Comparison of Integrated and External Arterial Filters in Patients Undergoing Pediatric Cardiac Surgery : A Prospective Randomized Controlled Trial (RCT)

Short running title: Prospective RCT Comparing Integrated and External Arterial Filters

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The corresponding author confirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Data Availability Statement:

The data that support the findings of this study are openly available in [Authorea] at DOI : ____________________________, reference number [reference number].

Informed Consent Statement:

This Prospective Randomized Controlled Trial (RCT) study was permitted by the Institutional Ethics Committee (IEC-2), H. M. Patel Centre for Medical Care and Education, Anand, Gujarat (Approval No. IEC/HMPCMCE/120/Faculty/20/125/20 dated 26/06/2020) and Clinical Trial Details (CTRI Number) CTRI/2020/09/028058 (Registered on 25/09/2020), the informed consent was signed and collected from the patient's parents

Abstract

Background and Aims

Innovative methodologies in cardiopulmonary bypass (CPB) configurations have been introduced, emphasizing the amalgamation of 'surface-coating', 'blood-filtration', and 'miniaturization' techniques. These advancements are aimed at addressing the critical issue of gaseous microemboli (GME) formation, predominantly originating from CPB circuit components, which are known to play a significant role in causing embolic organ damage and triggering systemic inflammatory responses. The introduction of arterial line filters stands as a testament to efforts made to curb the risk of embolisms, with their effectiveness in preventing such occurrences being well-documented.

The origin of neurological and neuropsychiatric complications following cardiac surgeries is often attributed to a myriad of factors including reduced cerebral blood flow during bypass procedures, and the presence of various embolic materials like calcium deposits, air, clots, and lipid particles, alongside the potential impact of anesthesia. Our research is directed towards evaluating the efficacy of an integrated arterial filtration system in mitigating systemic inflammation and improving neurological outcomes in pediatric patients undergoing surgery for congestive heart conditions.

Our study is meticulously designed to conduct a comparative analysis between the use of integrated and external arterial filters in pediatric cardiac surgeries. The focus will be on assessing changes in systemic inflammatory responses and neurological conditions before and after surgery. Additionally, an in-depth comparison of these results with neurocognitive and respiratory support indicators will be undertaken to

comprehensively understand the benefits of employing an integrated arterial filtration approach in such critical surgical procedures.

Methods

This is a prospective randomized controlled trial study on infants and pediatric patients who underwent cardiac surgery under cardiopulmonary bypass between July, 2020 to October, 2023. The study included 100 infant and pediatric patient's as per inclusion, exclusion criteria and randomization plan using winpepi software. In this study, we have divided the study population in two groups-

Group A, n = 50, 50 %, which consisted of Non-integrated arterial filter (NIn) [Membrane oxygenator – Capiox Baby RX 05, SORIN (Dideco D-901, Dideco D-902), Medtronic Affinity (Pixie), Capiox RX15, EUROSETS (Trilly) + External arterial filter – [EUROSETS Baby Sherlock, spictra arterial filter model]

Group B, n = 50, 50 % which comprised of integrated arterial filter (In) (Membrane oxygenator – Capiox Baby FX 05 [(In) oxygenator group])

The present study evaluated neurocognitive indices as per FOUR score test for both the groups which is the primary outcome variable. The secondary outcome variable viz. mechanical ventilation time in hours, cardiac surgical intensive care unit (CSICU) stay in hours, hospital stay in days were recorded in both the groups.

Results

The mean +/- standard deviation in group A for aortic cross-clamp time (ACC) and cardiopulmonary bypass (CPB) time were 88.0 ± 49.7 and 128 ± 66 respectively. The mean +/- standard deviation in group B for ACC ad CPB time were 70.2 ± 38.5 and 104 ± 48.1 respectively. P value derived was 0.04 and 0.03 for ACC and CPB variable respectively which is statistically significant. Post-operatively neurological function using FOUR score was similar for both groups viz. 16 out of 16. The mean ± standard deviation noted for mechanical ventilation in hours was 127 ± 267 (Group A) vs. 62 ± 80 (Group B) which was statistically insignificant (P value 0.103) The cardiac surgical intensive care unit (CSICU) stay observed is 201 ± 267 in Group A and 141 ± 116 for Group B which was statistically insignificant (P value 0.146). The hospital stay were 13 ± 11 (Group A) and 10 ± 5 days (Group B) respectively which was statistically insignificant (P value 0.138).

Conclusion

According to our analysis, integrated arterial filter oxygenator-capiox FX 05 may be a substitute for external arterial filter usage. Integrated arterial filter oxygenator capiox FX05 may reduce gaseous microemboli (GME) related neurological dysfunction along with hemodilution and systemic inflammatory response syndrome (SIRS).Capiox FX 05 could reduce CSICU and hospital stay and improve clinical outcomes of pediatric congenital heart disease(CHD) patients.

Key Words

- arterial filter,
- capiox,
- cardiac surgery,
- cardiopulmonary bypass,
- cognitive functions,
- gaseous microemboli,
- integrated arterial filter oxygenator
- membrane oxygenators,
- pediatric cardiac surgery,

1. Introduction

Cardiopulmonary bypass (CPB) technology has been closely linked to a range of post-surgical complications, driving the need for rigorous investigation into the origins of these issues and strategies for their mitigation. Recent findings suggest that circuits treated with specialized coatings can enhance patient recovery compared to conventional, non-coated systems.[1] These innovative coatings are designed to diminish the inflammatory response, reduce platelet activation and fibrinolysis, lessen the need for blood transfusions, and lower the incidence of postoperative brain dysfunction and heart damage.[2] A significant source of concern has been the production of gaseous microemboli within the CPB circuitry, which are known to contribute to embolic organ injuries and incite systemic inflammatory response syndrome.[3] To combat this, the use of arterial line filters has been advanced as a preventive measure, with their effectiveness in reducing embolic risks later validated.

Moreover, the adoption of smaller CPB devices has demonstrated potential in decreasing the volume of initial pump priming, curtailing inflammation, minimizing blood loss, and reducing the need for blood from donors, which are occasional repercussions of CPB operations.[4] CPB is recognized for triggering systemic inflammatory reactions that exacerbate postoperative morbidity and extend hospital stays.[5-7] The interplay between activated leukocytes and platelets, spurred by pro-inflammatory agents like complement, cytokines, thrombin, reactive oxygen species, and endotoxins, is central to these inflammatory processes.[5] In the context of CPB surgery, the artificial components of the bypass system and the membrane oxygenators emerge as critical factors in the activation of platelets and leukocytes.[6] Notably, the infiltration of activated neutrophils into the heart muscle contributes to the reperfusion injury observed following the restoration of blood flow to the aorta, with CPB surgery known to activate these inflammatory cells.[6,7]

This research introduces a refined CPB configuration that harmonizes 'surface-coating', 'blood-filtration', and 'device miniaturization' principles, notably through the combined use of arterial line filters and oxygenators. Despite the promising nature of these advancements, comparative studies between these novel systems and traditional CPB equipment remain scarce. The aim of this study was to compare integrated arterial filter oxygenator with membrane oxygenator along with external arterial filter in congenital heart disease (CHD) patients.

Objective of this study was to evaluate the impact of recent advanced integrated arterial filter oxygenator on post-operative neurological function with using of ‘FOUR’ score test and clinical outcomes in CHD.

