International Journal of Chemical and Biochemical Sciences
(ISSN 2226-9614)

Journal Home page: www.iscientific.org/Journal.html

Bosentan and sildenafil in pulmonary hypertension in cardiac anesthesia: Mansoura novel strategy

Magdy Mamdouh Mahmoud Atallah[1], Ola Taha Abdeldayem[1], Naglaa Abdelatief El-Negeery[2], Mohamed El Gamal [3], Mahmoud Nabil Badr-eldin[1]*

[1]*Faculty of Medicine, Mansoura University, Egypt.*

[2]*Faculty of Medicine, Mansoura University, Egypt.*

Abstract

The most frequent etiology of pulmonary hypertension (PHTN) globally is left-sided heart diseases and its presence in cases undergoing cardiac surgery could negatively affect outcomes. to assess the effect of bosentan on PHTN when added to sildenafil in mitral valve disease versus usage of sildenafil alone as a primary goal. This prospective randomized comparative study conducted on 80 patients undergoing cardiac procedures as mitral or double valve replacement surgery that required cardiopulmonary bypass (CPB) and median sternotomy at Cardiothoracic & Vascular Surgical Center, Mansoura University Hospitals over 24 months started from November 2021 till November 2023. The pulmonary artery systolic pressure (PASP) measured by preoperative TTE showed no significant difference between the two groups. Intraoperative TEE done pre bypass showed no significant statistical difference between the study groups in PASP, while TEE done post bypass demonstrated PASP was significantly lower in SB group when compared to S group. In ICU, Postoperative TTE done and demonstrated statistically significant decrease in PASP in SB group compared to S group. Vasoactive-inotropic score (VIS) was significantly statistically lower in the SB group in comparison to the S group in ICU at 6 hours, 12 hours and at 24 hours. Combination of sildenafil and bosentan offered a better patient outcome more stable hemodynamics, earlier extubation and shorter ICU stay. It offers less complications during and after surgery.

Keywords: Phosphodiesterase-5, Pulmonary Hypertension, cardiopulmonary bypass.

Full length article **Corresponding Author*, e-mail: **mahmoudbadr@mans.edu.eg**

1. Introduction

The most frequent etiology of PHTN globally is left-sided heart diseases and its existence in cases undergoing cardiac surgeries could negatively affect outcomes. Regression of PHTN is often partial following correction of the valvular lesions .[1] In the perioperative onset, management of PHTN is challenging and frequently involves sedation, maintaining low partial pressure of carbon dioxide (CO2) in arterial blood by hyperventilation, and the use of pulmonary vasodilators. Pulmonary vascular resistance (PVR) can be lowered with inhaled NO, which increases cyclic guanine monophosphate (cGMP). Although utilization of inhaled NO alone is of great efficiency, its usage is affected by the need for an exclusive delivery system and recurrent PHTN after its stoppage [2]. Phosphodiesterase-5 (PDE-5) is an enzyme present in high concentrations in the lungs and functions to degrade cGMP formed following NO attaches to soluble guanylate cyclase. Such degradation of cGMP has been demonstrated to be accompanied by impairment of pulmonary vasodilation (VD). The PDE-5 inhibitors (such as sildenafil) prevent cGMP degradation, as a result conserving NO bioavailability which ultimately ends in the production of selective pulmonary VD and evading the adverse events of its inhalation [3]. Bosentan, used to treat PHTN by blocking the action of endothelin (ET) molecules (ET-A and ET-B), is demonstrated to reduce the inflammatory processes, vasoconstriction (VC) and pulmonary vascular fibrosis [4,5]. The aim was to evaluate bosentan effect on pulmonary arterial hypertension when added to sildenafil in mitral valve disease versus usage of sildenafil alone as a primary goal, while the secondary goals were to identify the effect of bosentan on: dose of vasoactive medications during weaning from bypass, systemic blood pressure (BP) and circulation and on duration of ICU admission and hospital stay. TEE assessment of PASP and RV systolic function intraoperative.

2. Patients and methods

This double blinded prospective randomized comparative study carried out on 80 cases undergoing cardiac approaches as mitral or double valve replacement surgery which needed CPB and median sternotomy at Cardiothoracic & Vascular Surgical Center, Mansoura University Hospitals over 24 months started from November 2021 till November 2023. Patients were haphazardly assigned to one of two equal groups each comprises 40 patients, based on computer-generated randomization sequence: Sildenafil group (S group) and Sildenafil plus bosentan group (SB group).

2.1 Inclusion criteria

Adult patients of either gender, aged between 20 and 70 years with American Society of Anesthesiologists (ASA) physical status II & III, body mass index less than 40 kg/m^2 with PASP greater than 70 mmHg by transthoracic echocardiography scheduled for mitral or double valve replacement with median sternotomy that required CPB at Cardiothoracic & Vascular Surgical Center, Mansoura University Hospitals.

