“COMPARISON BETWEEN INTRAVENOUS AND INHALATIONAL ANAESTHETIC INDUCTION AGENTS ON ECHOCARDIOGRAPHIC PARAMETERS OF MITRAL STENOSIS PATIENTS UNDERGOING MITRAL VALVE REPLACEMENT SURGERY”

Dr. MOHAMMED JAFFER SHERIF. M

DM CARDIOTHORACIC AND VASCULAR
ANESTHESIOLOGY THESIS

2021- 2023

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND

TECHNOLOGY, TRIVANDRUM

An Institution of National Importance established by an Act of the Indian Parliament
(Act No.52 of 1980)

Dept. of Science and Technology, Govt. of India
www.sctimst.ac.in

“Comparison between intravenous and inhalational anaesthetic induction agents on echocardiographic parameters of mitral stenosis patients undergoing mitral valve replacement surgery”

A THESIS SUBMITTED BY

DR. MOHAMMED JAFFER SHERIF. M

TO

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM.

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE AWARD OF

DM CARDIOTHORACIC AND VASCULAR ANESTHESIOLOGY

YEAR 2021 TO 2023

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया.
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY
Thiruvananthapuram - 695 011, Kerala, India.
(An Institute of National Importance under Govt. of India)

DECLARATION BY THE STUDENT

I, Dr. Mohammed Jaffer Sherif. M, hereby certify that I had personally carried out the work depicted in the thesis titled, **"Comparison between intravenous and inhalational anaesthetic induction agents on echocardiographic parameters of mitral stenosis patients undergoing mitral valve replacement surgery".**

No part of this thesis has been submitted for the award of any other degree or diploma prior to this date.

Date: 28-08-2023

Signature Jaffer Sherif

Dr. Mohammed Jaffer Sherif. M,
Senior resident,
Division of Cardiothoracic and
Vascular Anaesthesiology,
Department of Anaesthesiology,
SCTIMST, Thiruvananthapuram.

तार : चित्रामेट Grams: Chitramet फोन Phone : +91- 471 - 2443152 फाक्स Fax : +91- 471 - 2550728 2446433 ई-मेइल E-mail : sct@sctimst.ac.in वेबसाइट Website : www.sctimst.ac.in

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया.
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY
Thiruvananthapuram - 695 011, Kerala, India.
(An Institute of National Importance under Govt. of India)

CERTIFICATE BY THE RESEARCH GUIDE

Name of the guide: **Dr. Prasanta kumar Dash.**
Department: Department of Anesthesiology.
Division: Division of Cardiothoracic and Vascular Anaesthesia.

This is to certify that Dr. Mohammed Jaffer Sherif. M, Senior resident in the division of Cardiothoracic and Vascular Anesthesiology, of this institute has fulfilled the requirements prescribed for the DM degree of the Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram.

The thesis entitled **"Comparison between intravenous and inhalational anaesthetic induction agents on echocardiographic parameters of mitral stenosis patients undergoing mitral valve replacement surgery"** was carried out under my direct supervision. No part of the thesis was submitted for the award of the degree or diploma prior to this date.

Clearance was obtained from the Institutional ethics committee for carrying out the study.

Date: 31/08/2023 Signature

Dr. Prasanta kumar Dash,
Professor Senior Grade,
Department of Anaesthesiology,
SCTIMST, Thiruvananthapuram.

तार : चित्रामेट Grams: Chitramet फोन Phone : +91- 471 - 2443152 फाक्स Fax : +91- 471 - 2550728 2446433 ई-मेइल E-mail : sct@sctimst.ac.in वेबसाइट Website : www.sctimst.ac.in

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया.
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY
Thiruvananthapuram - 695 011, Kerala, India.
(An Institute of National Importance under Govt. of India)

CERTIFICATE BY THE RESEARCH CO-GUIDE

Name of the guide: **Dr. Saravana Babu. M.S**
Department: Department of Anaesthesiology.
Division: Division of Cardiothoracic and Vascular Anaesthesia.

This is to certify that Dr. Mohammed Jaffer Sherif. M, Senior resident in the division of Cardiothoracic and Vascular Anaesthesiology, of this institute has fulfilled the requirements prescribed for the DM degree of the Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram.

The thesis entitled **"Comparison between intravenous and inhalational anaesthetic induction agents on echocardiographic parameters of mitral stenosis patients undergoing mitral valve replacement surgery"** was carried out under my direct supervision. No part of the thesis was submitted for the award of the degree or diploma prior to this date.

Clearance was obtained from the Institutional ethics committee for carrying out the study.

Date: 30/08/2023

Signature

Dr. Saravana Babu M.S
Associate Professor
Department of Anaesthesiology,
SCTIMST, Thiruvananthapuram

तार : चित्रामेट Grams: Chitramet फोन Phone : +91- 471 - 2443152 फाक्स Fax : +91- 471 - 2550728 2446433 ई-मेइल E-mail : sct@sctimst.ac.in वेबसाइट Website : www.sctimst.ac.in

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया.
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY
Thiruvananthapuram - 695 011, Kerala, India.
(An Institute of National Importance under Govt. of India)

CERTIFICATE BY THE RESEARCH CO-GUIDE

Name of the guide: **Dr. Thomas Koshy.**

Department: Department of Anaesthesiology.

Division: Division of Cardiothoracic and Vascular Anaesthesia.

This is to certify that Dr. Mohammed Jaffer Sherif, Senior resident in the division of Cardiothoracic and Vascular Anaesthesiology, of this institute has fulfilled the requirements prescribed for the DM degree of the Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram.

The thesis entitled **"Comparison between intravenous and inhalational anaesthetic induction agents on echocardiographic parameters of mitral stenosis patients undergoing mitral valve replacement surgery"** was carried out under my direct supervision. No part of the thesis was submitted for the award of the degree or diploma prior to this date.

Clearance was obtained from the Institutional ethics committee for carrying out the study.

Date: 23/08/2023

Signature

Thomas Koshy

Dr. Thomas Koshy,
Professor Senior Grade
Department of Anaesthesiology,
SCTIMST, Thiruvananthapuram

तार : चित्रामेट फोन : +91- 471 - 2443152 फाक्स : +91- 471 - 2550728 2446433 ई-मेइल : sct@sctimst.ac.in वेबसाइट : www.sctimst.ac.in
Grams: Chitramet Phone Fax E-mail Website

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया.
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY
Thiruvananthapuram - 695 011, Kerala, India.
(An Institute of National Importance under Govt. of India)

CERTIFICATE BY THE RESEARCH CO-GUIDE

Name of the guide: **Dr. SUBIN SUKESAN**
Department: Department of Anaesthesiology.
Division: Division of Cardiothoracic and Vascular Anaesthesia.

This is to certify that Dr. Mohammed Jaffer Sherif. M, Senior resident in the division of Cardiothoracic and Vascular Anaesthesiology, of this institute has fulfilled the requirements prescribed for the DM degree of the Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram.

The thesis entitled **"Comparison between intravenous and inhalational anaesthetic induction agents on echocardiographic parameters of mitral stenosis patients undergoing mitral valve replacement surgery"** was carried out under my direct supervision. No part of the thesis was submitted for the award of the degree or diploma prior to this date.

Clearance was obtained from the Institutional ethics committee for carrying out the study.

Date: 28/02/2023 Signature

Dr. Subin Sukesan,
Additional Professor,
Department of Anaesthesiology,
SCTIMST, Thiruvananthapuram

तार : चित्रामेट Grams: Chitramet फोन Phone : +91- 471 - 2443152 फाक्स Fax : +91- 471 - 2550728 2446433 ई-मेइल E-mail : sct@sctimst.ac.in वेबसाइट Website : www.sctimst.ac.in

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया.
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY
Thiruvananthapuram - 695 011, Kerala, India.
(An Institute of National Importance under Govt. of India)

CERTIFICATE BY THE RESEARCH CO-GUIDE

Name of the guide: **Dr. VARGHESE T PANICKER.**
Department: Department of Cardiovascular and thoracic surgery.

This is to certify that Dr. Mohammed Jaffer Sherif. M, Senior resident in the division of Cardiothoracic and Vascular Anaesthesiology, of this institute has fulfilled the requirements prescribed for the DM degree of the Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram.

The thesis entitled **"Comparison between intravenous and inhalational anaesthetic induction agents on echocardiographic parameters of mitral stenosis patients undergoing mitral valve replacement surgery"** was carried out under my direct supervision. No part of the thesis was submitted for the award of the degree or diploma prior to this date.

Clearance was obtained from the Institutional ethics committee for carrying out the study.

Date: 28-8-2023

Signature

Dr. Varghese T Panicker,
Professor,
Department of CVTS,
SCTIMST, Thiruvananthapuram.

तार : चित्रामेट Grams: Chitramet फोन Phone : +91- 471 - 2443152 फाक्स Fax : +91- 471 - 2550728 2446433 ई-मेइल E-mail : sct@sctimst.ac.in वेबसाइट Website : www.sctimst.ac.in

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया.
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY
Thiruvananthapuram - 695 011, Kerala, India.
(An Institute of National Importance under Govt. of India)

CERTIFICATE BY THE RESEARCH CO-GUIDE

Name of the guide: **Dr. Bineesh K. Radhakrishnan**
Department: Department of Cardiovascular and thoracic surgery.

This is to certify that Dr. Mohammed Jaffer Sherif. M, Senior resident in the division of Cardiothoracic and Vascular Anaesthesiology, of this institute has fulfilled the requirements prescribed for the DM degree of the Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram.

The thesis entitled **"Comparison between intravenous and inhalational anaesthetic induction agents on echocardiographic parameters of mitral stenosis patients undergoing mitral valve replacement surgery"** was carried out under my direct supervision. No part of the thesis was submitted for the award of the degree or diploma prior to this date. Clearance was obtained from the Institutional ethics committee for carrying out the study.

Date: 31/08/2023 Signature

Dr. Bineesh k. Radhakrishnan,
Additional Professor,
Department of CVTS,
SCTIMST, Thiruvananthapuram.

तार : चित्रामेट Grams: Chitramet फोन Phone : +91- 471 - 2443152 फाक्स Fax : +91- 471 - 2550728 2446433 ई-मेइल E-mail : sct@sctimst.ac.in वेबसाइट Website : www.sctimst.ac.in

ACKNOWLEDGEMENTS

I take this opportunity to express my sincere gratitude to Dr Prasanta Kumar Dash, Professor Senior grade, SCTIMST, my guide for the study and to Dr. Saravana Babu MS., for his expert guidance, constant review, kind help and keen interest at each step of the study.

I am thankful to Dr. Thomas Koshy, professor senior grade, Dr Varghese T Panicker, Dr Subin Sukesan, Dr Bineesh KR who were co guides in this study for their valuable input and help for the study.

I am thankful to Dr Suneel PR and Dr Unnikrishnan KP, addl. Prof. Department of Anesthesiology, nursing staff in cardiac surgical ICU, and my colleagues for their valuable input and assistance to the study. I am extremely grateful to my friends for their overwhelming support and constant encouragement. I take this opportunity to also thank Dr Santosh Kumar B, registrar of SCTIMST and his academic section team for all help rendered during thesis preparation.

This would not have been possible without the love and support from Mrs. Rafiathul Fasahriya and my parents.

I am greatly indebted to all my patients and their primary caregivers who participated in this study, without whose cooperation this study would not have been possible.

Above all, I thank the almighty god, for his constant blessings.

31st August 2022 Dr. Mohammed Jaffer Sherif. M

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

SL NO	ABBREVIATION	FULL FORM
1.	MS	Mitral Stenosis
2.	RMS	Rheumatic Mitral Stenosis
3.	NRMS	Non- Rheumatic Mitral Stenosis
4.	RHD	Rheumatic Heart Disease
5.	MVR	Mitral Valve Replacement
6.	MV	Mitral Valve
7.	MVA	Mitral Valve Area
8.	PHT	Pressure Half time
9.	DT	Decceleration Time
10.	PISA	Proximal Iso-velocity Surface Area
11.	HR	Heart Rate
12.	MAP	Mean Arterial Pressure
13.	CO	Cardiac Output
14.	SVR	Systemic Vascular Resistance
15.	RF	Rheumatic Fever
16.	MAC	Mitral Annular Calcification

17.	**LA**	**Left Atrium**
18.	**LV**	**Left Ventricle**
19.	**PASP**	**Pulmonary Systolic Pressure**
20.	**TR**	**Tricuspid regurgitation**
21.	**TEE**	**Trans Esophageal Echo**
22.	**TTE**	**Trans Thoracic Echo**
23.	**BMV**	**Balloon mitral Valvuloplasty**
24.	**2D**	**Two dimensional**
25.	**3D**	**Three Dimensional**
26.	**MR**	**Mitral Regurgitation**
27.	**AMI**	**Acute myocardial Infarction**
28.	**PLAX**	**Parasternal Long axis**
29.	**PSAX**	**Parasternal Short axis**
30.	**TAPSE**	**Tricuspid Annular Plane Systolic Excursion**

SYNOPSIS

"COMPARISON BETWEEN INTRAVENOUS AND INHALATIONAL ANAESTHETIC INDUCTION AGENTS ON ECHOCARDIOGRAPHIC PARAMETERS OF MITRAL STENOSIS PATIENTS UNDERGOING MITRAL VALVE REPLACEMENT SURGERY"

SYNOPSIS

By

DR. MOHAMMED JAFFER SHERIF. M

DM CARDIOTHORACIC
AND VASCULAR
ANESTHESIOLOGY

of

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL
SCIENCES ANDTECHNOLOGY, TRIVANDRUM

Synopsis

Background: Mitral Stenosis (MS) is the commonest presentation of rheumatic heart disease, but the prevalence of the disease has declined over years. Echocardiography plays a major role in the diagnosis as well as planning of treatment in MS patients. Most of the parameters used to grade the severity of valve stenosis are influenced by hemodynamic state of those patients. Significant fluctuations in hemodynamics are expected especially at the time of anaesthetic induction. Propofol and sevoflurane are the commonly used anaesthetic agents for induction of anaesthesia. Compared to propofol, sevoflurane is found to be relatively cardio-stable, but there are hardly any studies comparing these two agents with respect to the degree of hemodynamic change as-well as change in echocardiographic profile after the induction of General Anaesthesia (GA). Hence, we planned to undertake this prospective randomized comparative study.