2. Materials and Methods

2.1 Study Design

This prospective, single centre randomized controlled trial (RCT) study was approved by the Institutional Ethics Committee (IEC-2), H.M. Patel Centre for Medical Care and Education, Anand, Gujarat (Approval No. IEC/HMPCMCE/120/ Faculty/20/125/20 dated 26.06.2020). Informed consent was duly acquired from all participants involved in the study. A series of one hundred patients, sequentially admitted to the Pediatric Cardiac Surgery Department, Bhanubhai and Madhuben Patel Cardiac Centre, Bhaikaka University between July, 2020 to October, 2023, were prospectively included in the study. Block randomization method was used to divided patients in to two groups. In this study, Group A, n = 50 patients, comprising of 50 % of sample used Non-integrated arterial filter (NIn) (membrane oxygenator-Capiox Baby RX 05 + External arterial filter - Eurosets Baby Sherlock) Group B employed Integrated arterial filter (In) (membrane oxygenator Capiox Baby FX 05).

Individuals who declined participation in the research, those necessitating urgent surgical intervention, or individuals requiring further surgeries due to complications, single-ventricle physiology, redo-surgeries, were excluded from the study. The inclusion criteria consisted of patients upto less than 18 yrs. (≤18 yrs.) and weighing upto or less than 10 kgs. (≤10 kgs.) and having diagnosed to have congenital heart disease (CHD) and grown-up congenital heart disease (GUCH).

Table 1 - Master Chart of the patients participating in the study.

Group	Sr. No.	Sex	Age (months)	Height (cm)	Weight (kgs)	BSA (M^2)	Procedure	Oxygenator	FOUR Score	Ventilation Time (hrs)	CSICU Stay (hrs.)	Hospital stay (days)	ACC (min.)	CPB (min.)
A	1	Female	4	61	4.6	0.28	TAPVC Repair	RX 05	16	24	72	9	68	101
A	2	Female	36	88	9.5	0.48	ASD Closure	RX 05	16	27	72	8	47	72
B	3	Male	24	81	9.4	0.46	ICR	FX 05	16	98	144	12	112	163
B	4	Male	12	73	5.8	0.34	VSD Closure	FX 05	16	11	48	6	50	89
A	5	Male	0.5	45	2.2	0.16	TAPVC Repair	RX 05	16	768	816	35	54	100
B	6	Male	8	57	4.4	0.26	Truncus Repair	FX 05	16	48	72	3	35	52
A	7	Male	4	62	4.3	0.27	TAPVC Repair	RX 05	16	25	48	8	36	68
B	8	Female	11	70	6.25	0.34	VSD Closure	FX 05	16	7	48	5	73	112
A	9	Female	8	62	4.8	0.28	VSD Closure	RX 05	16	1560	1590	67	49	78
A	10	Female	36	91	9.4	0.48	ASD Closure	RX 05	16	9	48	5	38	70
A	11	Female	36	100	13.1	0.60	VSD Closure	RX 05	16	7	48	5	153	215
B	12	Male	5	66	5.15	0.30	VSD Closure	FX 05	16	26	72	7	110	159
A	13	Male	72	122	19	0.8	ASD Closure	D-902	16	7	48	6	48	65
A	14	Male	9	68	6.0	0.33	VSD Closure	RX 05	16	25	48	9	144	203
B	15	Male	6	64	4.27	0.27	VSD Closure	FX 05	16	25	72	8	48	67
A	16	Male	5	66	5.2	0.31	VSD Closure	RX 05	16	51	96	8	135	196
A	17	Male	3	57	3.3	0.23	TAPVC Repair	RX 05	16	873	1008	47	77	107
A	18	Female	48	93	14	0.6	ASD Closure + PA Plasty	D-902	16	51	144	18	106	184
B	19	Female	12	73	7.6	0.39	ASD Closure	FX 05	16	9	48	6	42	60
B	20	Male	36	75	7.1	0.38	ICR	FX 05	16	26	72	10	57	92
B	21	Male	3	62	3.5	0.25	VSD Closure	FX 05	16	337	480	27	53	80
B	22	Female	12	79	8.8	0.43	VSD Closure	FX 05	16	25	48	7	41	61
A	23	Male	96	123	17	0.76	ICR	RX 15	16	72	240	16	111	153
B	24	Male	6	57	3.4	0.23	VSD Closure	FX 05	16	72	96	6	45	80
B	25	Female	24	77	8.1	0.41	ASD Closure	FX 05	16	7	48	6	88	128
A	26	Male	7	66	5.5	0.31	VSD Closure	RX 05	16	26	96	11	66	118
B	27	Female	9	68	6.79	0.36	VSD Closure	FX 05	16	12	48	8	41	58
B	28	Female	4	58	4.5	0.26	VSD Closure	FX 05	16	76	144	12	36	54
B	29	Male	5	69	5.9	0.34	ASD Closure + VSD Closure	FX 05	16	26	72	8	56	84

A	30	Female	12	72	8.0	0.40	ASD Closure	RX 05	16	7	48	5	52	104
B	31	Male	5	64	5.2	0.3	VSD Closure + ASD Closure	FX 05	16	27	144	11	42	65
A	32	Female	48	96	10.5	0.53	ASD Closure + Pulmonary Valvotomy	PIXIE	16	8	96	9	87	116
B	33	Female	12	83	8.23	0.44	Coarctation repair + Mitral Valve Repair	FX 05	16	26	96	9	42	64
A	34	Male	144	135	26	0.99	VSD Closure + RVOT Repair	RX 15	16	8	96	7	51	77
B	35	Female	12	78	6.5	0.37	MV Repair	FX 05	16	27	72	9	51	81
A	36	Female	7	63	5.2	0.3	VSD Closure	RX 05	16	25	120	6	43	75
B	37	Male	7	61	3.7	0.35	VSD Closure	FX 05	16	25	120	6	32	65
B	38	Male	9	62	7	0.35	VSD Closure + ASD Closure	FX 05	16	8	72	6	63	87
B	39	Male	36	90	12	0.55	ASD Repair	FX 05	16	10	120	8	79	103
B	40	Male	4	60	4.22	0.27	VSD Closure	FX 05	16	192	264	16	54	94
B	41	Male	12	67	6.9	0.36	VSD Closure + ASD Closure	FX 05	16	24	96	8	60	90
A	42	Male	7	59	3.2	0.23	VSD Closure + Mitral Valve Repair	RX 05	16	361	456	20	82	125
A	43	Male	132	132	22.3	0.9	Aortic Valve Repair + Mitral Valve Repair	RX-15	16	27	168	09	247	368
A	44	Male	108	124	25.5	0.94	Aortic Valve Repair + Mitral Valve Repair	RX-15	16	29	170	10	207	272
B	45	Male	12	74	7.3	0.39	VSD Closure + ASD Closure	FX 05	16	24	120	10	64	95
A	46	Male	12?	84	12	0.53	VSD Closure	D-902	16	8	72	6	70	99
B	47	Female	24	86.5	9.06	0.46	VSD Closure	FX 05	16	50	96	10	52	87
B	48	Male	36	88.5	11.4	0.53	ASD Closure + PAPVC Re-routing	FX 05	16	12	72	8	67	117
B	49	Male	10	74	6.8	0.37	ASD Closure + PDA Closure	FX 05	16	24	120	9	88	135
B	50	Male	21	80	8.5	0.43	ICR	FX 05	16	122	264	14	152	196
B	51	Female	36	77	7.5	0.4	VSD Closure	FX 05	16	25	144	9	47	81
A	52	Female	11	69	6.63	0.36	VSD Closure	RX 05	16	7	96	6	45	67
A	53	Male	60	114	15	0.69	ASD Closure + PAPVC Re-routing	D-902	16	8	72	8	54	84
A	54	Female	12	69	6.5	0.35	ICR	RX 05	16	143	240	13	131	174
A	55	Male	11	61	4.88	0.29	Cor-triatriatum Repair	RX 05	16	49	168	11	76	117