2.2 Exclusion criteria

Cases with pulmonary dysfunction or COPD, preceding cardiothoracic surgeries, emergency surgeries, ejection fraction below 40%, uncontrolled diabetes (HbA1c>7), neurological or hematological disorders, cases with major hepatic or renal impairment were ruled out.

2.3 Ethical consideration

After approval of the IRB, Faculty of Medicine, Mansoura University with code number "MD.21.10.538". The study was registered on Pan African Clinical Trials Registry with Identifier number: PACTR202209903019732.Written informed consent was obtained from all cases before their participation. A pilot study was carried out to adjust the the doses. The participant's data were confidential and the patients were free to leave the research at any time without any penalty. There was no conflict of interest with any company or sponsor included in this study.

2.4 Study design and grouping

•Prospective randomized comparative study.
•Eligible 80 patients were randomly allocated to one of two equal groups each contains 40 patients, they were randomized according to computer-generated randomization sequence: Sildenafil group (S group) and Sildenafil plus bosentan group (SB group).

2.5 Statistical analysis

A priori G power analysis was done based on value of pulmonary artery pressure in previous study. Using the t-test for comparison and setting alpha to 0.05, we need minimally 46 cases to detect a similar difference with 80% power. A drop out of 10% of cases will be expected. Therefore, a total number of 50 cases will be needed (25 cases per group). Calculations were done using G power software Windows version 3.0.10.
IBM's SPSS statistics (Statistical Package for the Social Sciences) for windows (version 25, 2017) was used for statistical analysis of the collected data. Shapiro-Wilk test was used to check the normality of the data distribution in continuous variables. Continuous variables were expressed as mean ± SD while categorical ones were expressed as number and percentage. Independent samples t-test and Mann Whitney independent samples test were used to compare normally and abnormally distributed continuous variables with no follow up readings respectively. Repeated measures ANOVA model with Bonferroni post Hoc test and 95% confidence interval to compare the follow-up values of continuous data. Fisher exact test was used for inter-group comparison of nominal and ordinal data using the crosstabs function. Comparison of follow-up and basal values (intra-group) was conducted using Wilcoxon signed ranks test and McNemar test for ordinal and nominal data respectively. All tests were conducted with 95% confidence interval. Charts were generated using SPSS' chart builder. P (probability) value < 0.05 was considered statistically significant.

2.6 Methods

In the outpatient clinic, 40 patients were randomly assigned to 20mg sildenafil and placebo twice daily for 4-6 weeks and 40 patients were assigned to 20mg sildenafil twice daily plus bosentan 62.5mg twice daily for 4-6weeks.

2.6.1 Intraoperative

On the morning of surgery, peripheral venous cannula (16-18 gauge) was inserted, patient was premedicated with intravenous 2-3 mg midazolam and a loading dose of antibiotic (ceftriaxone 2 gram) and 2 gm of tranexamic acid in 500 ml saline was infused, basic monitoring equipment were attached to the patient (Electrocardiograph, pulse oximetry and noninvasive BP). Then arterial line (20-gauge catheter) was inserted in non-dominant hand after performing modified Allen test using local anaesthesia (lidocaine 2%) for invasive BP supervision and frequent arterial blood gas (ABG) samples. Induction, anaesthesia was induced by IV fentanyl 3-5 µg/kg, propofol 1-2mg/kg and atracurium 0.5mg/kg. All patients were mechanically ventilated using (GE Healthcare, AVANCE, CS2, United States) ventilator. Maintenance of anaesthesia was accomplished by isoflurane with concentration 0.5-1.5 % with FiO2 0.4 in air. Throughout CPB anesthesia was maintained by continuous infusion of Propofol at a rate of 2-4mg/kg/hr. and Atracurium at a rate of 10µg/kg/min. Transesophageal ECHO probe (Vivid T8 GE® TEE probe) was inserted. Surgical technique was done by a team of cardiothoracic consultant surgeons. Skin incision was done followed by sternotomy and pericardium was opened. Basal activated clotting time (ACT) was measured and recorded by (Hemochron: Actalyke MINI II) Activated clotting time test system. Heparin was given in a dose (300-400IU/kg) to achieve ACT of (400 for cannulation- 480 sec for going on CPB) after the surgeon started to take piercing sutures in the ascending aorta and right atrium, then aortic and bicaval atrial cannulation was done. Intraoperative hypotension means arterial blood pressure (MAP<60) before bypass was corrected by 250ml ringer acetate and if not corrected an incremental dose of norepinephrine was given. Bradycardia which occur before bypass was corrected by incremental doses of atropine.

During bypass time, non-pulsatile flow CPB was primed by total volume of 1300ml of the following constituent's mannitol (0.5gm/kg) and ringer acetate.