Our Primary objective was to assess and sevoflurane and propofol for their effects on the echocardiographic and Doppler parameters when used as an anaesthetic induction agent in MS patients undergoing Mitral Valve Replacement (MVR): 1. Mitral Valve Area (pressure half time and continuity equation) (MVA-P, MVA-C) 2. Peak velocity 3. Peak and mean gradient 4. Pressure half time (PHT) 5. Deceleration Time (DT). And, Our Secondary objective was to compare the change in hemodynamic parameters following Propofol and sevoflurane Induction like, a). Mean arterial pressure (MAP) b). Cardiac output (CO) c). Heart rate (HR).

Hypothesis: We hypothesized that anaesthetic induction with sevoflurane may reduce the echocardiographic MS pressure gradients and increase the estimated mitral valve area by maintaining stable hemodynamic parameters when compared with the propofol induction.

Methodology: Institutional Ethics Committee approval obtained and the stud was registered with the Clinicals Trials Registry of India (CTRI). After enrolling eligible participants exclusion was done based on our exclusion criterion and finally a total of 80 patients were selected. They were assigned randomly to receive induction of anaesthesia either with propofol (Group P, n=40) or sevoflurane (Group S, n=40). Patients of both genders aged 18- 70 years diagnosed with MS undergoing MVR were included. Standard Trans Thoracic Echocardiography (TTE) was performed at two time points- just before the induction and 3minutes after the induction of anaesthesia (just before tracheal intubation) and data stored for later analysis by the observer blinded for group allocation. Vital parameters recorded from multi

parameter monitor at baseline, 1minute and 3minute after induction. Data was analyzed statistically using SPSS version 20.0.

Results: We found that both anesthetic agents downgraded the severity of MS and altered the hemodynamic parameters to a considerable extent. The two groups in our study did not statistically differ with respect to demography of the patients except for the fact that there was increased number of female patients in either group [Group P (n, %) n=32, 80%, Group S (n, %) n=24,60%]. Symptomatic MS patients are classified to be in Stage D according to the updated ACC/AHA valvular heart diseases guidelines. More than 50% of them presented with dyspnea on exertion as their only symptom. Patients in both the study groups were of NYHA class 2 or 3 and none class 4. Clinical symptoms in MS are mainly due to increasing left atrial (LA) pressure. Chronically elevated LA pressure can trigger the onset of atrial fibrillation (AF) which the patient perceives as palpitations. More than 50% of the patients in both the group were in sinus rhythm at the time of presentation. As a standard of practice, the Doppler assessment was done as an average of 3 to 5 cardiac cycles in patients with sinus rhythm and average of 7 to 10 in those with AF.

The peak velocity dropped significantly after the induction of anesthesia in both the group (Group P pre vs post-**2.2 ± 0.3 vs 1.8 ± 0.4**, Group S pre vs post-**2.3 ± 0.4 vs 1.9 ± 0.3**) so as the maximum and mean gradients (Group P pre vs post **-11.1 ± 3.0** vs **7.1 ± 2.8,** Group S pre vs post **-11.3 ± 4.8 vs 8.0 ± 3.1).** But, the updated guidelines on valvular heart diseases did not consider either velocity or the mean gradients for classification of disease severity. That is because, the trans-mitral Doppler is heavily influenced by flow across the valve, which, in-turn is determined by the diastolic filling time and LA-LV compliance. The anaesthetic agents in our study are known to cause veno-dilatation which could reduce the preload significantly resulting in decreased flow across the reference valve, causing drop in velocity, peak and mean gradients.

. The Doppler derived mitral valve area did not vary much between pre and post anesthesia induction in group-P. But, the MVA estimated by PHT and continuity equation in group-S increased by **0.07 ± 0.08cm^2** and **0.06 ± 0.03cm^2** respectively, after anesthesia in group-S which was statistically significant. This agrees with the study by kuperstein et.al. where they had shown significant increase in MVA assessed after inducing general anesthesia. It could be the complex interplay between the heart rate, loading conditions of the heart, myocardial contractility and inter individual responses to anesthetic agents.

PHT derived valve area is dependent on heart rate and net compliance of the cardiac chambers. PHT of more than 150m.sec is considered valve stenosis according to ACC/AHA 2020 guidelines. Almost all patients had their baseline PHT more than 200m.sec which dropped significantly after induction of general anesthesia but the PHT did not fall below the cut-off of 150m.sec in any study subjects of both the groups. The slight but statistically insignificant increase in PHT derived valve area could be because of improved reservoir capacity of LA by propofol, which can potentially mis-classify the disease severity in borderline patients.

The Doppler parameters vary between the patients in sinus rhythm and those having atrial fibrillation and also with the different phases of respiration. These two confounding factors were overcome by averaging the Doppler analysis over several cardiac cycles, which could have masked the changes with rhythm as well as the respiratory cycle, that would have otherwise occurred.

Cardiac output measured after 3minutes of general anaesthetic induction was significantly lower in both the study groups compared to the baseline (Group P pre vs post- **4.1± 0.8** vs **3.1± 0.8,** Group S pre vs post- **4.0± 0.6 vs 2.9± 0.5**). All anesthetic agents have been found to reduce the cardiac output by various mechanisms, predominantly by reducing the preload because of venous dilatation due to sympathetic inhibition. Myocardial depression could be another mechanism which has been demonstrated at higher anaesthetic concentrations. Reduced CO together with the lower SVR is detrimental for coronary perfusion. Both the study drugs reduced CO as well as MAP significantly after general anesthesia induction, but there was no incidence of any major hemodynamic disturbances to cause ST-T changes. It has to be noted that the degree of fall in CO and MAP was relatively higher with propofol than with sevoflurane.

Other important hemodynamic goal during general anesthesia induction in patients with MS is to avoid tachycardia, as increase in heart rate reduces diastolic filling time and increases LA pressure which can increase the trans-mitral gradient. There was a statistically significant reduction in heart rate at 1st and 3rd minute following induction with sevoflurane and increase in heart rate seen in patients who received propofol for induction.

It is noteworthy that, increase in heart rate may increase myocardial strain which when combined with the reduction in CO and MAP as seen in group-P, can cause serious hemodynamic instability, which is not a case in group -S. Hence, sevoflurane appears to be a relatively cardio-stable anaesthetic induction agent.

To test the reproducibility of the Doppler measurements we randomly selected 10 patients and determined peak velocity, peak and mean gradients, PHT and mitral valve area based on the continuity equation method by one observer on two occasions (intra-observer variability). Another observer independently performed analysis for the same patients (inter-observer variability) for the same parameters. The observers were blinded to each other's results. The values had acceptable correlation among each other.

Conclusions: On comparison between sevoflurane and propofol induction, the post induction pressure gradients were significantly reduced and MVA were significantly increased in patients who received sevoflurane than in patients who received propofol.

Both propofol and sevoflurane reduced cardiac output and Mean Arterial Pressure significantly after induction of anaesthesia which is not desired in patients having MS. Induction of anaesthesia with a titrated dose of sevoflurane reduced heart rate significantly at 1st and 3rd minute, which is a favourable hemodynamic goal in patients with MS. In contrast, heart rate increased significantly in those patients who received propofol.

Hence, with respect to the hemodynamic goals for general anaesthesia induction in MS patients, induction with sevoflurane appears to be a good option when compared to propofol based anaesthesia.

INTRODUCTION

INTRODUCTION

Mitral Stenosis (MS) is one of the commonest valvular heart diseases and the major manifestation of Rheumatic Fever (RF), the incidence of which is declining in the developed countries. But it prevails in low-income countries with variable presentations and it has a prevalence of 2% among general population.[1] Rheumatic Mitral Stenosis (RMS) is commonly seen among women. Almost every part of the heart is involved in Rheumatic Heart Disease (RHD) with mitral valve being the most affected one. The inflammation is progressive in nature which leads to severe pathological changes in the form of chordal fusion, thickening, and restricted leaflet mobility resulting in mitral valve stenosis or regurgitation.[2] The clinical presentation of MS varies with the endemicity of the disease.[3] In low income countries where the disease is more prevalent, it tends to manifest in 4^{th} -5^{th} decades and the disease process follows a rapid progression[4] to severe clinical symptoms whereas in less prevalent areas the disease process follows a very slow progress[5] and it manifests very late and hence, those patients have poor outcome as a result of added disadvantages of ageing.

Degenerative MS is the next commonest aetiology of MS (Non- Rheumatic MS- NRMS) which is more prevalent in western countries in the form of Mitral Annular Calcification (MAC)[6]. The clinical signs and symptoms differ for rheumatic and nonrheumatic causes of MS. The valve area determines the severity of MS whereas it is the Left Atrial Pressure (LAP) which determines the onset of symptoms.[7]

Echocardiography is the main stay for diagnosis of MS.[7] The Echocardiographic modalities such as M-mode, two-dimensional (2D) echo, Doppler evaluation and recently three-Dimensional (3D) echo are utilized for assessment of the severity of the lesion. The echocardiographic parameters determining the severity of valve stenosis are greatly influenced by the hemodynamic status of the patient.[8] Hence, the echocardiography derived values are liable to change with the hemodynamics.

Patients presenting with symptomatic MS are offered either surgical or interventional mode of treatment based on the valve anatomy and dynamics.[9] Patients may be exposed to general anaesthesia for numerous reasons like, Trans Esophageal Echo (TEE) evaluation of MS, percutaneous Balloon Mitral Valvuloplasty (BMV), etc. Anaesthetic induction of MS patients is challenging, for the very reason that cardiac output is fixed and strictly preload dependent. Most of the anaesthetic agents reduce Systemic Vascular Resistance (SVR), depress myocardial contractility, and alter hemodynamic profile of the patient which are detrimental in MS patients as it can adversely affect flow profile of the stenotic valve.

Propofol and sevoflurane are the commonly used anaesthetic agents for induction of anaesthesia. Compared to propofol, sevoflurane is found to be relatively cardio-stable, but there are hardly any studies comparing these two agents with respect to the degree of hemodynamic change as-well as change in echocardiographic profile after the induction of General Anaesthesia (GA). Hence, we planned to undertake this prospective randomized comparative study.

AIMS AND OBJECTIVES

Aims & objectives

Primary objectives:

1. To assess sevoflurane and propofol for their effects on the echocardiographic and Doppler parameters when used as an anaesthetic induction agent in MS patients undergoing Mitral Valve Replacement (MVR): 1. Mitral Valve Area (pressure half time and continuity equation) (MVA-P, MVA-C) 2. Peak velocity 3. Peak and mean gradient 4. Pressure half time (PHT) 5. Deceleration Time (DT).
2. To compare the effects of sevoflurane and propofol on the echocardiographic and Doppler parameters in MS patients after induction of anaesthesia.

Secondary objectives:

1. To compare the change in hemodynamic parameters following Propofol and sevoflurane Induction like, a). Mean arterial pressure (MAP) b). Cardiac output (CO) c). Heart rate (HR)

Hypothesis

We hypothesized that anaesthetic induction with sevoflurane may reduce the echocardiographic MS pressure gradients and increase the estimated mitral valve area by maintaining stable hemodynamic parameters when compared with the propofol induction.

LITERATURE REVIEW

Review of literature

Mitral stenosis

Rheumatic Heart Disease (RHD) is the most common cause of MS in adult patients throughout the world. Rheumatic Fever (RF) as well as RMS has declined in prevalence among developed countries.[3,4] The patho-physiological changes in RMS that leads to clinical symptoms are commissural fusion; papillary muscle scarring and thickening as well as calcium deposition within the mitral leaflets. This pathological change is progressive in nature resulting in narrowing of valve orifice. As the valve area becomes more narrower, the trans-mitral pressure gradient and LA pressure increases which are the main reasons for various clinical symptoms of MS.[7]

Table 1: Causes of Mitral Stenosis (MS)

S.no	Causes	Variants
1.	Rheumatic heart disease	Chordal fusion, scarring of papillary muscles, doming of valve leaflets, commissural fusion.
2.	Degenerative	Calcification of valvar and sub-valvar apparatus
3.	Congenital	Single papillary muscle, mitral arcade, parachute mitral valve, mitral ring
4.	Autoimmune/Metabolic	Systemic Lupus Erythematosus, Mucopolysaccharidosis
5.	Infectious	Infective endocarditis
6.	Tumor	LA myxoma
7.	Thrombotic	Bal-valve thrombus

2020 ACC/AHA Guidelines on valvular heart diseases emphasized more of a contemporary approach in assessing the severity of MS.[9] The core concept is that, the patients may present in any phase of MS, stage A through stage D, where stage A represent patients at risk of developing progressive MS and stage D includes those who are symptomatic. The guideline for severity assessment takes into consideration, the features of MV anatomy, valve hemodynamics, and hemodynamic consequences, such as left atrial enlargement and elevated pulmonary artery pressures because of the valve lesion and patient symptoms. But less or no weightage has been given for mean pressure gradient when compared to previous guidelines.

Echocardiography

Echocardiography is the mainstay of diagnosis in MS patients. Popovic et al.[10] in their study shown that the non-invasive hemodynamic measurements done by Echocardiography has superseded the historically used pre-operative invasive measurements especially in isolated valvular heart disease patients. Currently, two-dimensional (2D), 3D and Doppler echocardiography has proven superiority over invasive Cath data in providing a complete evaluation of patients with MS.[11]

Trans mitral Doppler

The severity of MS is assessed by measuring the trans-mitral pressure gradient and/or the stenotic mitral valve area. The trans-mitral pressure gradient can be estimated non-invasively by measuring trans-mitral flow velocity with continuous-wave Doppler echocardiography and by applying the simplified Bernoulli equation.[12,13]

$$\text{Pressure gradient (mm Hg)} = 4v^2$$

where v represents the instantaneous velocity.