B	56	Male	12	68	5.5	0.32	VSD Closure + ASD Closure	FX 05	16	145	240	12	82	136
B	57	Female	9	59	5	0.29	Truncus Repair	FX 05	16	335	408	20	185	242
B	58	Female	24	78	7.13	0.39	ASD Closure	FX 05	16	7	72	5	38	63
A	59	Male	12	70	7.5	0.38	ICR	RX 05	16	169	264	13	163	208
A	60	Male	9	65	8	0.38	Rt. PA plasty + PAPVC Re-routing + ASD Closure	RX 05	16	26	96	7	109	155
B	61	Male	12	80	8.35	0.43	ASD Closure	FX 05	16	6	72	6	38	67
A	62	Female	36	88	10.5	0.51	ICR+ PAPVC Re-routing	D-902	16	25	120	10	136	187
B	63	Male	24	86	9.86	0.49	VSD Closure	FX 05	16	19	96	8	59	86
B	64	Male	10	69	6.4	0.35	VSD Closure	FX 05	16	11	120	9	51	81
A	65	Male	120	133	25	0.96	Aortic Valve Repair	D-902	16	26	72	05	96	132
B	66	Male	12	83	8.93	0.45	Cor-triatriatum Membrane Excision	FX 05	16	96	6	11	48	71
B	67	Male	11	75	6	0.35	ICR	FX 05	16	50	5	8	69	99
A	68	Male	108	123	15	0.72	MVR	D-902	16	26	144	21	144	203
B	69	Male	24	77	11.4	0.49	VSD Closure	FX05	16	25	120	22	66	109
A	70	Male	84	108	15.1	0.86	VSD Closure	D-902	16	8	72	5	43	63
B	71	Female	4	68	5.3	0.32	ASD Closure + VSD Closure	FX-05	16	27	120	8	61	109
B	72	Male	24	85	8.4	0.45	VSD Closure	FX-05	16	50	120	11	64	88
A	73	Male	72	107	15	0.67	ICR	D-902	16	193	288	15	164	205
A	74	Female	108	120	19.9	0.81	ASD Closure + Pulmonary Valvotomy	D-902	16	12	120	09	87	117
A	75	Female	10	70	7.6	0.38	ICR	D-902	16	139	312	17	139	183
A	76	Male	8	69	5.2	0.32	VSD Closure	D-902	16	110	185	08	47	73
A	77	Male	48	91	11.4	0.54	ASD Closure	D-902	16	06	48	07	45	64
A	78	Female	6	66	5	0.3	VSD Closure	TRILLY	16	119	216	09	48	86
B	79	Male	12	57	7.2	0.34	VSD Closure	FX-05	16	120	192	12	39	67
A	80	Female	108	122	17	0.76	ASD Closure	D-902	16	06	48	6	39	57
B	81	Female	96	111	14.4	0.66	ICR	FX-05	16	26	96	7	103	148
B	82	Male	6	67	6	0.33	VSD Closure + Pulmonary Valvotomy	FX-05	16	07	240	11	123	154
A	83	Male	192	158	35	1.24	ICR	TRILLY	16	72	144	10	127	173
B	84	Female	48	84	10.4	0.49	ICR	FX-05	16	26	264	14	143	189

A	85	Female	36	82	8.2	0.43	ICR	D-902	16	143	240	14	119	169
A	86	Female	8	60.5	3.7	0.25	AVCD Repair	D-901	16	119	216	21	141	235
B	87	Female	4	58	3.28	0.23	VSD Closure	FX-05	16	235	600	28	56	92
A	88	Female	60	104	14.5	0.62	ASD Closure	D-902	16	7	72	8	32	47
B	89	Male	72	103	13.2	0.61	ASD Closure	FX-05	16	25	168	15	69	91
A	90	Male	24	79	7.4	0.4	VSD Closure	D-902	16	185	115	20	45	60
A	91	Male	6	67	5.6	0.32	VSD Closure	D-902	16	289	120	22	52	86
B	92	Male	72	103	13.2	0.61	ASD Closure	FX-05	16	06	48	06	35	55
A	93	Female	24	81	8.8	0.44	VSD Closure	D-902	16	26	168	12	43	63
B	94	Male	48	97.5	11	0.54	ICR	FX-05	16	139	240	16	186	254
A	95	Female	12	70	6.6	0.36	ASD Closure	D-902	16	06	48	07	55	77
A	96	Female	36	86	9.8	0.48	ASD Closure	TRILLY	16	66	192	09	45	78
A	97	Female	6	60	4.1	0.26	VSD Closure	D-902	16	164	264	15	68	97
A	98	Male	84	114	16	0.71	ICR	D-902	16	216	336	18	138	187
B	99	Male	36	89	9.5	0.48	ICR	FX-05	16	195	298	17	161	212
B	100	Male	7	68	5.8	0.33	VSD Closure	FX-05	16	192	216	11	53	88

Key: TAPVC-Total anomalous pulmonary venous connection, ASD-Atrial septal defect, VSD-Ventricular septal defect, PA-Pulmonary artery, ICR-Intra-cardiac repair, MV-Mitral valve, RVOT-Right ventricular outflow tract, PAPVC-Partial anomalous pulmonary venous connection, AP-Aorto-pulmonary, AVCD-Atrio-ventricular canal defect.

2.2 Anesthesia and Surgical Procedure

Anesthesia was induced with 1-2 µg/kg. fentanyl, 0.5 mg./kg. ketamine, 0.02-0.03 mg./kg. midazolam and 0.08-0.1 mg./kg. vecuronium bromide. After tracheal intubation, right atrium catheterization was performed for monitoring central venous pressure (CVP). Anesthesia was maintained with sevoflurane and maintenance doses of fentanyl, midazolam, and vecuronium.

All operations were performed through a standard median sternotomy incision. During surgery, monitoring of CVP, invasive radial and femoral arterial pressure and transesophageal echocardiography (TEE) on completion of procedure. The surgical technique employed for various different surgical procedures were standardized and surgeon, surgical team remain unchanged.

2.3 Cardiopulmonary bypass protocol

All procedures were performed using a HL-20 roller pump (Maquet Jostra, Germany) in both groups. Polyvinyl chloride (PVC) tube was the same for both groups.

In Group A (NIn) hollow- fibre membrane oxygenator Capiox Baby RX 05 (Terumo Corporation, Tokyo, Japan), Dideco D-901, Dideco D-902, Pixie, Trilly, Capiox RX15 and external arterial filter Baby Sherlock (Euroset), Spictra BT were used. Whereas Group B (In) Capiox Baby FX 05 hollow-fibre membrane oxygenator along with inbuilt integrated arterial filter (Terumo Corporation, Tokyo, Japan) was used.

In both the groups, the prime volume was ≤ 600 ml. of crystalloid solution containing 200 ml. plasmalyte A, 10 ml. sodium bicarbonate and remaining volume was fresh frozen plasma (FFP) and packed cell volume (PCV) according to calculation of circulating oncotic pressure > 15 mm.Hg and ≥ 28 % circulating hematocrit respectively during CPB.