Patients were anaesthetized during bypass time using syringe pump containing Propofol at a rate of 2-4 mg/kg/hr. and Atracurium at a rate of 10 μg/kg/min. Temperature was kept between (32-34Ċ), flow rate not below 2.5 L/min/m2 to maintain perfusion pressure between 50 - 80mmHg and hematocrit (HCT) (25-30). On bypass, if hypotension occurred a norepinephrine was given if increasing flow rate not achieving the goal. Failure to correct hypotension on bypass, ABG and CBC was done and anemia and electrolyte disturbances was corrected if present. Cardioplegia was achieved by warm-blood cardioplegic solution after aortic cross clamping containing 10-20 mEq potassium chloride KCL, 1 gm magnesium, 250 mg xylocaine and 10 ml of 8.4 % sodium bicarbonate. Transesophageal echo (TEE) was set at TE aortic long axis (Ao LAX) view 120° to ensure competence of aortic valve during administration of cardioplegic solution. Weaning from bypass was done according to our institutional protocol which include heart rate (HR) > 80 beat / min with good ST segment analysis, temperature> 36.6 ℃, no bleeding from suture lines and normal ABG and electrolytes. After completion valve replacement, Resumption of MV was performed; gradual cardiac filling and gradual weaning from CPB was achieved when the patient reached stable hemodynamics After weaning from bypass, Venous cannulae were removed and the anti-coagulant effect of heparin was antagonized by administration of protamine sulphate. Protamine was first tested by slow i.v drip then administrated in a dose of 1-1.3 mg for each 100 IU heparin received by the patient. The aortic cannula was the last to be removed after heparin reversal using protamine sulphate. Then, blood and fresh frozen plasma were administrated once needed based on the current center strategy. The proper selection of adequate vasopressor/inotrope was performed by the aid of TEE examination using TG basal SAX view at zero degree to evaluate volume condition and contractility as well as RWMA. Once proper haemostasis was accomplished, the drainage tubes were introduced; the sternum was wired followed by closure of muscles, subcutaneous tissues and skin. Postoperative, intubated cases were transported to the ICU in which they were appropriately followed up monitored and mechanically ventilated. The patient postoperative monitoring continued with ECG (special focus on ST segment), pulse oximetry, invasive BP supervision, regular ABG and ACT, chest X-ray and strict supervision of chest tubes throughout the period of ICU admission. Vasopressor agents, inotropes and vasodilators were remained according to patients' hemodynamic parameters based on the current algorithm till complete weaning.

3. Results and Discussion

There was no significant statistical difference between all groups in terms of age (Table 1). The HR revealed no significant difference between the two groups at baseline as well as at tracheal intubation readings, 30 min pre bypass, 15 min,30 min and 60 min post bypass and 6 h,24 h postoperative. On the other hand, HR was significantly reduced in group SB in comparison with group S at skin incision, sternotomy, pre bypass 15 min, and 1 hour, 30 min postoperative and 12 hours postoperative (Table 2). The MAP revealed no significant difference between the two groups except at skin incision during pre-bypass period and at 30 min,60 min post (Table 3). The PASP measured by preoperative TTE showed no significant difference between the two groups. Intraoperative TEE done pre bypass showed no significant statistical difference between the study groups in PASP, while TEE done post bypass showed PASP was significantly lower in SB group when compared to S group. In ICU, postoperative TTE was done and showed a significant reduction in PASP in SB group in comparison with S group (Table 4).

Postsurgical data revealed no significant statistical difference in extubation times between the study groups. ICU stay (days) was statistically significant lower in group SB compared to group S (Table 5). Vasoactive-inotropic score (VIS) was significantly statistically lower in the SB group in comparison to the S group in ICU at 6 hours, 12 hours and at 24 hours (Table 6). The central venous pressure readings of both groups were lower than the basal value with statistical significance, it was lower in SB group in the pre bypass and post bypass period when compared to S group (p=0.001). In ICU the CVP readings were lower in S group than SB group at 12hours postoperative, otherwise there was no significant statistical difference between the two study groups. (Figure 1). As regard TASPE between the study group; there was no statistical significant difference in TAPSE at basal, preoperative and pre bypass. In TTE ICU, there was statistically significant increase in TAPSE in SB group (p=0.004) (Figure 2). The main findings of our study showed that preoperative oral intake of both bosentan and sildenafil in adult patients with left sided heart disease suffering from PAH resulted in more effective decrease in PASP than sildenafil alone. Although the pulmonary artery pressure showed significant lowering from basal values in both groups, bosentan had a better effect intraoperative which was ongoing postoperative. Also, this study showed that both sildenafil and bosentan effectively reduced mean arterial blood pressure MAP in the intraoperative and postoperative period. The heart rate after weaning was higher than basal slightly with both drugs then it builds up to normal values with no significant difference between both. We found that bosentan caused more clinical decline in central venous pressure before and after weaning from CPB which remained around normal levels in the postoperative ICU stay with no significant difference between both groups. This research; guided by TEE; showed that bosentan is better choice in lowering of pulmonary arterial pressure (PAP) than placebo due to its vasodilatory properties acting on pulmonary vascular smooth muscles and due to its action on the ET receptors.Sildenafil is well known to be used as a solo pulmonary vasodilator drug or with other drugs in reducing PASP [6]. Sildenafil is well known pulmonary vasodilator in cardiac surgery. Chang et al. conducted a prospective cohort study on neonates undergoing cardiac surgery. His results showed that sildenafil administration in neonates with low cardiac output (COP) after cardiac surgeries caused lowering of the filling pressures, systemic pressure and PHTN, and systemic and PVR, with improved cardiac index (CI)[7].