The Doppler diastolic mitral flow profile is traced, and the maximal and mean gradients are subsequently calculated automatically by integrated software (Figure 1). The maximal gradient is derived from peak mitral velocity and is strongly influenced by left atrial compliance and left ventricular diastolic function. The mean gradient is the major hemodynamic determinant of MS severity.

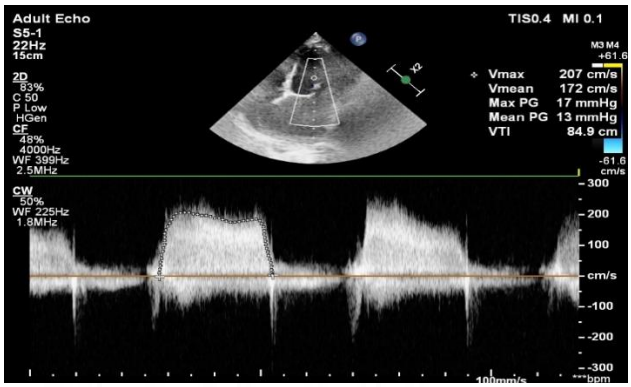

Figure 1: Trans-mitral spectral Doppler showing peak velocity, peak and mean gradients measurement.

Limitations- a. Doppler measurements are highly heart rate and flow dependent because the trans mitral gradient is a function of the square of the transvalvular flow rate and therefore dependent on the diastolic filling of the left ventricle. Hence, the degree of MS can be overestimated in patients with more than mild mitral regurgitation[14] due to an increase in forward flow through the mitral orifice even if the valve is only mildly stenotic.

b. Pressure gradients are underestimated if the angle between the sampling beam and the flow vector is large (>20°). Visualizing the inflow jet with color Doppler and aligning the sample beam with the color inflow can help minimize this proble.[15,16]

Despite these limitations, transvalvular gradients are very useful for the assessment of MS severity, particularly in patients in sinus rhythm.

Mitral Valve Area

The severity of MS is also estimated by calculating the Mitral valve area (MVA). MVA can be assessed by planimetry using either 2D or 3D imaging, pressure half-time (PHT), the continuity equation, and the proximal iso-velocity surface area (PISA) method. This can be done with the use of 2D and Doppler echocardiographic techniques.

Planimetry Valve Area

The 2D planimetry of the MVA is performed in a parasternal short-axis view at the tip of the leaflets when maximal excursion of the leaflets is seen. The inner edge of the MV orifice is traced in mid diastole (Fig). Planimetry has been shown to have the best correlation with anatomic MVA as assessed by explanted valves. Two-dimensional planimetry tends to overestimate MVA compared with 3D TEE measurements, especially in patients with a large left atrium.[17,18,19]

Limitations- a. High gain settings -may underestimate MVA.

b. Inadequate imaging plane orientation - The stenotic MV looks like a funnel in diastole, the narrowest part being the commissural tip of the valve. Measuring too superiorly, in the body of the leaflets, can overestimate the valve area.[17-19]

c. In patients who have undergone mitral valvuloplasty, the valve area may be underestimated because of the inability to measure the extent of the commissural fractures with planimetry.

Pressure Half-Time

The pressure half-time describes the time required for the atrioventricular pressure difference to decrease from the maximum to one-half of that value and it is quantitatively related to the degree of MS. As MS becomes more severe, the rate of pressure decline between the LA and LV is proportionally slower, and consequently the gradient between the LA and LV is maintained for a longer period. In a normal MV, the pressure half-time is less than 60ms.[8,14]

Pressure Half-Time Calculation: PHT is obtained by tracing the deceleration slope of the E-wave on Doppler spectral display of trans-mitral inflow. The MVA can be calculated from the pressure half-time by using the formula originally described by Hatle and Angelsen.[20]

MV area (cm2) = 220/PHT (ms)

Drawbacks of PHT and its limitations- a. PHT is highly influenced by hemodynamic factors and depend on the compliance of the LA and LV. Decreased LV compliance and severe aortic regurgitation can cause a rapid rise in the LV diastolic pressure, with a resultant shortening of the pressure half-time measurement and an overestimation of the MV area.[21]

b. The accuracy of the PHT method is also affected by conditions like previous mitral valvuloplasty, atrial septal defect, atrial tachycardia, and restrictive cardiomyopathy.[17,18]

Deceleration Time

The Deceleration Time (DT) is another simple means of evaluating the MV area. The deceleration time is the interval between the peak velocity and the time at which the extrapolated inflow velocity reaches baseline.[16]

The following formula describes the relationship of the DT to the MVA

MVA (cm2) = 759/DT (ms)

Continuity Equation method- The continuity equation for calculating the area of a valve is based on the law of conservation of mass in hydrodynamics. In the absence of valvular regurgitation[14] or shunts, flow volume at the MV should equal that at another valve according to the following equation.[4]

Volumetric flow = area1 × VTI1 = area2 × VTI2 VTI- Velocity Time Integral By rearranging the equation, the area of the reference valve can be derived

Limitations-The continuity equation is theoretically independent of transvalvular pressure gradients, LV compliance, and changing hemodynamic conditions, such as the increased forward flow that occurs during exercise. The continuity equation does not apply in circumstances of

regurgitation in the reference valve because the forward volumetric flows are not equal, so that significant error is introduced.[21,22,23]

Proximal Iso-velocity Surface Area Method (PISA): The proximal iso-velocity surface area (PISA) method, or flow convergence method, applies the continuity principle to color flow Doppler mapping in the region of the MV orifice where flow is converging from the LA.[24,25] It enables the assessment of mitral flow based on the hemispheric shape of the convergence zone of mitral flow in diastole on the left atrial side as seen by color Doppler. Subsequently, the MVA is calculated by dividing the mitral volume flow by the maximum velocity of mitral flow in diastole, as assessed by continuous wave Doppler.

$$Q = 2\pi r\ 2 \times \alpha/180° \times v\ a$$

$$MVA\ (cm2) = Q/v\ P\ (cm/s)$$

where Q is the volumetric flow rate, r is the radius of the hemispheric convergence zone (in centimeters), V-a is the aliasing velocity (in centimeters per second), V p is the peak velocity of mitral inflow assessed by continuous-wave Doppler (cm/s), and α is the opening angle of mitral leaflets relative to flow direction.

Advantages- a. The PISA method is technically demanding, but it can be used in the presence of severe mitral regurgitation (MR). The integration of color M-mode, enabling simultaneous measurements of velocity and flow, improves the accuracy of this method.

b. Several investigators have validated the use of the flow convergence method in the calculation of MV area by direct comparisons with anatomic and calculated measurements of orifice size.[26] Calculation of MV area by the flow convergence method can be time consuming; however, its accuracy is not influenced by associated mitral or aortic regurgitation.

c. This method of calculating MV area may be best under the circumstances in which 2D planimetry is technically limited, when the continuity equation cannot be applied with the use of a

reference volumetric flow, and when the pressure half-time method is affected by hemodynamic changes.[27,28]

Three-dimensional (3D) echocardiography

Three-dimensional (3D) echocardiography has demonstrated accuracy for measuring MV area both for calcific (41) and rheumatic MS.[29]

Messika-Zeitoun et al.[30] examined the use of real-time 3D echocardiography in the setting of percutaneous mitral commissurotomy. 3D echocardiography provided accurate and reproducible MV area measurements that were like 2D echocardiography.

In patients with rheumatic MS, Zamorano et al.[29] reported real-time 3D was not only accurate and reproducible for measurement of MV area, but also the most accurate when compared to (gold standard) invasive methods.

Karamnov et al.[31] recently compared conventional echocardiography obtained measurements to assess degree of rheumatic MS (i.e., MV area determined by 2D planimetry, pressure half-time, PISA, continuity equation) with a novel 3D method which minimizes geometric assumptions present with 2D methods. Orifice areas with 3D were obtained offline with commercially available software. The authors found that the 3D method used to calculate MV orifice area reported greater or more severe degree of MS compared to conventional measurement techniques (48).

According to Sugeng et al.[32] direct 3D planimetry from the left ventricular side is the most accurate method for MVA evaluation. The PISA method was the most accurate of all 2D techniques, followed by the PHT method, and 2D planimetry.

Recent investigations have demonstrated that the pressure gradient across the stenotic valve is subject to hemodynamic changes. On the other hand, stenotic valve area remains constant in various hemodynamic conditions. Thus, the stenotic valve area seems more useful than the pressure gradient across the stenotic valve in assessing the severity of valve stenosis.

Propofol

Propofol is an intravenous anaesthetic induction agent which was introduced in 1970's is the most frequently used anaesthetic agent in the present days. The most prominent hemodynamic effect of propofol after using it as an inducing agent is hypotension.[33] It produces around 25%-40% fall in systolic blood pressure, diastolic blood pressure and Mean Arterial Pressure (MAP). This decrease in arterial pressure is associated with fall in cardiac index by around 15%, stroke volume index by 20%, systemic vascular resistance (SVR) by 15-25% and heart rate does not change significantly with use of propofol. In patients with valvular heart disease pulmonary artery and pulmonary capillary wedge pressure also is reduced, a finding that implies the resultant decrease in pressure is due to fall in preload and afterload.[34,35,36]

The effect of propofol may be affected by the underlying myocardial pathology. For instance, Sprung et.al.[37] studied the direct effects of propofol on the myocardial contractility and they concluded that at concentrations higher than that used clinically, propofol exerted a direct negative inotropic effect in nonfailing and failing human myocardium. But, since the negative inotropic effect was reversible with β-adrenergic stimulation, it suggested that propofol does not alter the contractile reserve but may shift the dose responsiveness to adrenergic stimulation.

Another study assessed effects of propofol and pentobarbital on integrated cardiovascular function[38] in pigs at baseline and after an acute increase in ventricular afterload which had shown a greater negative inotropic effect of barbiturates when compared to propofol. A decrease in arterial pressure with propofol is consistent with the drug acting as a vasodilator. Propofol affects ventricular and atrial function.[39] Propofol depresses contractility of the left atrial myocardium and reduces the active left atrial contribution to left ventricular filling in vivo. Compensatory decreases in chamber stiffness contribute to relative maintenance of left atrial reservoir function during the administration of propofol.

Imura et.al.[40] In their study examined the effects of propofol on resistance arteries in which, they concluded that propofol attenuated nor-epinephrine induced contraction through inhibition of Ca2+ release and Ca2+ influx through L-type Ca2+ channels, partially explaining the effects of propofol on vascular adrenergic signaling. Propofol may modulate vascular tone by interfering with other signaling pathways as well which are involved in Vaso regulation, such as ET1. Propofol also may attenuate the myogenic tone or response in pressure-flow autoregulation.[41,42]

In a well-designed study in which the effect of a local infusion of propofol into the brachial artery was compared with systemic intravenous administration with induction of anesthesia, direct brachial infusion had little effect on resistance and capacitance, whereas the effect of intravenous administration was like the effect observed with sympathectomy induced by stellate ganglion block. The peripheral vascular effects of propofol appear to be mediated primarily by reduced sympathetic vasoconstrictor nerve activity.[43]

Sevoflurane

Sevoflurane is an inhalational anaesthetic agent first described in 1972 for clinical use in patients undergoing surgical procedures. It causes dose dependant fall in MAP, SVR, myocardial contractility and little decrease in heart rate. However, it has relatively fewer undesirable effects on change in hemodynamics especially in patients with known cardiovascular diseases.

Different volatile agents are not identical in this regard, and the preponderance of information indicates that halothane and enflurane exert equal but more potent myocardial depression than isoflurane, desflurane, or sevoflurane, in part because of reflex sympathetic activation with the latter agents. In the setting of preexisting myocardial depression, volatile agents have a greater effect than in normal myocardium.[44,45] Early studies indicating that volatile agents did not have a deleterious effect on function in the setting of acute myocardial infarction (AMI) likely reflected the fact that the limited infarction did not compromise overall myocardial function.[46,47]

Studies of sevoflurane and desflurane showed similar results that were consistent with a mild direct coronary vasodilator effect of these agents.[48,49]The effect of volatile anesthetics is agent specific. For example, halothane causes flow-independent pulmonary vasoconstriction. In contrast, the hypoxic pulmonary vasoconstrictor response does not appear to be altered by sevoflurane and desflurane.[50]

All volatile agents attenuate the baroreceptor. The inhibition by halothane and enflurane is more potent than that observed with isoflurane, desflurane, or sevoflurane, each of which has a similar effect.[51,52]

Cardio-protective effects of anesthetic agents

Volatile anesthetics agents that augment IPC, there is no good evidence that intravenous hypnotic agents demonstrate these protective effects. There is, however, emerging evidence that propofol, the mainstay of induction agents, may enhance antioxidant activity in the heart and may prevent lipid peroxidation after ischemia and reperfusion, offering a potential protection of the heart.[53]

Propofol is a widely used intravenous induction agent and is preferred for its early recovery facilitating day care surgeries. With the introduction of inhalational sevoflurane in anesthesia practice, a new era in the induction of anesthesia has begun due to its ability to smooth induction.[54,55]But Patient acceptance is an important criterion for the selection of an inducing agent. Dhande et al. assessed the acceptance of anesthesia induction from the patient's perspective and found it comparable in the two groups. About 90% of patients in the propofol group and 85% in sevoflurane groups were willing to receive the same anesthetic in the future. These findings agree with those by Sloan et al., who reported that sevoflurane odor to be pleasant, and it was popular among almost all patients.[56]

Justification of the study

1. Anesthetic medications may underestimate the pressure gradients across the stenotic mitral valve due to their hemodynamic effects. There is limited literature regarding the effects of induction agents like Propofol and sevoflurane on echocardiographic parameters of mitral stenosis, which prompted us to compare the routinely used induction agents like propofol and sevoflurane in mitral stenosis patients.
2. There are hardly any studies comparing the hemodynamic effects of propofol and sevoflurane when used for anaesthesia induction in MS patients.
3. No research on this topic is available from our institute.