In CPB circuit, Euroset blood cardioplegia device was used for cold cardioplegia delivery and Maxlife D 0.30 hollow-fibre hemo concentrator was used in all the patients.

During CPB surgery, additional dose of heparin were administered in case of need to keep activated clotting time above 480 secs. Arterial flow was maintained with an aortic cannula implanted inside ascending aorta, while for venous return, bicaval cannulation with metal angled cannula was used. A cannula was implanted in ascending aorta for cardioplegia and vent, and then the operation was proceeded with CPB. Moderate degrees of systemic hypothermia (26^0 C -30^0 C) were used intra-operatively.

Following aortic cross-clamping of ascending aorta, a blood cardioplegia of Del Nido [either authentic Del Nido (1:4), or modified Del Nido (4:1)] was given at a dose of 30 ml./kg along with maintenance dose given at dose of 10 ml/kg. at every 60 minutes with temperature of 4-6^0 C. Cardioplegia techniques employed with either calafiore method or by syringe (manually) through antegrade route to achieve cardiac arrest.

Extra-corporeal circulation with continuous flows of 2.4 - 3.0 L/min/m^2 of body surface area was maintained. Mean arterial pressure was monitored continuously and maintained between 40-70 mm. Hg. during CPB. To keep maintaining target mean perfusion pressure during CPB, phenylephrine at mild dose was sometimes considered. After de-clamping, re-warming was done to a nasal temperature of 35.5° C before weaning from CPB. The myocardium was supported to one-third of the aortic cross-clamp time before coming off CPB. At the end of CPB, protamine was administered as required to return the activated clotting test (ACT) to the baseline values.

2.4 Data collection.

Patient's post-operative neurocognitive status was evaluated by using FOUR score which included eye response, motor response, brainstem reflexes, and respiration pattern for patients in both groups. This tests was conducted in both groups after 12 hours of extubation, total ventilation in hours, total CSICU stay in hours and hospital stay in days were mentioned and compared between both the groups by statistician. The primary outcome variable was neurocognitive indices as per FOUR score test. The secondary outcome variable was ventilation hours, CSICU stays and hospital stays.

2.5 Statistical Analysis

All the patients' data were entered into Microsoft Excel, and the analysis while it was carried out by STATA 14.2, randomization plan using WINPEPI (PEPI-for-Windows) software.

Descriptive statistics (Mean ± SD] were used to depict baseline characteristics and clinical profile of the study participants. The demographic characteristics of all patients as well as primary outcome variable, patient's post-operative neurocognitive status which was evaluated by using FOUR score and secondary outcome variable like total ventilation time, CSICU stay and hospital stay were compared using independent sample t-test by institutional statistician statistical significance was considered for $p < 0.05$.

3. Results

This study was conducted over a thirty-nine months period with the principal aim of evaluation of neurological dysfunction by using FOUR score test method with using integrated arterial filter oxygenator.

I Demographic variables observations

The study subjects consisted of 100 CHD patients of whom 61 were males and 39 were females. For more detailed break-up, in group A males were 27 (54 %) and females were 23 (46 %), where in group B males were 34 (68 %) and females were 16 (32 %).

Age of the subjects were 42.9 ± 45.7 and 19.6 ± 19.4 (Mean ± Standard Deviation) in group A and group B respectively which was statistically significant (p value 0.001). The age and gender is shown in Table 2 and Figure 1,2.

Table 2 Comparison of Demographic variables between two groups

Variables	Mean ± Standard Deviation OR Number (Percentage)		P Value
	Group: A NIn	Group: B In	
Age(months)	42.9 ± 45.7	19.6 ± 19.4	0.001
Male	27 (54%)	34 (68%)	0.151
Female	23 (46%)	16 (32%)	

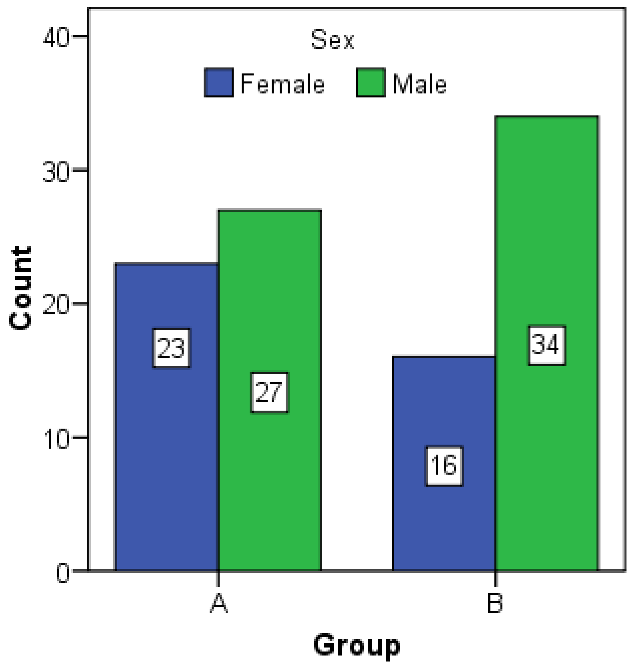

Figure 1 Shows the sex of both the groups and according to statistical analysis p value of this variable is 0.151 which is statistically insignificant.