Table 1: Socio-demographic characteristics of the studied groups

	S group N=40	**SB group N=40**	**Test of significance**
Age / years Mean ±SD	50.38±8.73	51.60±8.03	t=0.653 p=0.516
Gender Male Female	N(%) 6(15.0) 34(85.0)	N(%) 8(20.0) 32(80.0)	χ^2=0.346 P=0.556
Weight (kg) Mean ±SD	82.63±11.31	80.50±9.44	t=0.912 p=0.365
Height (meter) Mean ±SD	1.67±0.09	1.66±0.07	t=0.713 p=0.478
BMI(Kg/m^2) Mean ±SD	29.54±3.61	29.25±3.31	t=0.378 p=0.706

Table 2: Comparison of heart rate change between studied groups

Heart rate (b/min)	**S group N=40**	**SB group N=40**	**Test of significance**
Basal	84.05±8.62	83.33±10.43	t=0.339 p=0.736
Intubation	83.25±8.80	81.60±10.28	t=0.771 p=0.443
Skin	81.78±9.77	74.13±12.47	t=3.05 p=0.003*
Sternum	81.58±11.09	75.23±14.06	t=2.24 p=0.028*
Pre bypass 15 min	81.13±11.99	74.88±13.69	t=2.17 p=0.03*
Pre bypass 30min	81.25±11.81	76.75±14.83	t=1.50 p=0.137
Pre 1 h	81.68±12.14	75.03±12.78	t=2.39 p=0.019*
Post bypass 15 min	97.95±9.36	93.63±11.82	t=1.82 p=0.073
Post by pass 30 min	98.13±8.61	95.33±10.27	t=1.32 p=0.190
Post by pass 60 min	97.38±7.28	95.48±10.49	t=0.940 p=0.350
30 min postoperative	96.20±8.46	91.50±9.11	t=2.39 p=0.019*
6 h postoperative	88.45±7.61	85.93±9.74	t=1.29 p=0.200
12H postoperative	86.15±8.73	81.78±9.26	t=2.18 p=0.032*
24 H postoperative	81.10±9.08	80.03±7.42	t=0.580 p=0.564

t: Student t test, *statistically Significant

Table 3: Comparison of mean arterial blood pressure change between studied groups

Mean arterial blood pressure (mm/Hg)	S group N=40	SB group N=40	Test of significance
Basal	93.10±12.03	92.80±12.98	t=0.107 p=0.915
Intubation	89.15±8.75	84.98±11.47	t=1.83 p=0.071
Skin	89.83±10.68	83.98±11.43	t=2.37 p=0.02*
Sternum	88.28±10.93	84.25±13.21	t=1.48 p=0.142
Pre bypass 15 min	86.10±10.79	83.85±11.43	t=0.905 p=0.368
Pre bypass 30min	84.63±11.26	84.48±10.69	t=0.061 p=0.951
Pre 1 h	83.50±11.59	84.20±11.32	t=0.273 p=0.786
Post bypass 15 min	73.45±8.42	70.20±6.47	t=1.94 p=0.056
Post by pass 30 min	78.60±6.52	75.15±6.77	t=2.32 p=0.023*
Post by pass 60 min	84.18±8.35	80.38±6.24	t=2.31 p=0.024*
30 min postoperative	86.40±8.36	84.18±6.16	t=1.36 p=0.179
6 h postoperative	87.58±7.56	85.45±6.62	t=1.34 p=0.185
12H postoperative	89.78±7.21	88.83±7.03	t=0.597 p=0.552
24 H postoperative	93.48±8.63	93.23±8.53	t=0.130 p=0.897

t: Student t test, *statistically Significant

Table 4: Comparison of PASP change between studied groups

PASP	S group N=40	SB group N=40	Test of significance
Pre-operative	85.38±6.34	88.15±9.37	t=1.55 p=0.125
Pre bypass	76.98±7.09	73.65±7.89	t=1.98 p=0.051
Post bypass	69.98±7.62	65.58±8.48	t=2.44 p=0.017*
TTE ICU	65.23±6.64	58.68±7.07	t=4.27 p<0.001*

