 1 | 1 | 1 | 0 | 5 | 7 | 21 | 50 | 26 | 288 | 0 | 0 | 0 | 0 | 0 | 5 | 5 | 5 | 5 | 5 | 5 | 165 | 94 |
| 0 | 1 | 6 | 4 | 4 | 3 | 1 | 1 | 1 | 1 | 0 | 6 | 8 | 51 | 62 | 22 | 288 | 0 | 78 | 51 | 0 | 0 | 15 | 15 | 15 | 10 | 5 | 5 | 149 | 120 |
| 0 | 0 | 40 | 36 | 30 | 30 | 0 | 0 | 0 | 0 | 0 | 5 | 7 | 17 | 36 | 24 | 288 | 0 | 0 | 0 | 0 | 0 | 5 | 5 | 5 | 5 | 5 | 5 | 234 | 161 |
| 1 | 0 | 20 | 28 | 30 | 20 | 0 | 0 | 0 | 0 | 0 | 2 | 5 | 3 | 24 | 16 | 288 | 0 | 0 | 0 | 0 | 300 | 6 | 5 | 5 | 5 | 5 | 5 | 120 | 67 |
| 0 | 0 | 16 | 10 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 5 | 7 | 17 | 40 | 32 | 288 | 0 | 120 | 0 | 0 | 0 | 10 | 10 | 10 | 10 | 10 | 5 | 159 | 128 |
| 0 | 0 | 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 4 | 6 | 40 | 24 | 288 | 0 | 0 | 0 | 0 | 0 | 5 | 5 | 5 | 5 | 5 | 5 | 88 | 64 |
| 0 | 0 | 14 | 10 | 14 | 28 | 1 | 1 | 1 | 1 | 0 | 3 | 5 | 19 | 42 | 18 | 288 | 0 | 0 | 0 | 0 | 0 | 5 | 5 | 5 | 5 | 5 | 5 | 160 | 103 |
| 0 | 0 | 23 | 20 | 15 | 15 | 1 | 1 | 1 | 1 | 0 | 4 | 6 | 6 | 30 | 15 | 288 | 0 | 0 | 0 | 0 | 0 | 5 | 5 | 5 | 5 | 5 | 5 | 109 | 84 |
| 1 | 0 | 20 | 22 | 20 | 18 | 1 | 1 | 1 | 1 | 0 | 4 | 8 | 15 | 50 | 40 | 288 | 0 | 0 | 0 | 0 | 0 | 5 | 5 | 5 | 5 | 5 | 5 | 140 | 92 |
| 0 | 0 | 15 | 10 | 5 | 2 | 0 | 0 | 0 | 0 | 0 | 3 | 8 | 27 | 38 | 20 | 288 | 12 | 66 | 0 | 0 | 0 | 10 | 10 | 10 | 5 | 5 | 5 | 136 | 88 |
| 0 | 0 | 9 | 4 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 4 | 5 | 19 | 40 | 18 | 288 | 69 | 0 | 0 | 0 | 0 | 5 | 5 | 5 | 5 | 5 | 5 | 103 | 66 |
| 1 | 0 | 30 | 26 | 26 | 28 | 1 | 1 | 1 | 1 | 0 | 4 | 7 | 23 | 60 | 28 | 288 | 17 | 15 | 0 | 0 | 0 | 10 | 5 | 5 | 5 | 5 | 5 | 198 | 136 |
| 0 | 0 | 13 | 18 | 20 | 26 | 0 | 0 | 0 | 0 | 0 | 5 | 9 | 7 | 84 | 100 | 288 | 0 | 0 | 0 | 0 | 0 | 5 | 5 | 5 | 5 | 5 | 5 | 138 | 93 |
| 1 | 0 | 7 | 6 | 4 | 3 | 0 | 0 | 0 | 0 | 0 | 4 | 7 | 20 | 24 | 44 | 288 | 0 | 0 | 0 | 0 | 0 | 5 | 5 | 5 | 5 | 5 | 5 | 115 | 83 |
| 0 | 0 | 14 | 10 | 14 | 28 | 1 | 1 | 1 | 1 | 0 | 3 | 5 | 19 | 42 | 18 | 288 | 0 | 0 | 0 | 0 | 0 | 5 | 5 | 5 | 5 | 5 | 5 | 160 | 103 |