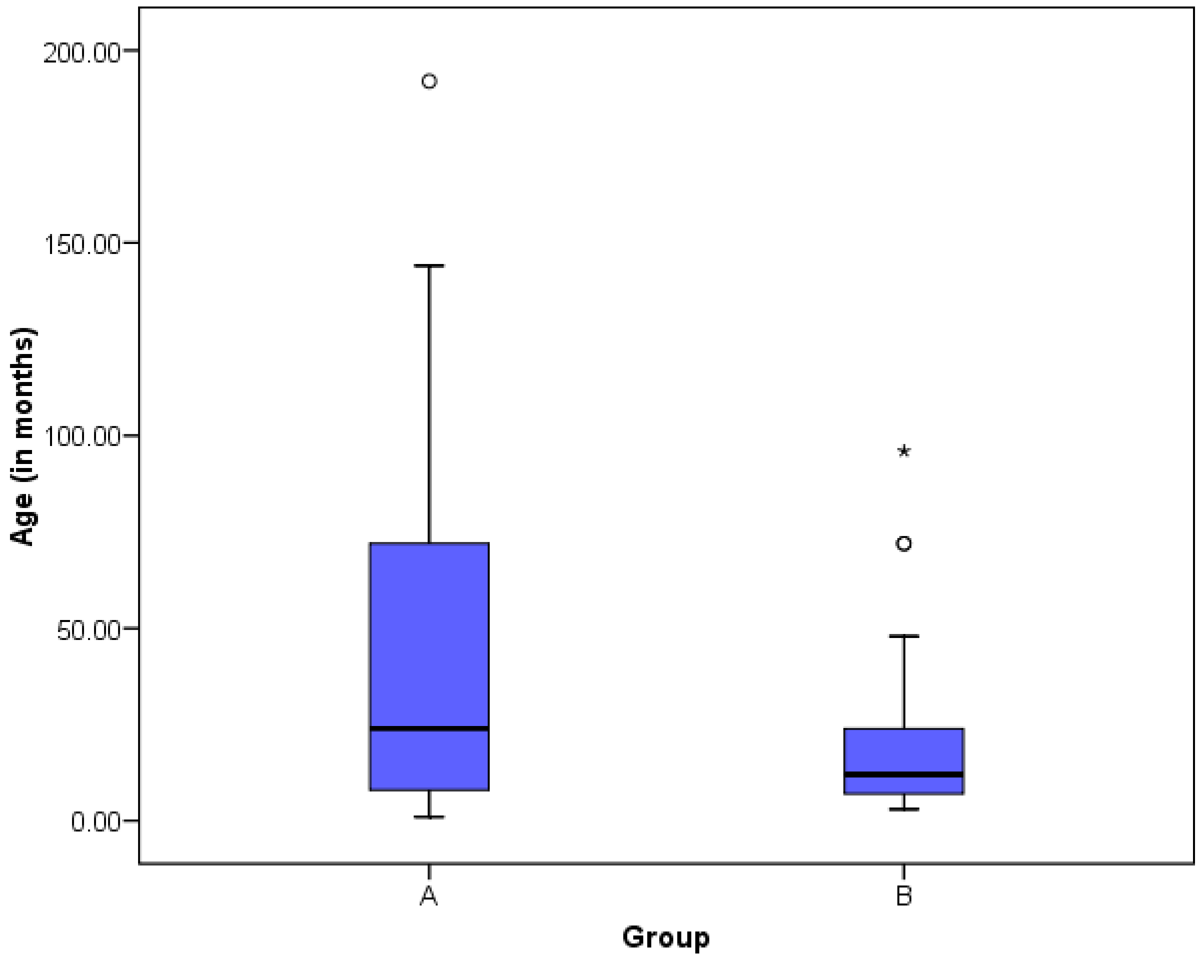

Figure 2 Shows the age of both the groups and according to statistical analysis p value of this variable is 0.001which is statistically significant.

Body surface area was calculated by the using of Mosteller formula with using of height and weight parameters. In group A height and weight were 87.5 ± 26.6 and 10.9 ± 7.1(Mean ± Standard Deviation). In group B height and weight were 74.7 ± 12.7 and 7.4 ± 2.6(Mean ± Standard Deviation). P value were 0.003 and 0.001in height and weight respectively, which were statistically significant.

In both groups, BSA were 0.51 ± 0.24 and 0.39 ± 0.10 in group A and group B respectively. P value was 0.002, which was statistically significant. (Table 3), (Figure 3,4,5)

Table 3 Comparison of height, weight and body surface area between the two groups

Variables	Number (Percentage) OR Mean ± Standard Deviation		P Value
	Group: A NIn	Group: B In	
Height(cm)	87.5 ± 26.6	74.7± 12.7	0.003
Weight(kg)	10.9 ± 7.1	7.4 ± 2.6	0.001
Body Surface Area(m^2)	0.51 ± 0.24	0.39 ± 0.10	0.002

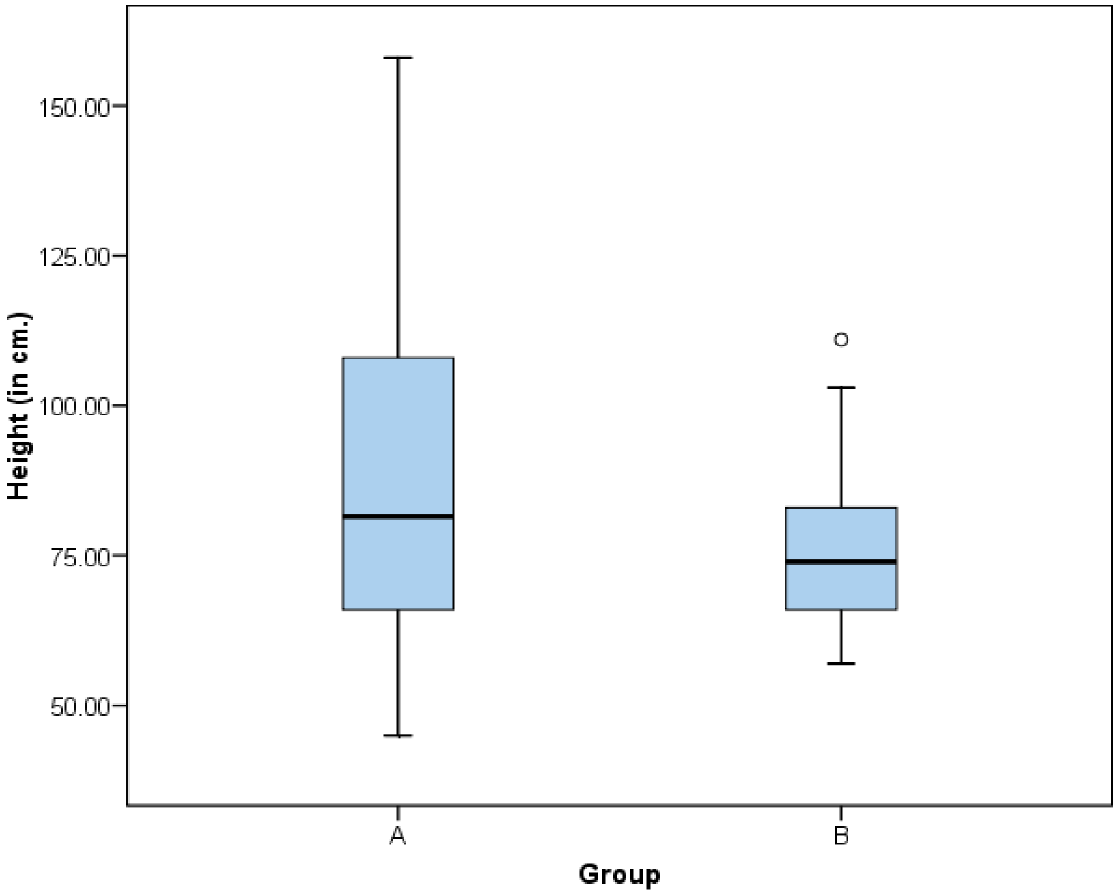

Figure 3 Shows the Height of both the groups and according to statistical analysis p value of this variable is 0.003 which is statistically significant.