MATERIALS AND METHODS

MATERIALS AND METHODS

This prospective randomized double-blind study was conducted in a tertiary referral center, operating 1200 adult cardiac surgical patients annually. The study was approved by the Institutional Ethics Committee prior to enrollment of study population.

Inclusion criteria

1. Symptomatic mitral stenosis patients (Stage D) undergoing elective mitral valve replacement under cardiopulmonary bypass.
2. Age >18 and < 70 years of either gender.

Exclusion criteria

1. Patients not willing to participate in study
2. More than mild mitral regurgitation.
3. Patients with associated aortic, pulmonary, and tricuspid valve disease
4. Patients with associated symptomatic coronary artery disease.
5. Redo-surgeries
6. Emergency surgeries
7. Preoperative inotropic or mechanical circulatory supports.
8. Sub-optimal pre-induction and post-induction transthoracic echo images
9. Patients having post balloon mitral valvotomy/ closed mitral valvotomy atrial septal defect or any significant pathology that would affect hemodynamic parameters and echocardiographic profile.

Institutional ethics committee (IEC) approval

IEC approval was taken prior to starting of study. SCT/IEC/1509/september/2021

Clinical Trial Registry

The study was registered with the clinical trial registry of India- with CTRI- Reg. No- 056224

Sample size calculation

Based on previous study by Soro et al.[57] a sample size of 34 patients per group is needed to detect a minimum of 0.5 correlation between the pre-induction and post-induction mean pressure gradient with 80% power and 5% alpha error. Considering 10% drop-out rate because of technical reasons such as poor echocardiographic images, we decided to finalize the sample size to 40 in each group. The required sample size was calculated using the following formula as proposed by Kirkwood BR et al.[58]

Formula used for sample size calculation:

$$N = \frac{(u + v)^2(\sigma_1^2 + \sigma_0^2)}{(\mu_1 - \mu_0)^2}$$

N	= Sample size
μ_1 , μ_0	= Difference between the means (μ_1=39 and μ_0=29)
σ_1, σ_0	= Standard deviations (σ_1=15 and σ_0=15)
u	= Two sided percentage point of the normal distribution corresponding to 100 % - the power = 80%, u =0.84
v	= Percentage point of the normal distribution corresponding to the (two sided) significance level for significance level = 5%, v = 1.960

Randomization

After enrolling the eligible participants and excluding patients based on exclusion criteria, all patients were randomized into two groups. Numbered, sealed, opaque envelopes were used to randomly allocate patients to one of our study groups: Sevoflurane group (Group - S) or propofol group (Group – P).

Informed consent

Informed consent in English or Malayalam was obtained from the patient before start of the surgery.

Study protocol

Patients included in the study were educated about the study in the presence of a witness. The witness could counter question the patient whether he/she has really understood the proposed study, of which he/she would be a part. An informed consent form was signed by patient or relative of the patient according to the institute protocol.

Patients were instructed to continue all medications excluding oral hypoglycemic drugs, insulin, angiotensin - converting enzyme inhibitors and angiotensin - receptor blockers. Angiotensin-converting enzyme inhibitors and Angiotensin - receptor blockers were stopped 48 hours prior to surgery. Insulin and oral hypoglycemic drugs were omitted on the morning of surgery. Oral diazepam 0.2 mg/kg was administered for sedation, the night before surgery.

In the operating room, after attaching the ASA standard non-invasive monitors (ECG and SpO2), invasive arterial cannulation was done under local anaesthesia.

General anesthesia Induction in Sevoflurane group (Group-S)

The induction of general anesthesia in the Sevoflurane group (Group-S) consisted of fentanyl (5 mcg/kg), midazolam (0.05 mg/kg), and incremental dose of sevoflurane with 100% oxygen as

carrier gas titrated to the loss of eyelash reflex followed by pancuronium (0.1 mg/kg) to facilitate tracheal intubation.

Induction of general anesthesia in the propofol group (Group-P)

The induction of general anesthesia in the propofol group (Group-P) consisted of fentanyl (5 mcg/kg), midazolam (0.05 mg/kg), and incremental dose of propofol (starting with 1mg/kg) titrated to the loss of eyelash reflex followed by pancuronium (0.1 mg/kg) to facilitate tracheal intubation.

Phenylephrine was utilized to keep mean arterial pressure (MAP) within 20% from baseline, ensuring MAP more than 65 mm Hg in both the groups.

Pre-induction TTE

Prior to general anaesthesia induction baseline TTE of the heart was performed and the data were stored for later analysis. The perioperative echocardiographer used S5-1 probe of ultrasound machine (iE33: Philips, Bothell, USA). The following TTE views were imaged to obtain the echocardiographic parameters: a. Apical 4 chamber view (Figure 2), b. Apical 5 chamber view (Figure 3), c. Parasternal long axis (PLAX) (Figure 4) and d. Parasternal basal short axis (PSAX) (mitral valve) view (Figure 5). The following 2D echocardiography and Doppler parameters were noted: 1. Mitral valve area (pressure half time MVA-P, and continuity equation MVA-C); 2. Peak velocity; 3. Peak and mean gradients; 4. Pressure half time (PHT); 5. Deceleration Time (DT); (6) Tricuspid Annular Plane Systolic Excursion (TAPSE) (7) Left Ventricular Outflow tract (LVOT) diameter and VTI.

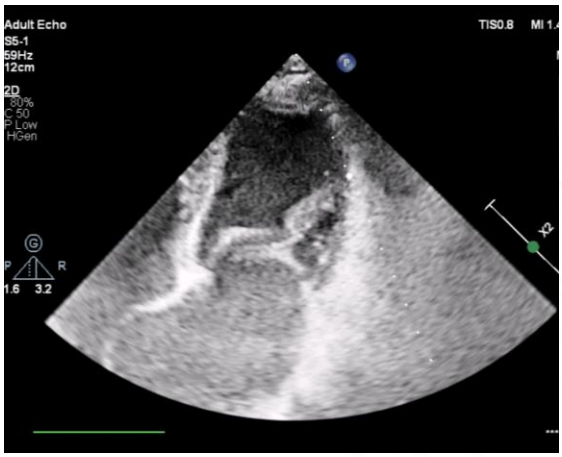

FIGURE 2 – Apical 4C view

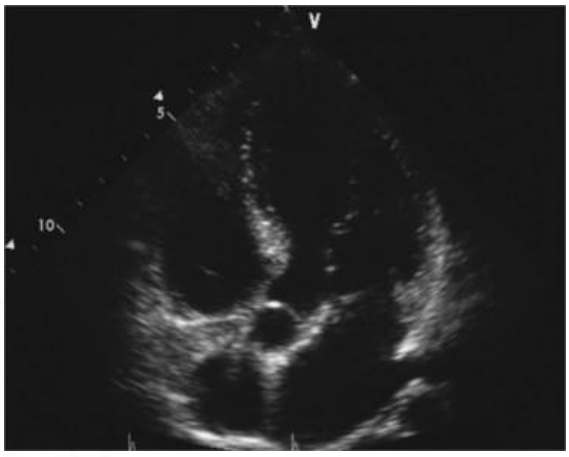

FIGURE 3 – Apical 5C view

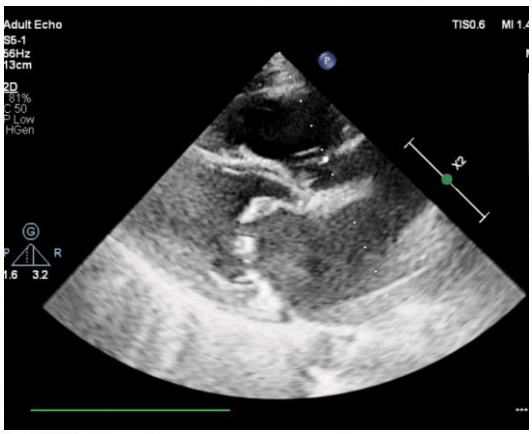

FIGURE 4 – PLAX view

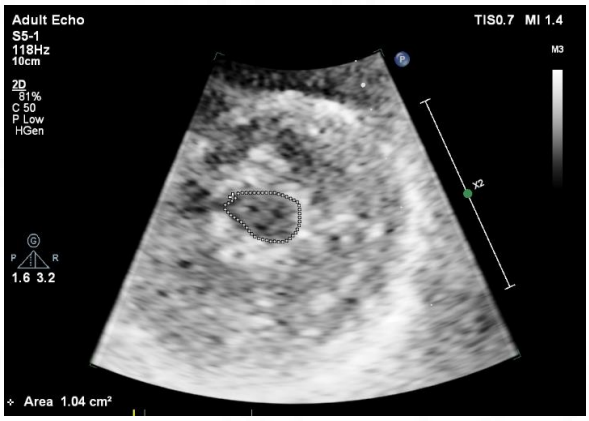

FIGURE 5 – PSAX view

Post induction TTE

Post induction Echocardiographic examination was performed after 3minutes of anaesthetic induction. The same pre-induction echocardiographic and Doppler parameters were noted. All the data were recorded according to ASE guidelines.

Echo evaluation was done as an average of 3-5 cardiac cycles in patients with sinus rhythm and 7-10 in those patients who were in AF.

Patient's hemodynamic parameters (MAP, HR, CO) were noted before induction (baseline), 1minute and 3 minutes after induction.

Blinding

The study was conducted in a double-blinded manner. Sealed envelope was used to convey the attending anaesthesiologist about the allocated group for that patient. An independent echocardiographer performed the pre-induction TTE and stored the Echo loops and images for later analysis. Similarly, post induction TTE was performed and data stored for analysis. The attending anaesthesiologist was blinded to the echocardiographic data and the echocardiographer was blinded to the allocated study groups.

Reliability and reproducibility of data

To test the reproducibility of the Doppler measurements we planned to collect random data from 10 patients. Tests for both inter as well as intra-observer variability was planned to be assessed.

STATISTICAL ANALYSIS

Statistical tests used

Categorical and quantitative variables were expressed as frequency (percentage) and mean ± SD respectively. Independent t test was used to compare quantitative parameters between two groups. Paired t test was used to compare quantitative parameters before and after intervention. Chi-square test was used to find association between categorical variables. Intra class correlation coefficient was calculated for intra and inter observer reliability assessment. For all statistical interpretations, $p<0.05$ was considered the threshold for statistical significance. Statistical analyses were performed by using statistical software package SPSS, version 20.0

RESULTS

OBSERVATIONS AND RESULTS

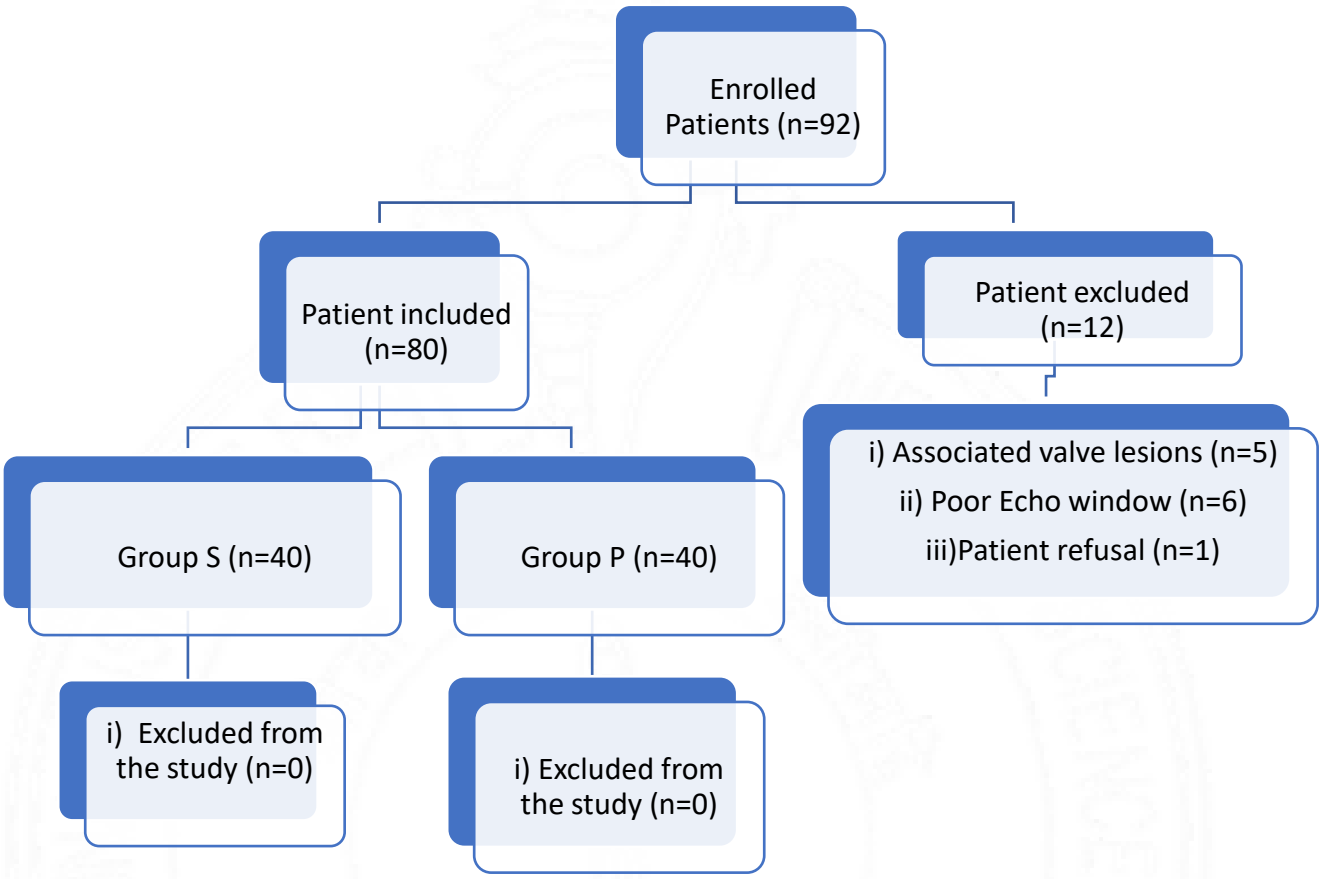

Figure 6: Consort Diagram For patient selection

Consort diagram explaining patient selection. 92 patients were recruited for the study. 12 patients were excluded based on the exclusion criteria. A total of 80 patients with 40 in each group were included in the final data analysis.