t: Student t test, *statistically Significant

Table 5: Comparison of extubation and ICU stay duration between studied groups

	S group N=40	SB group N=40	Test of significance
Extubation	6.20±0.88	6.13±0.97	t=0.363 p=0.718
ICU Stay (days)	3.25±0.54	2.43±0.50	t=7.07 p<0.001*

t: Student t test, *statistically Significant

Table 6: Comparison of VIS between studied groups

VIS	S group N=40	SB group N=40	Test of significance
6 H	62.50±10.56	46.50±9.49	t=7.13 p<0.001*
12 H	55.25±9.67	38.63±8.16	t=8.31 p<0.001*
24 H	48.63±9.47	32.13±8.39	t=8.25 p<0.001*

t:Student t test , *statistically Significant

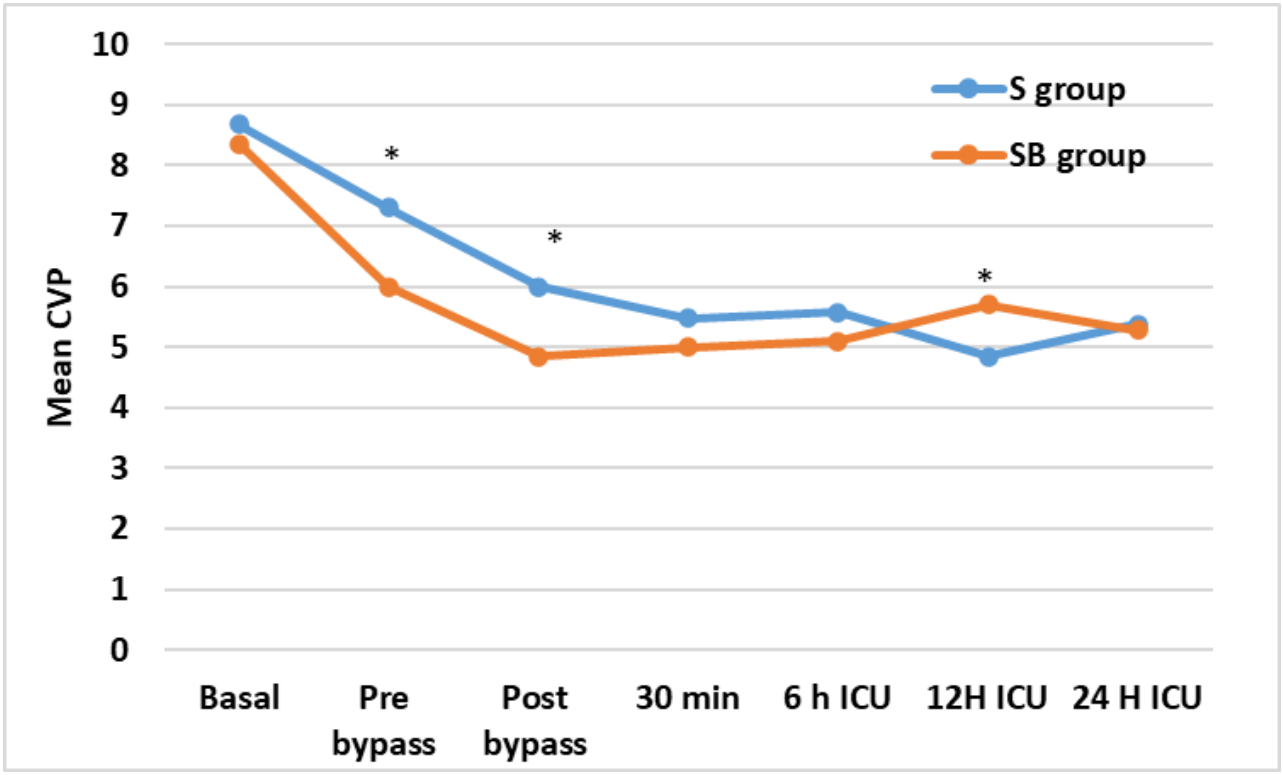

Figure 1: CVP change between studied groups

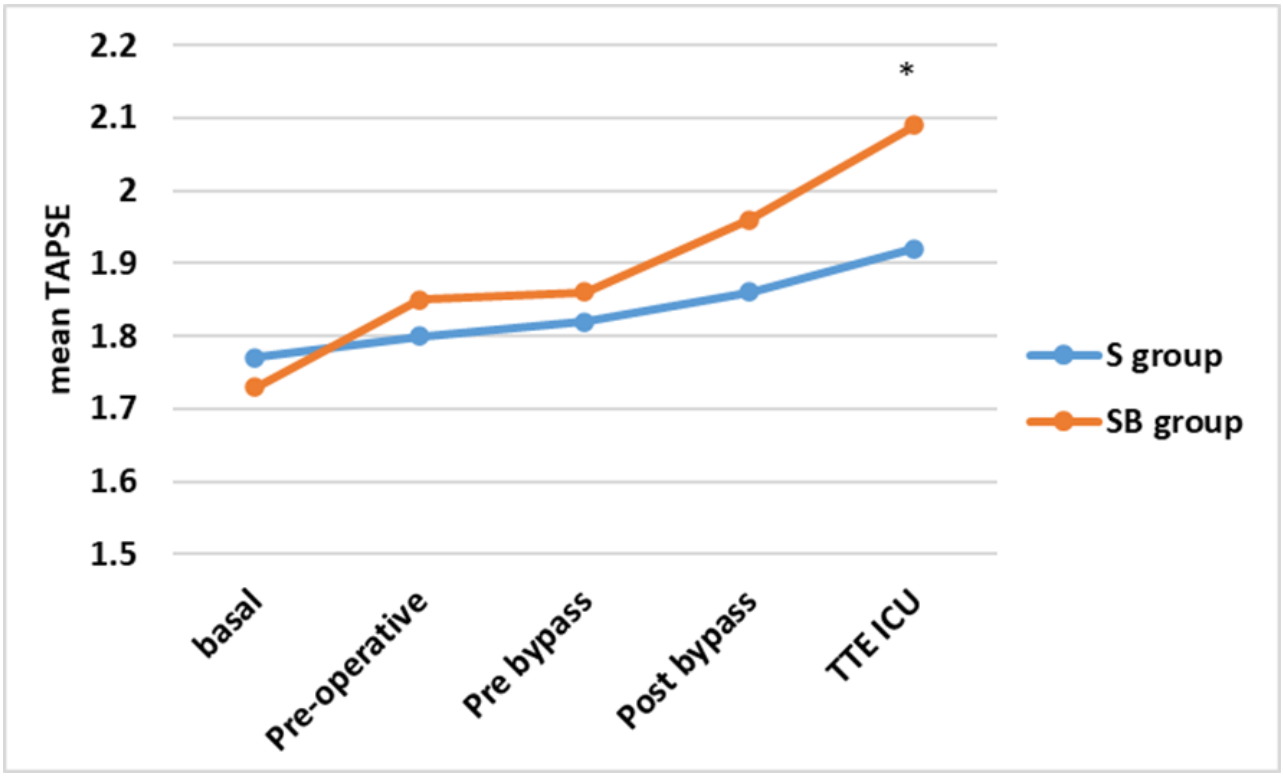

Figure 2: Mean TAPSE between studied groups

The Prophylactic oral intake of sildenafil after cardiac surgery among pediatrics established sildenafil use in pediatric cardiac surgery [8].Its vasodilator properties rendered it a good choice to treat neonatal persistent pulmonary hypertension as evidenced in 2006 by the work of bassler and his colleagues [9].ELshafay et al systemic review and meta-analysis included papers comparing the effects of bosentan with sildenafil versus bosentan and placebo hemodynamics of cases with Eisenmenger syndrome. Both were in favor of bosentan as a pulmonary vasodilator that improve hemodynamics in Eisenmenger syndrome with good safety profile [10]. The Chen et al systemic review and meta-analysis on bosentan therapy for PHTN and chronic thromboembolic PHTN (CTEPH) main outcomes were six minute walk distance, hemodynamic parameters including mean PAP, CI, PVR and mRAP. The results of such meta-analysis showed that bosentan significantly improved cardiopulmonary hemodynamic parameters, comprising mPAP, PVR, CI and improved exercise capacity in comparison to the controls after 12-26 weeks of therapy. The differences in efficiency of bosentan between PAH and CTEPH could be due to their different natures. Vascular remodeling and persistent VC in addition to the increase in ET-I level have been considered as primary pathological vascular changes of PAH. Targeting abnormal ET signaling pathway, bosentan may suppress pulmonary VC and exhibit antiproliferative effect, and thus improve hemodynamics and exercise capacity as assessed with 6MWD. On the other hand, chronic intraluminal thrombus organization and fibrous obliteration are major etiology of CTEPH. Without reversal of vascular mechanical obstruction, the limited VD effects of bosentan could affect come hemodynamic parameters of CTEPH and wouldn't transform into clinical benefits with regard to 6MWD, functional class, and time to clinical deteriorating. Additionally, on the contrary to PAH, ET-I isn't upregulated in CTEPH, and the VD effect of bosentan for CTEPH may be less efficient [11].