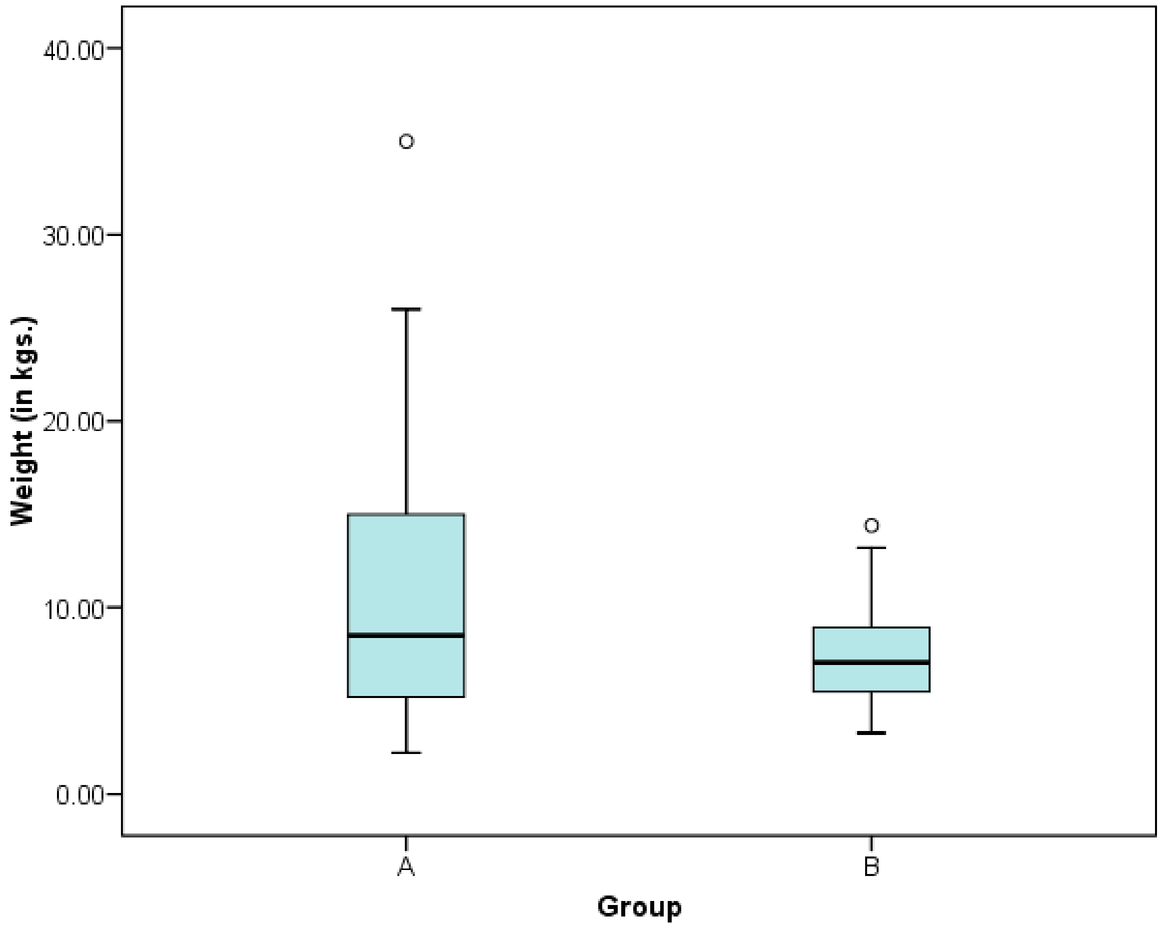

Figure 4 Shows the weight of both the groups and according to statistical analysis p value of this variable is 0.001 which is statistically significant.

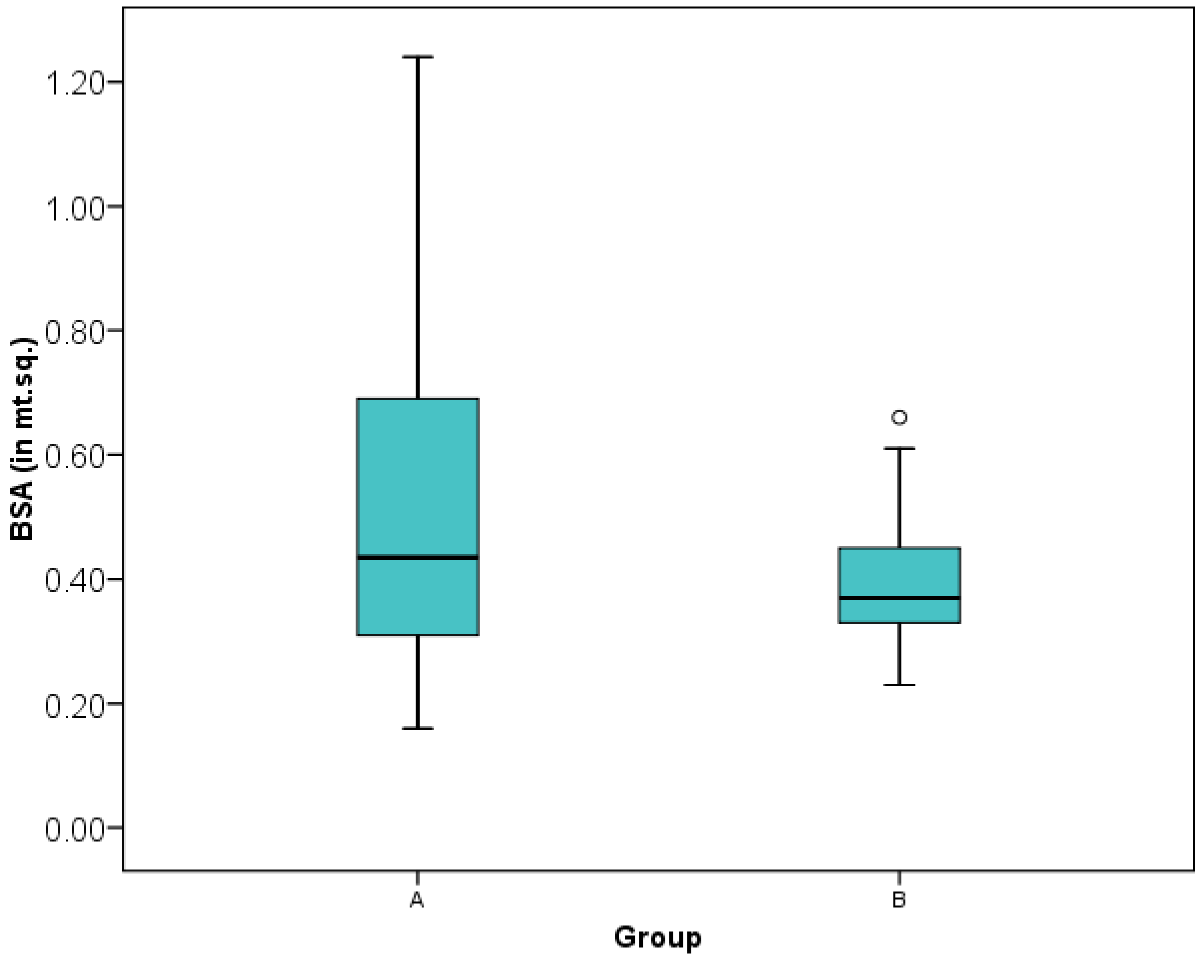

Figure 5 Shows the BSA of both the groups and according to statistical analysis p value of this variable is 0.002 which is statistically significant.

In group A Aortic cross clamp time and CPB time were 88.0 ± 49.6 and 128.3 ± 66.8 (Mean ± Standard Deviation). In group B Aortic cross clamp time and CPB time were 70.2 ± 38.5 and 104 ± 48.1(Mean ± Standard Deviation). P value were 0.047 and 0.039 in Aortic cross clamp time and CPB time respectively which were statistically significant. (Table 4), (Figure 6,7)

Table 4 Comparison of CPB variables between the two groups

Variables	Number (Percentage) OR Mean ± Standard Deviation		P Value
	Group: A NIn	Group: B In	
Aortic cross clamp time (minutes)	88.0 ± 49.6	70.2 ± 38.5	0.047
CPB time (minutes)	128.3 ± 66.8	104 ± 48.1	0.039