RESULTS

Results: A total of 80 patients were included in the final analysis.

I. Demography

Table 2. Comparison of demographic parameters between two study groups (n=80)

Demographic parameter	Study Groups (Mean± SD)		*p - value*
	Group-S (n=40)	Group-P (n=40)	
Age (years)	49.6 ± 7.2	50 ± 7.0	0.8150
Weight (kilograms)	66.2 ± 10	62.5 ± 6.8	0.0540
GENDER	n (%)	n (%)	
Male	16 (40.0%)	8 (20%)	0.0510
Female	24(60%)	32(80%)	

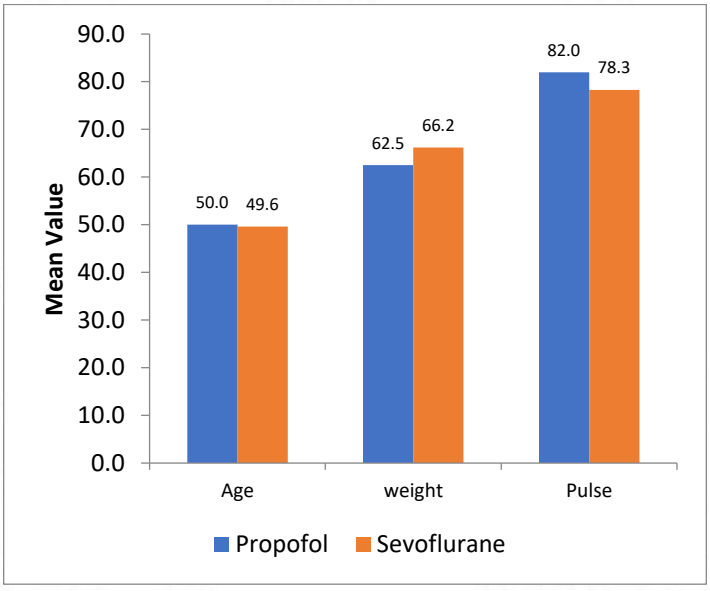

Figure 7: Bar chart of comparison of age, weight, baseline pulse between two groups

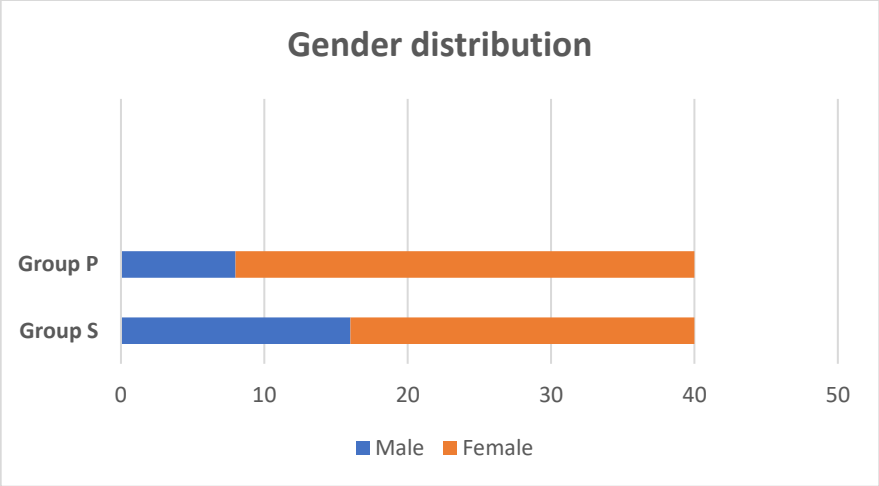

Figure 8: Stacked bar chart of comparison of gender between two groups

On comparing the demographic parameters between the study groups, no significant difference was observed in terms of age and weight but there was increased prevalence of mitral stenosis among female in both the group.

Table 3: Comparison of preoperative functional status between two groups

Functional class		Group-P (n=40)	Group-S (n=40)	χ^2	p
		n (%)	n (%)		
NYHA	Class 2	20 (50.0%)	22 (55.0%)	0.2	0.654
	Class 3	20 (50.0%)	18 (45.0%)		

Table 3 showing the classification of patients based on functional class, most of the patients were either NYHA class 2 or 3. No patient were in class 1 or 4.

Table 4: Comparison of baseline rhythm between two groups

Rhythm	Group-P (n=40) n (%)	Group-S (n=40) n (%)	χ^2	p
Sinus	24 (60.0%)	24 (60.0%)	0	1.000
Non-sinus	16 (40.0%)	16 (40.0%)		

Table 4 shows that patients in sinus rhythm were more in number as compared to those in non-sinus rhythm, but the difference is statistically insignificant.

Table 5: Comparison of pre-operative and Pre-induction TTE parameters between two groups

	Parameters	Group-P (n=40) (Mean± SD)	Group-S (n=40) (Mean± SD)	p- value
Pre-operative TTE	**Mean gradient**	**12.09 ± 4.12**	**13.18 ± 5.10**	**0.2963**
	MVA-P	**0.93 ± 0.20**	**0.96 ± 0.24**	**0.5454**
Pre-Induction TTE	**Mean gradient**	**11.12 ± 3.02**	**11.30 ± 4.84**	**0.8424**
	MVA-P	**0.88 ± 0.21**	**0.91 ± 0.11**	**0.4259**

Preoperative TTE data obtained by cardiologist and pre-induction TTE data obtained by cardiac anesthesiologists are comparable.

The baseline echocardiographic parameters of both the study groups are comparable and there was no statisticallly difference berween them.

Table 6: Comparison of pre-induction and post induction variables in group- P

Doppler parameters	Group- P (n=40) (Mean± SD)		p- value
	Pre-induction	Post induction	
Peak velocity (m/s)	2.2 ± 0.3	1.8 ± 0.4	<0.0001
Peak gradient (mmHg)	20.4 ± 6.1	13.9 ± 5.9	<0.0001
Mean gradient (mmHg)	11.1 ± 3.0	7.1 ± 2.8	<0.0001
PHT (sec)	261.9 ± 66.9	250.3 ± 55.8	0.4023
DT (sec)	846.0 ± 192.8	831.4 ± 250.8	0.7711
MVA- C (cm^2)	0.90 ± 0.21	0.91 ± 0.26	0.8504
MVA-P (cm^2)	0.88 ± 0.21	0.92 ± 0.29	0.4819
TAPSE (mm)	18.6 ± 2.7	17.9 ± 1.8	0.1764
Cardiac output (L/min)	4.1 ± 0.8	3.1 ± 0.8	<0.0001

Table 6: comparing the pre-induction with post induction echocardiographic parameters in group P shows that there is statistically significant change in peak velocity, peak and mean gradient, cardiac output and TAPSE with respect to the pre-induction baseline values.

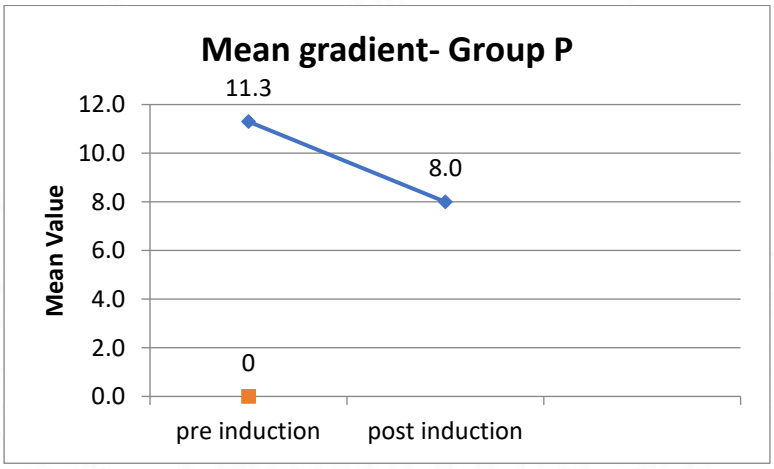

Figure 9: Graph showing the trend of mean gradient in group-P pre- and post-induction

Table 7: Comparison of pre-induction and post induction variables in group- S

Doppler parameters	Group-S (n=40) (Mean± SD)		p- value
	Pre-induction	Post induction	
Peak velocity (m/s)	2.3 ± 0.4	1.9 ± 0.3	<0.0001
Peak gradient (mmHg)	20.4 ± 6.0	14.6 ± 4.0	<0.0001
Mean gradient (mmHg)	11.3 ± 4.8	8.0 ± 3.1	<0.0001
PHT (sec)	240.6 ± 57.5	224.6 ± 58.5	<0.0001
DT (sec)	811.8 ± 201.7	767.6 ± 179.7	0.0030
MVA- C (cms)	0.99 ± 0.28	1.05 ± 0.31	0.0080
MVA-P (cms)	0.91 ± 0.11	0.98 ± 0.19	0.0472
TAPSE (mm)	18.2 ± 3.4	17.9 ± 3.2	0.6856
Cardiac output (l/min)	4.0 ±0.6	2.9 ± 0.5	<0.0001

Table 7 comparing the pre-induction with post induction echocardiographic parameters in group S shows that there is statistically significant change in peak velocity, peak and mean gradient, MVA-C, MVA-P, PHT, DT, and cardiac output with respect to the pre-induction baseline values.

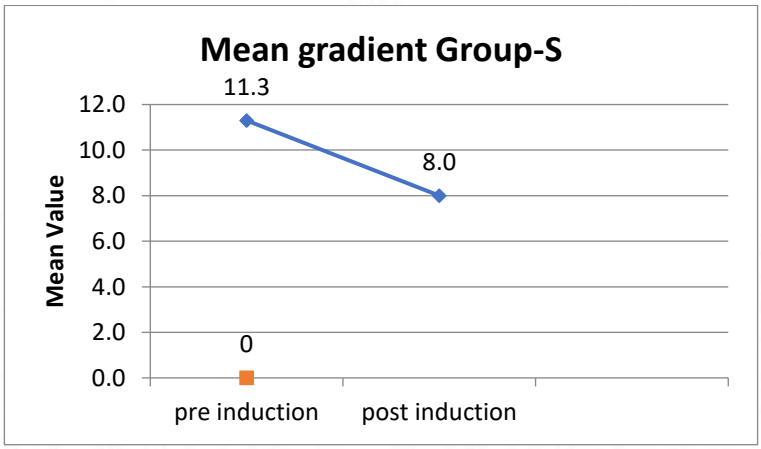

Figure 10: Graph showing the trend of mean gradient in group-S pre- and post-induction

Table 8: Comparison of post induction change in severity of MS between two groups

	Group-P (n=40)	Group-S (n=40)	χ^2	p
	(n, %)	(n, %)		
Mild MS (Mean gradient<5 mmHg)	**12 (30.0%)**	**06 (15.0%)**	**2.5480**	**0.1104**
Moderate and severe MS (Mean gradient >5 mmHg)	**28 (70.0%)**	**16 (40.0%)**		

Table 8 depicting the fraction of patients whose mean gradient dropped below the cut-off of 5mmHg post anesthesia induction. 30% of patients in group-P and 15% in group-S had their mean gradient below 5mmHg after induction of anaesthesia.

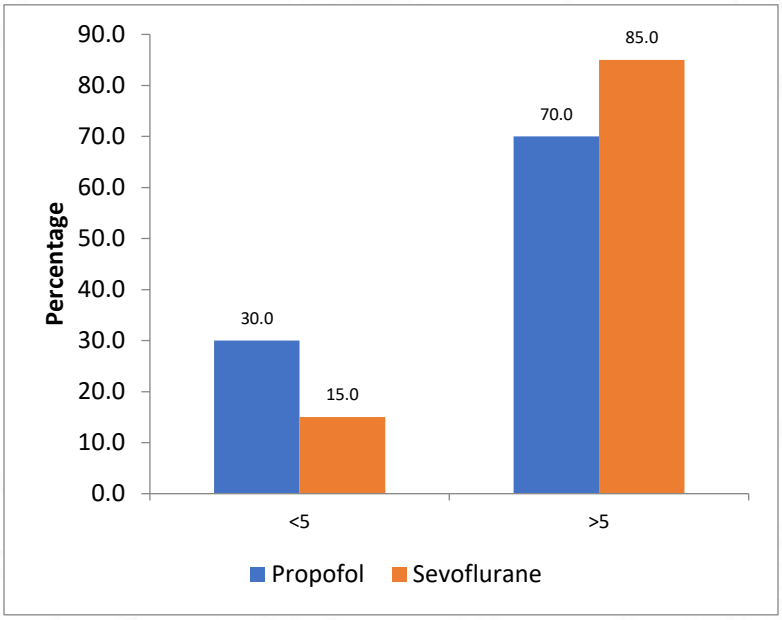

Figure 11: Comparison of post induction change in severity of MS between two groups

Table 9: Comparison of post induction variables between two groups

	Group-P (n=40)	Group-S (n=40)	P
	Mean ± SD	Mean ± SD	
Peak velocity (m/s)	2.2 ± 0.3	1.9 ± 0.3	<0.0001
Peak gradient (mmHg)	20.4 ± 6.1	14.6 ± 4.0	<0.0001
Mean gradient (mmHg)	11.1 ± 3.0	8.0 ± 3.1	<0.0001
PHT (sec)	250.3 ± 55.8	224.6 ± 58.5	0.0478
DT (sec)	846.0 ± 192.8	767.6 ± 179.7	0.0637
MVA- C (cm^2)	0.91 ± 0.21	1.05 ± 0.31	0.0205
MVA-P (cm^2)	0.88 ± 0.21	0.98 ± 0.19	0.0284
TAPSE (mm)	18.6 ± 2.7	18.2 ± 3.2	0.214
Cardiac output (L/min)	4.1 ± 0.8	2.9 ± 0.5	<0.0001

Table 9 comparing the post induction echocardiographic and Doppler parameters of both the study groups, showing statistically significant change in peak velocity, peak and mean gradients, MVA-C,P, and cardiac output in group-S as compared to group-P.