Also, Reesink et al. study in cases with CTEPH prepared for pulmonary endarterectomy, after sixteen weeks of therapy with bosentan Vs placebo the average differences from baseline between the groups were as follows: total pulmonary resistance 299 dynes. s.cm-5 (P=0.004), six-min walk distance 33m (P =0.014), mean pulmonary artery pressure 11mmHg (P=0.005), and CI 0.3L.min-1.m-2 (P=0.08) [12]. The vasoactive-inotropic score (VIS) predicts morbimortality following pediatric cardiac surgeries. Our study assessed whether VIS could in addition predict the outcomes among adult subjects following cardiac surgeries or not [13]. The high VIS following cardiac surgeries indicates right ventricular dysfunction. our study showed that VIS was significantly statistically lower in the SB group compared with the S group in ICU at 6 hours, 12 hours and at 24 hours. As regard TASPE between the study group; there was no statistical significant difference in TAPSE at basal, preoperative and pre bypass. In TTE ICU, there was statistically significant increase in TAPSE in SB group (p=0.004). Ting and his colleagues revealed that presurgical RV dysfunction has been considered as an independent predisposing factor for postsurgical high VIS. Pre-incisional

TAPSE is a valid modality for prediction of high VIS following cardiac surgeries. Cases with high VIS were demonstrated to be accompanied by an increase in postoperative complications [14]. In contrast to our study, Iversen and his colleagues recorded the safe (non-significant) effects of combined therapy in terms of exercise capacities as well as of hemodynamic parameters among cases with eisenmenger syndrome [15]. In our study, evaluation of PASP and RV systolic function depended on TEE. In contrast to our study, study done by Schulze-Neick and his colleagues in adult patients with CHD and PAH the assessment of pulmonary hemodynamics done by cardiac catheterization [16]. Also, The COMPASS-2 research failed to reveal significant effects on the primary endpoint of time to 1st confirmed morbimortality events by the addition of bosentan to sildenafil [17]. Our study was done to compare the effect of sildenafil only and sildenafil with bosentan in adults with left sided heart disease. Most of studies done on the effect of bosentan were done in pediatrics, one of these studies done by Fatima N et al in newborns with persistant pulmonary hypertension [18]. Another study by Maneenil G et al done to study the effect of persistent pulmonary hypertension in newborn [19].Both studies showed clinical improvement reflected by reduction in tricuspid regurgitation within short duration after the start of therapy with reduction in morbidity and mortality. Despite the promising outcomes, the current study has certain limitation; first, there was no pulmonary artery catheterization done for evaluation of mean pulmonary artery pressure which is more accurate than systolic pulmonary artery pressure in PAH. The TEE is less invasive than pulmonary artery catheter but still need more studies for evaluation of pulmonary artery pressure to be in place of the right sided catheter [20]. Second, patients were not eligible for 6-MWD due to inability for accurate measurement of preoperative walk distance around the duration of treatment. Third, Long-term follow up was required to evaluate the mortality rate with PAH-specific drug therapy which is bosentan in our study. Forth, the study did not include measurement of plasma BNP to recognize cases with right heart dysfunction, known to be a predisposing factor for a more complicated postsurgical course [21].Finally, the small sample size of this study needed multicenter assessment of bosentan safety and effect on hemodynamics on wider population.

4. Conclusion

Combination of sildenafil and bosentan offered a better patient outcome more stable hemodynamics, earlier extubation and shorter ICU stay. It offers less complications during and after surgery

References

[1] P. Gosain, M. Larrauri-Reyes, C.G. Mihos, E. Escolar, O. Santana. (2016). Aortic and/or mitral valve surgery in patients with pulmonary hypertension performed via a minimally invasive approach. Interactive CardioVascular and Thoracic Surgery. 22(5): 668-670.

[2] K. Hirata, A. Adji, C. Vlachopoulos, M.F. O'Rourke. (2005). Effect of sildenafil on cardiac performance in patients with heart failure. The American journal of cardiology. 96(10): 1436-1440.

[3] S. Bhogal, O. Khraisha, M. Al Madani, J. Treece, S.J. Baumrucker, T.K. Paul. (2019). Sildenafil for pulmonary arterial hypertension. American journal of therapeutics. 26(4): e520-e526.

[4] V.V. McLaughlin, S.J. Shah, R. Souza, M. Humbert. (2015). Management of pulmonary arterial hypertension. Journal of the American College of Cardiology. 65(18): 1976-1997.

[5] S. Roux, L.J. Rubin. (2002). Bosentan: a dual endothelin receptor antagonist. Expert opinion on investigational drugs. 11(7): 991-1002.

[6] M. Licker, J. Diaper, V. Cartier, C. Ellenberger, M. Cikirikcioglu, A. Kalangos, T. Cassina, K. Bendjelid. (2012). Clinical review: management of weaning from cardiopulmonary bypass after cardiac surgery. Annals of cardiac anaesthesia. 15(3): 206-223.