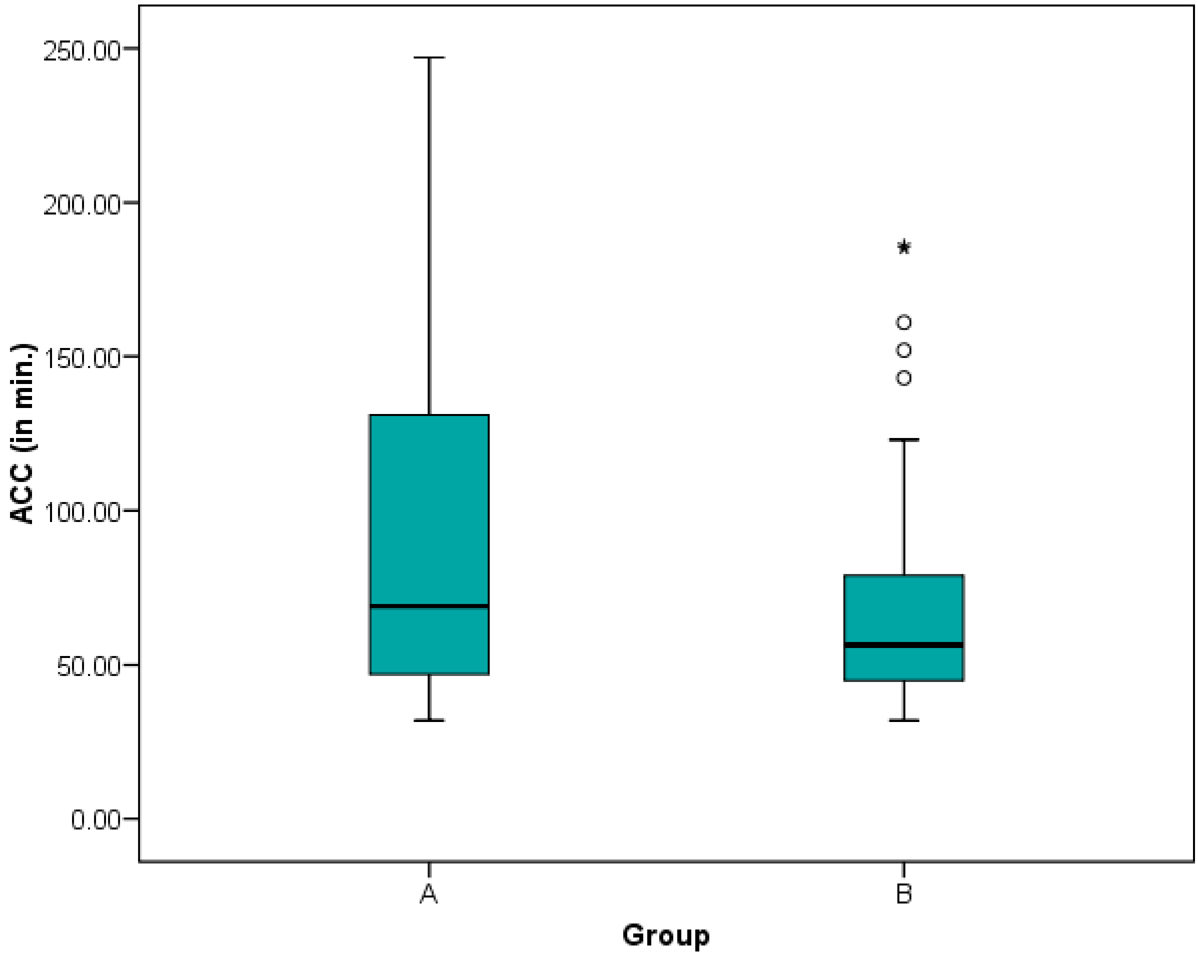

Figure 6 Shows the Aortic cross clamp time of both the groups and according to statistical analysis p value of this variable is 0.047 which is statistically significant.

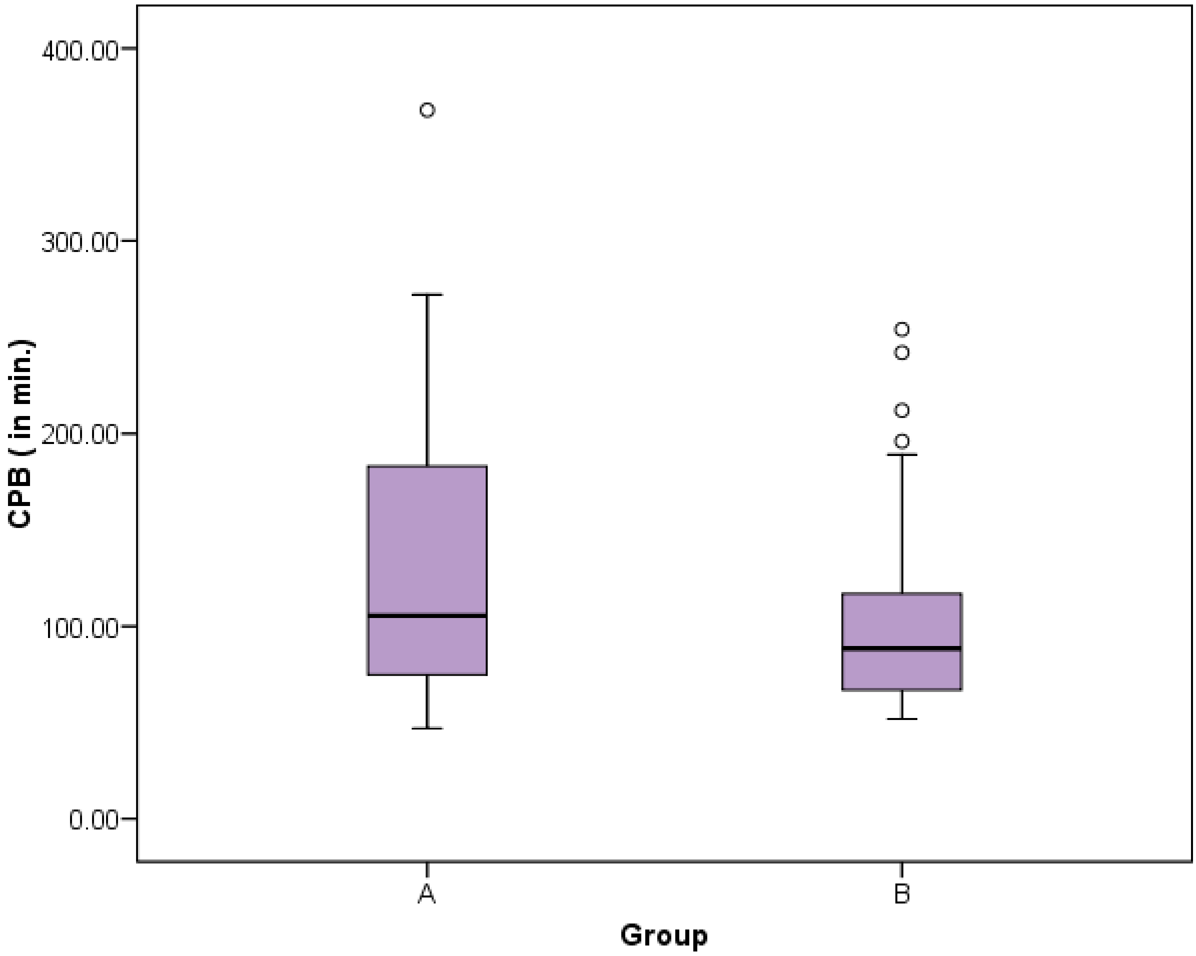

Figure 7 Shows the CPB time of both the groups and according to statistical analysis p value of this variable is 0.039 which is statistically significant.