Table 10: Comparison of heart rate at different time points between two groups

Heart rate	Study Groups (Mean± SD)		*p - value*
	Group-S (n=40)	Group-P (n=40)	
Baseline	**82.4 ± 19.5**	**83.8 ± 15.1**	**0.7210**
1st minute after induction	**78.1 ± 18.1**	**86.2 ± 14.8**	**0.0310**
3rd minute after induction	**76.7 ± 16.9**	**89.1 ± 16.1**	**0.0010**

Table 10 comparing the trend of heart rate over different time points since the time of induction, showing statistically significant drop-in heart rate at 1st and 3rd minute following anesthetic induction. Simultaneously, the heart rate increased over time in propofol group.

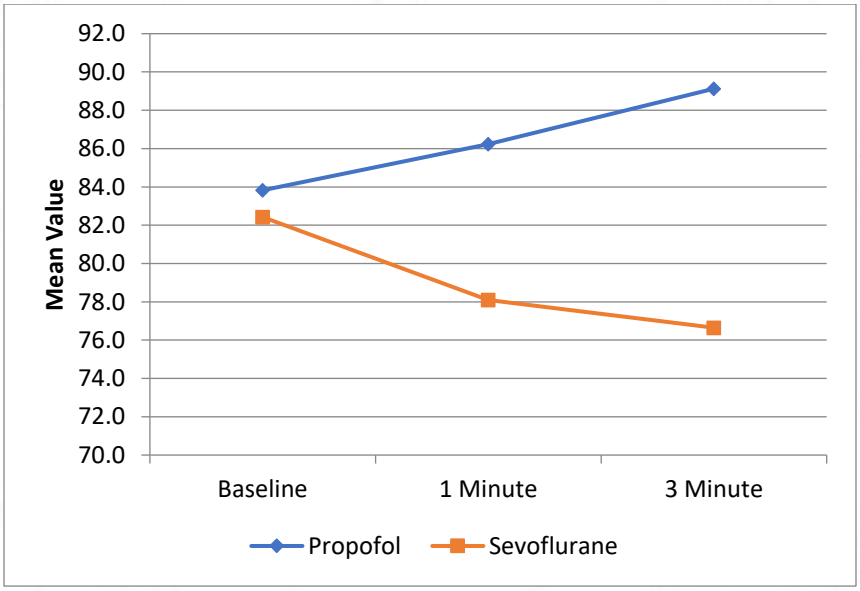

Figure 12: Graphical representation comparing trend of heart rate at different time points between two groups

Table 11: Comparison of MAP at different time interval based on group

MAP	Study Groups (Mean± SD)		*p - value*
	Sevoflurane (n=40)	Propofol (n=40)	
Baseline	**105.7 ± 10.5**	**105.0 ± 7.3**	**0.7131**
1st minute after induction	**89.1 ± 8.1**	**91.6 ± 6.5**	**0.1263**
3rd minute after induction	**85.4 ± 8.8**	**85.8 ± 6.4**	**0.8173**

MAP reduced over 1st and 3rd minute following anesthetic induction in both the study groups and the degree of fall in MAP is comparable in either group.

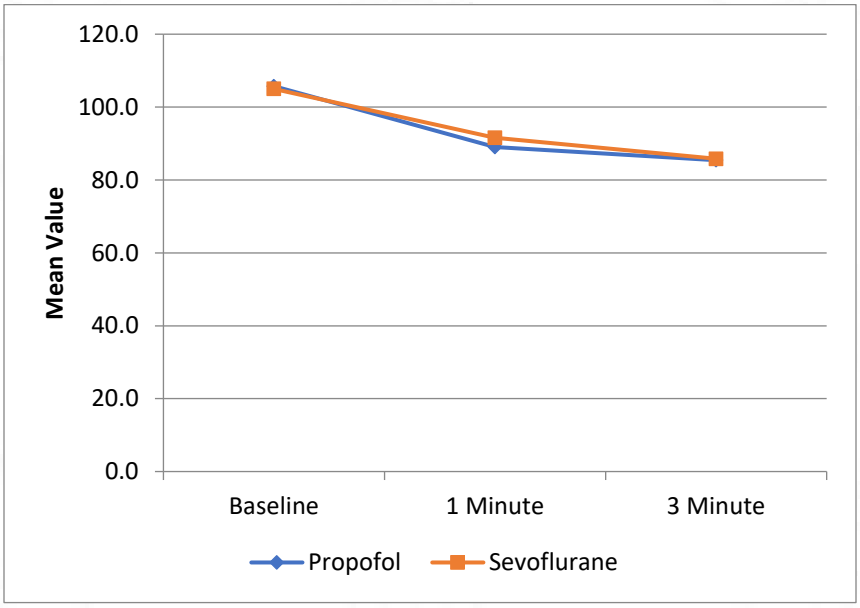

Figure 13: Graphical representation comparing the trend of MAP at different time interval between two groups

Table 12: Intra-class coefficient- inter and intra-observer reliability of values

	INTRA-CLASS COEFFICIENT Inter – Observers (Observer A and Observer B)	95% Confidence Interval		P value	INTRA-CLASS COEFFICIENT Intra- Observer (2 different points of time)	95% Confidence Interval		P value
		Lower Bound	Upper Bound			Lower Bound	Upper Bound	
Peak Velocity	.994	.976	.999	0.0001	.995	.980	.999	0.0001
Peak gradient	.992	.968	.998	0.0001	.990	.960	.998	0.0001
Mean gradient	.991	.965	.998	0.0001	.997	.988	.999	0.0001
PHT	.992	.970	.998	0.0001	.998	.992	1.000	0.0001
MVA	.986	.942	.996	0.0001	.984	.937	.996	0.0001

Table 12 showing intraclass correlation coefficient of values measured by different observer (interobserver variability) and by the same observer at two different time points (intra observer variability) that revealed statistically significant good correlation among the measured values.

Intra-class correlation coefficient between 0.7 to 0.9 is good correlation.

DISCUSSION

DISCUSSION

This was a prospective randomized study for comparison of sevoflurane and propofol as induction anesthetic agents for their effects on hemodynamics to influence changes in echocardiographic assessment of mitral stenosis patients. We found that both anesthetic agents downgraded the severity of MS and altered the hemodynamic parameters to a considerable extent.

The two groups in our study did not statistically differ with respect to demography of the patients except for the fact that there was increased number of female patients in either group [Group P (n, %) n=32, 80%, Group S (n, %) n=24,60%].

Symptomatic MS patients are classified to be in Stage D according to the updated ACC/AHA valvular heart diseases guidelines. More than 50% of them presented with dyspnea on exertion as their only symptom. Patients in both the study groups were of NYHA class 2 or 3 and none class 4. Clinical symptoms in MS are mainly due to increasing left atrial (LA) pressure. Chronically elevated LA pressure can trigger the onset of atrial fibrillation (AF) which the patient perceives as palpitations. More than 50% of the patients in both the group were in sinus rhythm at the time of presentation. As a standard of practice, the Doppler assessment was done as an average of 3 to 5 cardiac cycles in patients with sinus rhythm and average of 7 to 10 in those with AF.

Patients scheduled for elective mitral valve replacement had their preoperative Trans thoracic echocardiography performed by cardiologists as a part of pre-surgical workup. Yet, another Echocardiographic assessment was done for all subjects enrolled in the study as a standard protocol just before the induction and it was labelled as baseline.

It brought us to the question how reliable the severity is when assessed by anesthesiologists as compared to cardiologists' preoperative evaluation. Mitral valve area estimated by pressure half time and mean gradient across the MV were the constant parameters available from the preoperative workup record. Hence, these two variables were compared with the data analyzed by anesthesiologists at pre-induction. Both Mitral valve area as well as mean gradient were comparable and there was no statistically significant difference among them. Hence, the pre-induction rather than pre-operative echo data was taken into consideration for comparison with post induction data.

Normal flow velocity across the MV is less than 1.3 m/s. As the valve area reduces with disease progression, the velocity of flow across the stenotic valve increases. Peak velocity dropped significantly after the induction of anesthesia in both the group (Group P pre vs post-**2.2 ± 0.3 vs 1.8 ± 0.4**, Group S pre vs post-**2.3 ± 0.4 vs 1.9 ± 0.3**) so as the maximum and mean gradients (Group P pre vs post **-11.1 ± 3.0** vs **7.1 ± 2.8,** Group S pre vs post **-11.3 ± 4.8 vs 8.0 ± 3.1).** But, the updated guidelines on valvular heart diseases did not consider either velocity or the mean gradients for classification of disease severity. That is because, the trans-mitral Doppler is heavily influenced by flow across the valve, which, in-turn is determined by the diastolic filling time and LA-LV compliance.[12,13] The anaesthetic agents in our study are known to cause veno-dilatation which could reduce the preload significantly resulting in decreased flow across the reference valve, causing drop in velocity, peak and mean gradients.

Despite these limitations, mean gradient serves as a very important and convenient measurement to decide upon the severity of stenosis that is in use for a longer time. Gradient of less than 5mmHg can be called as mild or no stenosis whereas gradient more than 10mmHg indicates severe stenosis. When this criterion is considered, it was surprising to find that

approximately 25% of the patients who were documented to have severe stenosis, had their mean gradient less than 5mmHg post induction (Group P- 12/40, 30% Group S- 6/40, 15%), which was predominantly seen in patients induced with propofol. This is a clinically alarming phenomenon under anesthesia, where mis-classification of severity could easily happen.

Mitral valve area has been shown to be constant at varying degrees of hemodynamic change and hence it serves as a most reliable marker of disease severity. Updated valvular heart disease guidelines recognizes this phenomenon and utilized MVA to classify the disease severity. Patients whose MVA estimated to be less than $1.5cm^2$ were considered to have severe stenosis. MVA can be estimated by planimetry, continuity equation, PHT and by PISA method. MVA estimation by planimetry and PISA were difficult to perform because satisfactory images could not be obtained uniformly from all the study participants which we presumed might lead to erroneous results. Moreover, dense calcification of the mitral leaflets precludes accurate measurement by 2D-planimetry, which otherwise would overestimate the MVA.[17-19] Hence, MVA was estimated by PHT and continuity equation for all patients in both the study groups. The Doppler derived mitral valve area did not vary much between pre and post anesthesia induction in group-P. But, the MVA estimated by PHT and continuity equation in group-S increased by **$0.07 \pm 0.08cm^2$** and **$0.06 \pm 0.03cm^2$** respectively, after anesthesia in group-S which was statistically significant. This agrees with the study by kuperstein et.al.[65] where they had shown significant increase in MVA assessed after inducing general anesthesia. The exact reason for increase in valve area under anesthesia is not completely understood. It could be the complex interplay between the heart rate, loading conditions of the heart, myocardial contractility and inter individual responses to anesthetic agents.[59,60]

PHT derived valve area is dependent on heart rate and net compliance of the cardiac chambers. PHT of more than 150m.sec is considered valve stenosis according to ACC/AHA 2020 guidelines. Almost all patients had their baseline PHT more than 200m.sec which dropped significantly after induction of general anesthesia but the PHT did not fall below the cut-off of 150m.sec in any study subjects of both the groups. The slight but statistically insignificant increase in PHT derived valve area could be because of improved reservoir capacity of LA by propofol, which can potentially mis-classify the disease severity in borderline patients.

Baseline heart rhythm as well the respiro- phasic changes are the other important influencing factor in assessing the Doppler parameters.[59,60] As a part of the general anesthesia induction, patients are ventilated with the positive pressure after achieving muscle relaxation, which again could potentially alter the Doppler parameters because the baseline measurements were recorded in a spontaneously breathing patients. In addition to that, the Doppler parameters vary between the patients in sinus rhythm and those having atrial fibrillation.[66] These two confounding factors were overcome by averaging the Doppler analysis over several cardiac cycles, which could have masked the changes with rhythm as well as the respiratory cycle, that would have otherwise occurred.

Cardiac output measured after 3minutes of general anaesthetic induction was significantly lower in both the study groups compared to the baseline (Group P pre vs post- **4.1± 0.8** vs **3.1± 0.8,** Group S pre vs post- **4.0± 0.6 vs 2.9± 0.5**). All anesthetic agents have been found to reduce the cardiac output by various mechanisms, predominantly by reducing the preload because of venous dilatation due to sympathetic inhibition. Myocardial depression could be another mechanism which has been demonstrated at higher anaesthetic concentrations. Reduced CO together with the lower SVR is detrimental for coronary perfusion. Both the study drugs reduced CO as well as

MAP significantly after general anesthesia induction, but there was no incidence of any major hemodynamic disturbances to cause ST-T changes. It has to be noted that the degree of fall in CO and MAP was relatively higher with propofol than with sevoflurane.

Other important hemodynamic goal during general anesthesia induction in patients with MS is to avoid tachycardia, as increase in heart rate reduces diastolic filling time and increases LA pressure which can increase the trans-mitral gradient.[61-63] Like previous studies,[64] our study also had shown statistically significant reduction in heart rate at 1st and 3rd minute following induction with sevoflurane and increase in heart rate seen in patients who received propofol for induction. The increase in heart rate with propofol has been verified by many other investigators previously, which occurs mainly as a reflex response to fall in SVR and may also be due to pain experienced by some patients on propofol injection.

It is noteworthy that, increase in heart rate may increase myocardial strain which when combined with the reduction in CO and MAP as seen in group-P, can cause serious hemodynamic instability, which is not a case in group -S. Hence, sevoflurane appears to be a relatively cardio-stable anaesthetic induction agent.

To test the reproducibility of the Doppler measurements we randomly selected 10 patients and determined peak velocity, peak and mean gradients, PHT and mitral valve area based on the continuity equation method by one observer on two occasions (intra-observer variability). Another observer independently performed analysis for the same patients (inter-observer variability) for the same parameters. The observers were blinded to each other's results. The values had acceptable correlation among each other.