[7] A.C. Chang, A.M. Atz, G. Wernovsky, R.P. Burke, D.L. Wessel. (1995). Milrinone: systemic and pulmonary hemodynamic effects in neonates after cardiac surgery. Critical care medicine. 23(11): 1907-1914.

[8] T.M. Hoffman, G. Wernovsky, A.M. Atz, J.M. Bailey, A. Akbary, J.F. Kocsis, D.P. Nelson, A.C. Chang, T.J. Kulik, T.L. Spray. (2002). Prophylactic intravenous use of milrinone after cardiac operation in pediatrics (PRIMACORP) study. American heart journal. 143(1): 15-21.

[9] D. Bassler, K. Choong, P. McNamara, H. Kirpalani. (2006). Neonatal persistent pulmonary hypertension treated with milrinone: four case reports. Neonatology. 89(1): 1-5.

[10] A. Elshafay, D.H. Truong, M.M. AboElnas, H. Idrees, H.G. Metwali, N.L. Vuong, O.A. Saad, K. Hirayama, N.T. Huy. (2018). The effect of endothelin receptor antagonists in patients with eisenmenger syndrome: a systematic review. American Journal of Cardiovascular Drugs. 18(2): 93-102.

[11] X. Chen, Z. Zhai, K. Huang, W. Xie, J. Wan, C. Wang. (2018). Bosentan therapy for pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: A systemic review and meta-analysis. The clinical respiratory journal. 12(6): 2065-2074.

[12] H.J. Reesink, S. Surie, J.J. Kloek, H.L. Tan, R. Tepaske, P.F. Fedullo, P. Bresser. (2010). Bosentan as a bridge to pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. The Journal of thoracic and cardiovascular surgery. 139(1): 85-91.

[13] T. Koponen, J. Karttunen, T. Musialowicz, L. Pietiläinen, A. Uusaro, P. Lahtinen. (2019). Vasoactive-inotropic score and the prediction of morbidity and mortality after cardiac surgery. British journal of anaesthesia. 122(4): 428-436.

[14] P.-C. Ting, V.C. Wu, C.-C. Liao, A.-H. Chou, F.-C. Tsai, P.-J. Lin, C.-Y. Chen, S.-W. Chen. (2019). Preoperative right ventricular dysfunction indicates high vasoactive support needed after cardiac surgery. Journal of cardiothoracic and vascular anesthesia. 33(3): 686-693.

[15] K. Iversen, A.S. Jensen, T.V. Jensen, N.G. Vejlstrup, L. Søndergaard. (2010). Combination therapy with bosentan and sildenafil in Eisenmenger syndrome: a randomized, placebo-controlled, double-blinded trial. European heart journal. 31(9): 1124-1131.

[16] I. Schulze-Neick, N. Gilbert, R. Ewert, C. Witt, E. Gruenig, B. Enke, M.M. Borst, P.E. Lange, M.M. Hoeper. (2005). Adult patients with congenital heart disease and pulmonary arterial hypertension: first open prospective multicenter study of bosentan therapy. American heart journal. 150(4): 716. e7-716. e12.

[17] V. McLaughlin, R.N. Channick, H.-A. Ghofrani, J.-C. Lemarié, R. Naeije, M. Packer, R. Souza, V.F. Tapson, J. Tolson, H. Al Hiti. (2015). Bosentan added to sildenafil therapy in patients with pulmonary arterial hypertension. European Respiratory Journal. 46(2): 405-413.

[18] N. Fatima, S. Arshad, A.I. Quddusi, A. Rehman, A. Nadeem. (2018). Comparison of the efficacy of sildenafil alone versus sildenafil plus bosentan in newborns with persistent pulmonary hypertension. Journal of Ayub Medical College Abbottabad. 30(3): 333-336.

[19] G. Maneenil, A. Thatrimontrichai, W. Janjindamai, S. Dissaneevate. (2018). Effect of bosentan therapy in persistent pulmonary hypertension of the newborn. Pediatrics & Neonatology. 59(1): 58-64.

[20] S. Yu, S. Peffley, M. Fabbro II, A.N. Mohammed. (2022). A narrative review of the 2020 guidelines for use of transesophageal echocardiography to assist with surgical decision-making by the cardiac anesthesiologist in the operating room. Journal of cardiothoracic and vascular anesthesia. 36(1): 258-274.

[21] S. Sardo, V.F. Tripodi, F. Guerzoni, M. Musu, A. Cortegiani, G. Finco. (2023). Pulmonary Vasodilator and Inodilator Drugs in Cardiac Surgery: A Systematic Review With Bayesian Network Meta-Analysis. Journal of cardiothoracic and vascular anesthesia.