Limitations

- It was a single centre study and the study sample size was less.
- In-spite of having numerous inhalational and intravenous anaesthetic agents we restricted to propofol and sevoflurane, as they are the commonly used anaesthetic agents in many centres and their hemodynamic profile is not well described in MS patients.
- ACC/AHA guideline suggested planimetred area for classification of disease severity, but we utilised PHT and continuity equation derived valve areas for their simplicity in assessment and also for the fact that, the Doppler interrogation was restricted by time, as the patient was under anaesthesia un-intubated.
- Pulmonary Artery Systolic Pressure (PASP), another important criterion to classify MS severity, was not evaluated in our study, since not all the patient had Tricuspid Regurgitation (TR) and central venous catheter could not be placed in awake patients.
- Both hemodynamics as well as valve dynamics are altered by baseline rhythm and by the changes induced during respiratory cycle. Sub- group analysis in patients who had AF would have yielded some more clarity on the changing dynamics. Similarly, standardisation of the phase of respiratory cycle at which measurements were performed would have given us much more accurate results.

CONCLUSIONS AND SUMMARY

Conclusions

- Both inhalational as well as intravenous anaesthetic induction agents employed in our study downgraded the trans-mitral pressure gradients after induction of general anaesthesia in patients with mitral stenosis.
- There was a statistically significant increase in MVA from pre-induction to post induction in patients who received sevoflurane in comparison to patients who received propofol.
- On comparison between sevoflurane and propofol induction, the post induction pressure gradients were significantly reduced and MVA were significantly increased in patients who received sevoflurane than in patients who received propofol.
- Both propofol and sevoflurane reduced cardiac output and Mean Arterial Pressure significantly after induction of anaesthesia which is not desired in patients having MS.
- Induction of anaesthesia with a titrated dose of sevoflurane reduced heart rate significantly at 1^{st} and 3^{rd} minute, which is a favourable hemodynamic goal in patients with MS. In contrast, heart rate increased significantly in those patients who received propofol.
- With respect to hemodynamic goals for general anaesthesia induction in MS patients, induction with sevoflurane appears to be a good option when compared to propofol based anaesthesia.

REFERENCES

BIBLIOGRAPHY

1. Tiange Luo, Jie Han, Xu Meng. Features of rheumatic mitral valves and a grading system to identify suitable repair cases in China. *J Thorac Dis* 2017;9(9):3138-3147.

2. Ganesan G. How to assess mitral stenosis by echo - A step-by-step approach. J Indian Acad Echocardiogr Cardiovasc Imaging 2017;1:197-205.

3. Zuhlke L, Karthikeyan G, Engel ME, et al. Clinical outcomes in 3343 children and adults with rheumatic heart disease from 14 low- and middle- income countries: two- year follow- up of the global Rheumatic Heart Disease Registry (the REMEDY study). Circulation. 2016;134:1456–1466.

4. Zuhlke L, Engel ME, Karthikeyan G, et al. Characteristics, complications, and gaps in evidence- based interventions in rheumatic heart disease: The Global Rheumatic Heart Disease Registry (the REMEDY study). Eur Heart J. 2015;36:1115–1122.
5. Shaw TR, Sutaria N, Prendergast B. Clinical and haemodynamic profiles of young, middle aged, and elderly patients with mitral stenosis undergoing mitral balloon valvotomy. Heart. 2003;89: 1430–1436.
6. Kato N, Padang R, Scott CG, et al. The natural history of severe calcific mitral stenosis. J Am Coll Cardiol. 2020;75:3048–3057.
7. Chandrashekhar Y, Westaby S, Narula J. Mitral stenosis. Lancet. 2009;374:1271–1283.
8. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38:2739–2791.
9. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. J Am Coll Cardiol. 2021;77:e25–197.
10. Popovic AD, Thomas JD, Neskovic AN, et al. Time-related trends in the preoperative evaluation of patients with valvular stenosis. Am J Cardiol 1997;80(11):1464-1468.
11. Wunderlich NC, Beigel R, Siegel RJ. Management of mitral stenosis using 2D and 3D echo-Doppler imaging. JACC Cardiovasc Imaging. 2013; 6(11): 1191–1205

12. Hatle L, Brubakk A, Tromsdal A, et al. Noninvasive assessment of pressure drop in mitral stenosis by Doppler ultrasound. Br Heart J 1978;40(2):131-140.

13. Oh JK, Seward JB, Tajik AJ. Hemodynamic assessment. In: The Echo Manual. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999:59-71.

14. Bruce CJ, Nishimura RA. Clinical assessment and management of mitral stenosis, valvular heart disease. Cardiol Clin 1998; 16 (3):375-403.

15. Hatle L, Brubakk A, Tromsdal A, et al. Noninvasive assessment of pressure drop in mitral stenosis by Doppler ultrasound. Br Heart J 1978;40(2):131-140.

16. Weyman AE, ed. Left ventricular inflow tract I: The mitral valve. In: Principles and Practice of Echocardiography. 2nd ed. Philadelphia, PA: Lea & Febiger; 1994:391-497.

17. Henry WL, Griffith JM, Michaelis LL, et al. Measurement of mitral orifice area in patients with mitral valve disease by real time, two-dimensional echocardiography. Circulation 1975;51(5):827-831. 23.

18. Martin RP, Rakowski H, Kleiman JH, et al. Reliability and reproducibility of two-dimensional echocardiographic measurement of the stenotic mitral valve orifice area. Am J Cardiol 1979;43(3):560-568.

19. Wann LS, Weyman AE, Feigenbaum H, et al. Determination of mitral valve area by cross-sectional echocardiography. Ann Intern Med 1978;88(3):337-341.

20. Hatle L, Angelsen B, eds. Pulsed and continuous wave Doppler in the diagnosis and assessment of various heart lesions. In: Doppler Ultrasound in Cardiology: Physical Principles and Clinical Applications. Philadelphia, PA: Lea & Febiger; 1982:76-89.

21. Braverman AC, Thomas JD, Lee RT. Doppler echocardiographic estimation of mitral valve area during changing hemodynamic conditions. Am J Cardiol 1991;68(15):1485-1490.

22. Nakatani S, Masuyama T, Kodama K, et al. Value and limitations of Doppler echocardiography in the quantification of stenotic mitral valve area: comparison of the pressure half-time and the continuity equation methods. Circulation. 1988; 77(1): 78–85.

23. Karp K, Teien D, Eriksson P. Doppler echocardiographic assessment on the valve area in patients with atrioventricular valve stenosis by application of the continuity equation. J Intern Med 1989;225(4):261-266.

24. Rodriguez L, Thomas JD, Monterroso V, et al. Validation of the proximal flow convergence method. Calculation of orifice area in patients with mitral stenosis. Circulation 1993;88(3):1157-1165.

25. Rifkin R, Harper K, Tighe D. Comparison of proximal isovelocity surface area method with pressure half-time and planimetry in the evaluation of mitral stenosis. J Am Coll Cardiol 1995;26(2):458-465.

26. Faletra F, Pezzano A Jr., Fusco R, et al. Measurement of mitral valve area in mitral stenosis: four echocardiographic measurements compared with direct measurements of anatomic orif ices. J Am Coll Cardiol 1996;28: 1190–7.

27. Min SY, Song JM, Kim YJ, et al. Discrepancy between mitral valve areas measured by two-dimensional planimetry and three dimensional transesophageal echocardiography in patients with mitral stenosis. Heart 2013;99:253–8.

28. Schlosshan D, Aggarwal G, Mathur G, et al. Real-time 3D transesophageal echocardiography for the evaluation of rheumatic mitral valve stenosis. J Am Coll Cardiol 2011;4: 580–8.

29. Zamorano J, Cordeiro P, Sugeng L, et al. Real-time three-dimensional echocardiography for rheumatic mitral valve stenosis evaluation: an accurate and novel approach. J Am Coll Cardiol 2004;43(11):2091-2096.

30. Messika-Zeitoun D, Brochet E, Holmin C, et al. Three-dimensional evaluation of the mitral valve area and commissural opening before and after percutaneous mitral commissurotomy in patients with mitral stenosis. Eur Heart J 2007;28(1):72-79.

31. Karamnov S, Burbano-Vera N, Huang C, et al. Echocardiographic assessment of mitral stenosis orifice area: a comparison of a novel three-dimensional method versus conventional techniques. Anesth Analg 2017;125(3):774-780.

32. Sugeng L, Weinert L, Lammertin G, et al. Accuracy of mitral valve area measurements using transthoracic rapid freehand 3-dimensional scanning: comparison with noninvasive and invasive measurements. J Am Soc Echocardiogr 2003; 16: 1292–300.
33. Rouby JJ, Andreev A, Leger P, et al. Peripheral vascular effects of thiopental and propofol in humans with artificial hearts. Anesthesiology. 1991;75(1):32–42.
34. Biddle NL, Gelb AW, Hamilton JT. Propofol differentially attenuates the responses to exogenous and endogenous norepinephrine in the isolated rat femoral artery in vitro. Anesth Analg. 1995;80(4):793–799.
35. Chang KSK, Davis RF. Propofol produces endothelium-independent vasodilation and may act as a Ca2+ channel blocker. Anesth Analg. 1993;76(1):24–32. 154. Gelb AW, Zhang C, Hamilton JT. Propofol induces dilation and inhibits constriction in guinea pig basilar arteries. Anesth Analg. 1996;83(3):472–476.
36. Park WK, Lynch C 3rd, Johns RA. Effects of propofol and thiopental in isolated rat aorta and pulmonary artery. Anesthesiology. 1992;77(5):956–963.
37. Sprung J, Ogletree-Hughes ML, McConnell BK, et al. The effects of propofol on the contractility of failing and nonfailing human heart muscles. Anesth Analg. 2001;93(3):550–559.
38. Kolh P, Lambermont B, Ghuysen A, et al. Comparison of the effects of propofol and pentobarbital on left ventricular adaptation to an increased afterload. J Cardiovasc Pharmacol. 2004;44(3): 294–301.
39. Van Klarenbosch J, Stienen GJ, de Ruijter W, et al. The differential effect of propofol on contractility of isolated myocardial trabeculae of rat and guinea-pig. Br J Pharmacol. 2001;132(3):742–748.
40. Imura N, Shiraishi Y, Katsuya H, et al. Effect of propofol on norepinephrine-induced increases in [Ca2+] (i) and force in smooth muscle of the rabbit mesenteric resistance artery. Anesthesiology. 1998;88(6):1566–1578.
41. Horibe M, Ogawa K, Sohn JT, Murray PA. Propofol attenuates acetylcholine-induced pulmonary vasorelaxation: role of nitric oxide and endothelium-derived hyperpolarizing factors. Anesthesiology. 2000;93(2):447–455.

42. Kondo U, Kim SO, Murray PA. Propofol selectively attenuates endothelium-dependent pulmonary vasodilation in chronically instrumented dogs. Anesthesiology. 2000;93(2):437–446.
43. Robinson BJ, Ebert TJ, O'Brien TJ, et al. Mechanisms whereby propofol mediates peripheral vasodilation in humans. Sympathoinhibition or direct vascular relaxation? Anesthesiology. 1997;86(1): 64–72.
44. Kemmotsu O, Hashimoto Y, Shimosato S. Inotropic effects of isoflurane on mechanics of contraction in isolated cat papillary muscles from normal and failing hearts. Anesthesiology. 1973;39(5):470–477.
45. Kemmotsu O, Hashimoto Y, Shimosato S. The effects of fluroxene and enflurane on contractile performance of isolated papillary muscles from failing hearts. Anesthesiology. 1974;40(3):252–260.
46. Lowenstein E, Foëx P, Francis CM, et al. Regional ischemic ventricular dysfunction in myocardium supplied by a narrowed coronary artery with increasing halothane concentration in the dog. Anesthesiology. 1981;55(4):349–359.
47. Prys-Roberts C, Roberts JG, Foëx P, et al. Interaction of anesthesia, beta-receptor blockade, and blood loss in dogs with induced myocardial infarction. Anesthesiology. 1976;45(3):326–329.
48. Glower DD, Spratt JA, Kabas JS, et al. Quantification of regional myocardial dysfunction after acute ischemic injury. Am J Physiol. 1988;255(1 Pt 2):H85–H93.
49. Glower DD, Spratt JA, Snow ND, et al. Linearity of the Frank-Starling relationship in the intact heart: the concept of preload recruitable stroke work. Circulation. 1985;71(5):994–1009.
50. Lesitsky MA, Davis S, Murray PA. Preservation of hypoxic pulmonary vasoconstriction during sevoflurane and desflurane anesthesia compared to the conscious state in chronically instrumented dogs. Anesthesiology. 1998;89(6):1501–1508.
51. Ebert TJ, Harkin CP, Muzi M. Cardiovascular responses to sevoflurane: a review. Anesth Analg. 1995;81(suppl 6):S11–S22.
52. Muzi M, Ebert TJ. A comparison of baroreflex sensitivity during isoflurane and desflurane anesthesia in humans. Anesthesiology. 1995;82(4):919–925.

53. Kato R, Foëx P. Myocardial protection by anesthetic agents against ischemia-reperfusion injury: an update for anesthesiologists. Can J Anaesth. 2002;49(8):777–791.
54. Thwaites AJ, Edmends S, Smith I: Inhalation induction with sevoflurane: a double-blind comparison with propofol. Brit J of Anesth. 1997, 78:356-361.
55. Mashour GA: Consciousness unbound, towards a paradigm of general anesthesia. Anesthesiology. 2004, 100:428-433.
56. Sloan MH, Conard PF, Karsunky PK, Gross JB: Sevoflurane versus isoflurane: induction and recovery characteristics with single - breath inhaled induction of anesthesia. Anesth Analg 1996, 82:528-532.
57. Soro M, Gallego L, Silva V, et al. Cardioprotective effect of sevoflurane and propofol during anaesthesia and the postoperative period in coronary bypass graft surgery: a double-blind randomised study. Eur J Anaesthesiol 2012; 29: 561–9
58. Kirkwood B, Sterne J. Essential Medical Statistics, 2nd edition, Wiley-Blackwell, Chapter 35.
59. Soni N, Williams P. Positive pressure ventilation: what is the real cost? Br J Anaesth. 2008; 101(4): 446–457.
60. Michard F. Changes in arterial pressure during mechanical ventilation. Anesthesiology. 2005; 103(2): 419–28
61. Ashcom TL, Johns JP, Bailey SR, Rubal BJ. Effects of chronic beta blockade on rest and exercise hemodynamics in mitral stenosis. Cathet Cardiovasc Diagn 1995;35:110-5.
62. Klein HO, Sareli P, Schamroth CL, Carim Y, Epstein M, Marcus B. Effects of atenolol on exercise capacity in patients with mitral stenosis with sinus rhythm. Am J Cardiol 1985;56:598-601.
63. Neema PK, Waiker HD. Atenolol premedication in patients undergoing closed mitral commissurotomy. Ann Card Anaesth 2003;6:42-6.
64. Dhande K, Kshirsagar J, Dhande A, Patil N, V P Jr. Hemodynamic Stability, Patient Acceptance and Cost of Intravenous Propofol and Inhalational Sevoflurane for Induction of Anaesthesia: A Prospective, Randomized Comparative Study. Cureus. 2020 Apr 16;12(4):e7687.

65. Kuperstein R et al., Influence of anesthesia on hemodynamic assessment of mitral stenosis severity. Cardiol J. 2022;29(2):245-251.
66. Rijsterborgh H, Mayala A, Forster T, et al. The reproducibility of continuous wave Doppler measurements in the assessment of mitral stenosis or mitral prosthetic function: the relative contributions of heart rate, respiration, observer variability and their clinical relevance. Eur Heart J. 1990; 11(7): 592–600.
67. Belik J, Light RB. Effect of increased afterload on right ventricular function in newborn pigs. J Appl Physiol 1989; 66: 863-9.
68. Vlahakes GJ, Turley K, Hoffman JI. The pathophysiology of failure in acute right ventricular hypertension: Hemodynamic and biochemical correlations. Circulation 1981; 63: 87-95.

ANNEXURES

I. STUDY PROFORMA

Sree Chitra Tirunal Institute for Medical Sciences and Technology

Trivandrum

Observation Chart

Hospital No: Height (cm): Weight (Kg):

BSA: Date of surgery:

Diagnosis: **Group S / Group P**

Preoperative features:

Presenting complaints: NYHA class: Heart rate and rhythm:

Pre-op TTE findings:

LVEF (%): MS gradient (mm Hg): MVA (cm^2):

PHT(ms): RVSP (mm Hg): TR/PR grade:

2D Echocardiographic and Doppler parameters of Mitral valve

	Pre-Induction TTE findings	Post-Induction TTE findings
MS peak velocity (m/sec)		
Peak gradient(mm Hg)		
Mean gradient(mm Hg)		
Pressure Half Time (msec)		
Deceleration Time (msec)		
Mitral valve area by PHT (cm^2)		
Mitral valve area by planimetry(cm^2)		
Pulmonary artery systolic pressure (mm Hg)		
LVEF (%)		
TAPSE (mm)		
Cardiac Output/ Cardiac index		

Hemodynamic parameters

	Pre-induction	0 min after induction	1 min after induction	2 min after induction	3 min after induction
Heart rate					
MAP (mm Hg)					
SBP (mm Hg)					
DBP (mm Hg)					
Stroke volume (ml)					

II. IEC APPROVAL

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)

DUPLICATE

SCT/IEC/1509 /August/ 2021

20.09.2021

Dr. Mohammed Jaffer Sherif
Senior Resident
Department of Anaesthesiology
SCTIMST, Thiruvananthapuram

Dear Dr. Mohammed Jaffer Sherif,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled "COMPARISON BETWEEN INTRAVENOUS AND INHALATIONAL ANAESTHETIC INDUCTION AGENTS ON ECHOCARDIOGRAPHIC PARAMETERS OF MITRAL STENOSIS PATIENTS UNDERGOING MITRAL VALVE REPLACEMENT SURGERY (IEC/1509)" on 18th August, 2021.

The following members of the Ethics Committee were present at the meeting held on 18th August, 2021 at Residences and Offices of IEC Members via Video Conference

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Prof. C.C. Kartha	MBBS,MD	Male	Basic Medical Scientist (Chairman)	No
2.	Dr. Kala Kesavan P	MBBS,MD	Female	Basic Medical Scientist	No
3.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
4.	Dr. Pradeep S	MBBS, MD	Male	Basic Medical Scientist	No
5.	Dr. Achuth Sankar S. Nair	Ph.D (i.Engineering ii.Music)	Male	Social Scientist	No
6.	Dr. Rejnish Kumar	MBBS,MD ,DNB	Male	Clinician	No
7.	Adv. N Anand	BAL, L.LB	Male	Legal Expert	No
8.	Adv. Priya Kaimal	LLM, MBL	Female	Legal Expert	No
9.	Dr. Harikrishna Varma P. R	Ph.D (Materials Sciences)	Male	Medical Technology	Yes
10.	Dr. Manikandan.S	MBBS,MD,PDCC	Male	Clinician	Yes
11.	Dr. Narayanan Namboodiri. K K	MBBS,MD,DM	Male	Clinician	Yes
12.	Dr. Biju Soman	MBBS,MD, DPH, MSc, DLSHTM	Male	Basic Medical Scientist	Yes
13.	Dr. Srinivas G	PhD	Male	Basic Medical Scientist (Member Secretary)	Yes

The following documents were reviewed:

Original submission

1. Covering letter addressed to the Chairman, IEC, SCTIMST dated 09.07.2021 from Dr. Mohammed Jaffer Sherif, regarding the change of primary investigator
2. Covering letter addressed to the Chairman, IEC, SCTIMST dated 09.07.2021 from Dr. Nagarjuna P, regarding no objection for the change of primary investigator
3. New IEC Application Form
4. Old IEC Application Form

Revised submission

1. Covering letter addressed to the Chairperson, IEC, SCTIMST dated 14.09.2021
2. Covering letter addressed to the Chairman, IEC, SCTIMST dated 09.07.2021 from Dr. Mohammed Jaffer Sherif, regarding the change of primary investigator
3. Covering letter addressed to the Chairman, IEC, SCTIMST dated 09.07.2021 from Dr. Nagarjuna P, regarding no objection for the change of primary investigator
4. Covering letter addressed to the Chairman, IEC, SCTIMST dated 13.09.2021 from Dr. Prasanta Kumar Dash, Senior Professor Department of Anaesthesiology, SCTIMST
5. Study Proposal
6. IEC Application Form
7. Patient Information Sheet in English and Malayalam
8. Informed Consent Form in English and Malayalam
9. Observation Chart
10. Old study proposal
11. Old IEC Application Form
12. Old Patient Information Sheet in English and Malayalam
13. Old Informed Consent Form in English and Malayalam
14. Old Observation Chart

IEC Decision

The IEC recommended the continuation of the study.

This approval is in continuation of IEC Regn No. ECR/189/Inst/KL/2013/RR-16, subject to IEC Renewal pending process with CDSCO

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,

G. Srinivas
Member Secretary, IEC

III. CONSENT FORMS

INFORMED CONSENT

I, _____(**Participant's name): Date of Birth / Age (in years)** _____Son / daughter of _____

(Please tick boxes) •

Declare that I have read the above information provide to me regarding the study:

TITLE: "Comparison between intravenous and inhalational anaesthetic induction agents on echocardiographic parameters of mitral stenosis patients undergoing mitral valve replacement surgery"

And 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 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:

(Person Obtaining Consent)

കാര്യബോധത്തോടെയുള്ള സമ്മതപത്രം

ഞാൻ.....(പങ്കെടുക്കുന്നയാളുടെ പേര്): ജനനതിയതി/വയസ്സ് (വർഷത്തിൽ).....
.....യുടെ മകൻ/മകൾ

(ദയവായി കോളങ്ങളിൽ ശരി അടയാളമിടുക)

മിട്രൽ വാൽവ്മാറ്റ ശസ്ത്രക്രിയയ്ക്ക് വിധേയരാകുന്ന മിട്രൽ സ്റ്റെനോസിസ് രോഗികളിൽ മയക്കാൻ വെയിനിലൂടെ മയക്കൽ മരുന്ന് കുത്തിവയ്ക്കുന്നതിന്റെയും ശ്വസിപ്പിക്കുന്നതിന്റെയും എക്കോകാർഡിയോഗ്രഫി സ്വഭാവവിശേഷങ്ങളുടെ താരതമ്യം എന്ന പഠനസംബന്ധമായി മുകളിൽ നൽകിയ വിവരങ്ങൾ ഞാൻ വായിച്ചു എന്നു പ്രസ്താവിക്കുന്നു.

എനിക്കുണ്ടായ സംശയങ്ങളെല്ലാം പരിഹരിച്ചു. [ ]

ഈ പഠനത്തിലുള്ള എന്റെ പങ്കാളിത്തം പൂർണ്ണമായും സ്വമേധയാ ആണെന്നും എന്റെ പതിവ് ചികിത്സയെയോ നിയമപരമായ അവകാശങ്ങളെയോ ബാധിക്കാതെ ഏതുസമയത്തും പങ്കെടുക്കുന്നതിനുള്ള അനുവാദം പിൻവലിക്കാമെന്നും ഞാൻ മനസ്സിലാക്കുന്നു.[ ]

ഞാൻ പഠനത്തിൽനിന്നും പിൻമാറിയാലും എന്റെ ആരോഗ്യ രേഖകൾ പഠനസംഘത്തിനും ഇൻസ്റ്റിറ്റൂഷണൽ എത്തിക്സ് കമ്മിറ്റി അംഗങ്ങൾക്കും പരിശോധിക്കാൻ എന്റെ അനുവാദം ആവശ്യമില്ലെന്ന് ഞാൻ മനസ്സിലാക്കുന്നു. അതിന് ഞാൻ സമ്മതിക്കുന്നു. [ ]

മൂന്നാംകക്ഷികൾക്ക് നൽകുമ്പോഴോ പ്രസിദ്ധീകരിക്കുമ്പോഴോ എന്റെ വ്യക്തിവിവരങ്ങൾ നൽകില്ലെന്ന് ഞാൻ മനസ്സിലാക്കുന്നു. [ ]

ഞാൻ സമേധയാ പഠനത്തിൽ പങ്കെടുക്കാൻ സമ്മതിക്കുന്നു. [ ]

ഈ സമ്മതപത്രത്തിന്റെ ഒപ്പിട്ട ഒരു പ്രതി എനിക്ക് ലഭിച്ചു

പേര്

ഒപ്പ്

തിയതി

സാക്ഷിയുടെ പേര്

പങ്കെടുക്കുന്നയാളുമായുള്ള ബന്ധം

സമ്മതപത്രം വാങ്ങുന്നയാൾ

മെഡിക്കൽ റിസർച്ച് പ്രോജക്ടിനാവശ്യമായ സമ്മതപത്രത്തിനു വേണ്ടുന്ന എല്ലാ ഘടകങ്ങളും തൃപ്തികരമായി നിർവഹിച്ചിരിക്കുന്നുവെന്ന് ഞാൻ ബോധ്യപ്പെടുത്തുന്നു. പഠനപങ്കാളിയുമായി ഗവേഷണപദ്ധതിയെപ്പറ്റി സാങ്കേതികേതര പദങ്ങളുപയോഗിച്ച് എല്ലാ വിവരങ്ങളെപ്പറ്റിയും ചർച്ച നടത്തുകയും പ്രതീക്ഷിക്കാവുന്ന അപകടസാധ്യതകളും പാർശ്വഫലങ്ങളും

വിശദീകരിക്കുകയും ചെയ്തു. പങ്കാളിയെ ചോദ്യങ്ങൾ ചോദിക്കാൻ പ്രേരിപ്പിക്കുകയും എല്ലാ ചോദ്യങ്ങൾക്കും ഉത്തരം നൽകുകയും ചെയ്തു എന്നും ഞാൻ സാക്ഷ്യപ്പെടുത്തുന്നു.

IV. PLAGIARISM REPORT

Document Information

Analyzed document	Dr Jaffer Thesis.docx (D173259027)
Submitted	2023-08-30 16:00:00
Submitted by	Dr P K Dash
Submitter email	dash@sctimst.ac.in
Similarity	0%
Analysis address	sadh.sctims@analysis.urkund.com

Sources included in the report

Entire Document

Synopsis Title: "Comparison between intravenous and inhalational anaesthetic induction agents on echocardiographic parameters of mitral stenosis patients undergoing mitral valve replacement surgery" Background: Mitral stenosis is the commonest presentation of rheumatic heart disease, but the prevalence of the disease has declined over years. Echocardiography plays a major role in the diagnosis as well as planning of treatment in MS patients. Most of the parameters used to grade the severity of valve stenosis are influenced by hemodynamic state of those patients. Significant fluctuations in hemodynamic is expected especially at the time of anaesthetic induction. The literature is scarce with respect to the influence of various anaesthetic agents on echocardiographic parameters. Hence, this study was conducted. Hypothesis: Anaesthetic induction with sevoflurane may reduce the pressure gradients with stable hemodynamic parameters when compared to propofol induction Methodology: Institutional Ethics Committee approval obtained. Total of 80 patients were assigned randomly to receive Induction of anaesthesia either with propofol (Group P, n=40) or sevoflurane (Group S, n=40). Patients of both genders aged 18- 70 years diagnosed with MS undergoing MVR were included. Standard trans thoracic echocardiography was performed at two time points- just before the induction and 3minutes after the induction of anaesthesia (just before tracheal intubation) and data stored for later analysis by the observer blinded for the type of intervention. Vital parameters recorded from multi parameter monitor at baseline, 1minute and 3minute after induction. Data was analyzed statistically using SPSS version 20.0. Results: 70% of the patients recruited in the study were female, reflecting the disease more prevalent among them. Half of the patients presented