II Primary variables observations

According to aim of this study, we evaluated post-operative neurological function with using FOUR score and both groups were showing similar FOUR score of 16 out of 16. FOUR score values was observed by pediatric cardiac surgeon. Due to similar value of all subject, statistical analysis were not possible. (Figure 8)

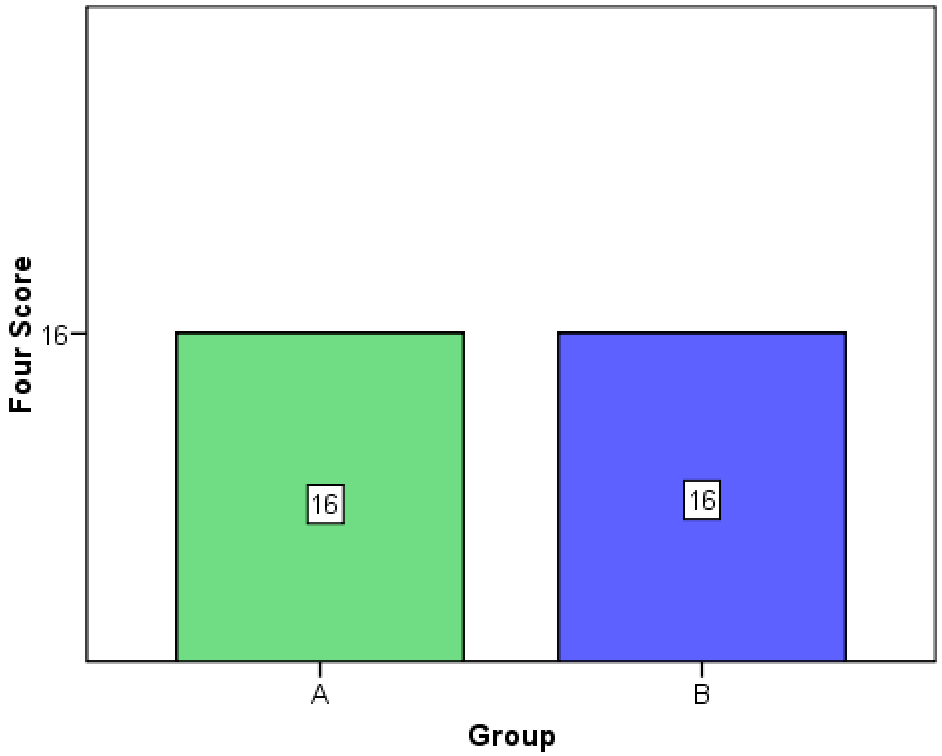

Figure 8 Shows Four score of both the groups, as the four score values for both the groups is same evaluation of P value is not possible.

III Secondary variables observations

Neurological dysfunction was also dependent of following secondary variables and this study outcomes might be affected by following parameters. We were evaluating mechanical ventilation time in hours which were 127.2 ± 267.1 (Mean ± Standard Deviation) vs 62.4 ± 80.8 in group A vs group B along with statistical insignificant P value which was 0.103.

ICU stay was observed 201.5± 267.8 in group A and group B was observed 141.1 ± 116.5 hours, which were statistically insignificant. P value was 0.146.

Group A and group B were showed 13 ± 11 and 10 ± 5 days hospital stay respectively. P value was 0.138. (Table 5), (Figure 9,10,11,12)

Secondary data are presented in **Table 5.** Both the groups were comparable with respect to Mechanical ventilation time, CSICU stay, and Hospital stay.

Table 5 Comparison of secondary variables between two groups

Variables	Number (Percentage) OR Mean ± Standard Deviation		P Value
	Group: A NIn	Group: B In	
Mechanical Ventilation Time (hours)	127.2 ± 267.1	62.4 ± 80.8	0.103
CSICU stay(hours)	201.5 ± 267.8	141.1 ± 116.5	0.146
Hospital stay(days)	13 ± 11	10 ± 5	0.138

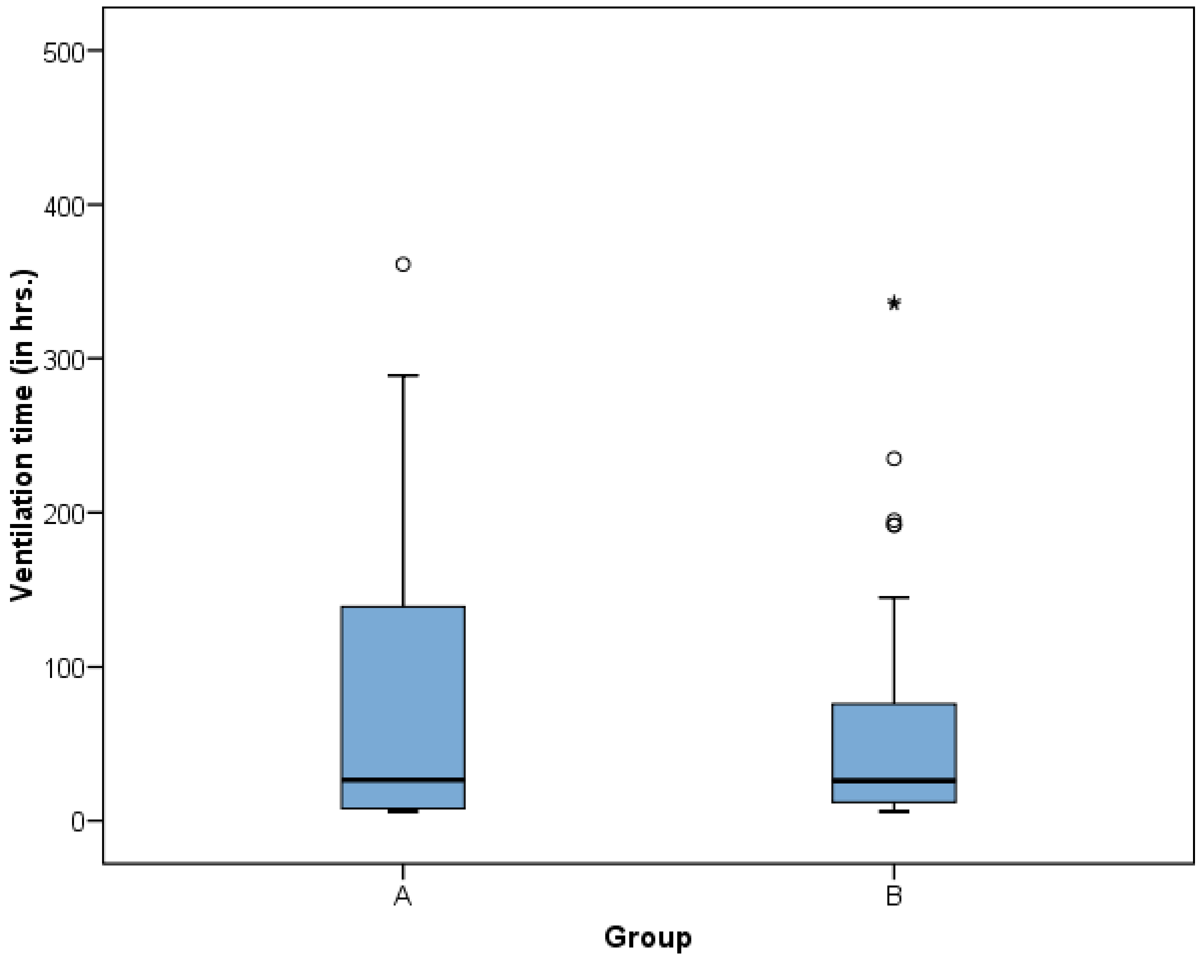

Figure 9 Shows the ventilation time of both the groups and according to statistical analysis p value of this variable is 0.103 which is statistically insignificant.

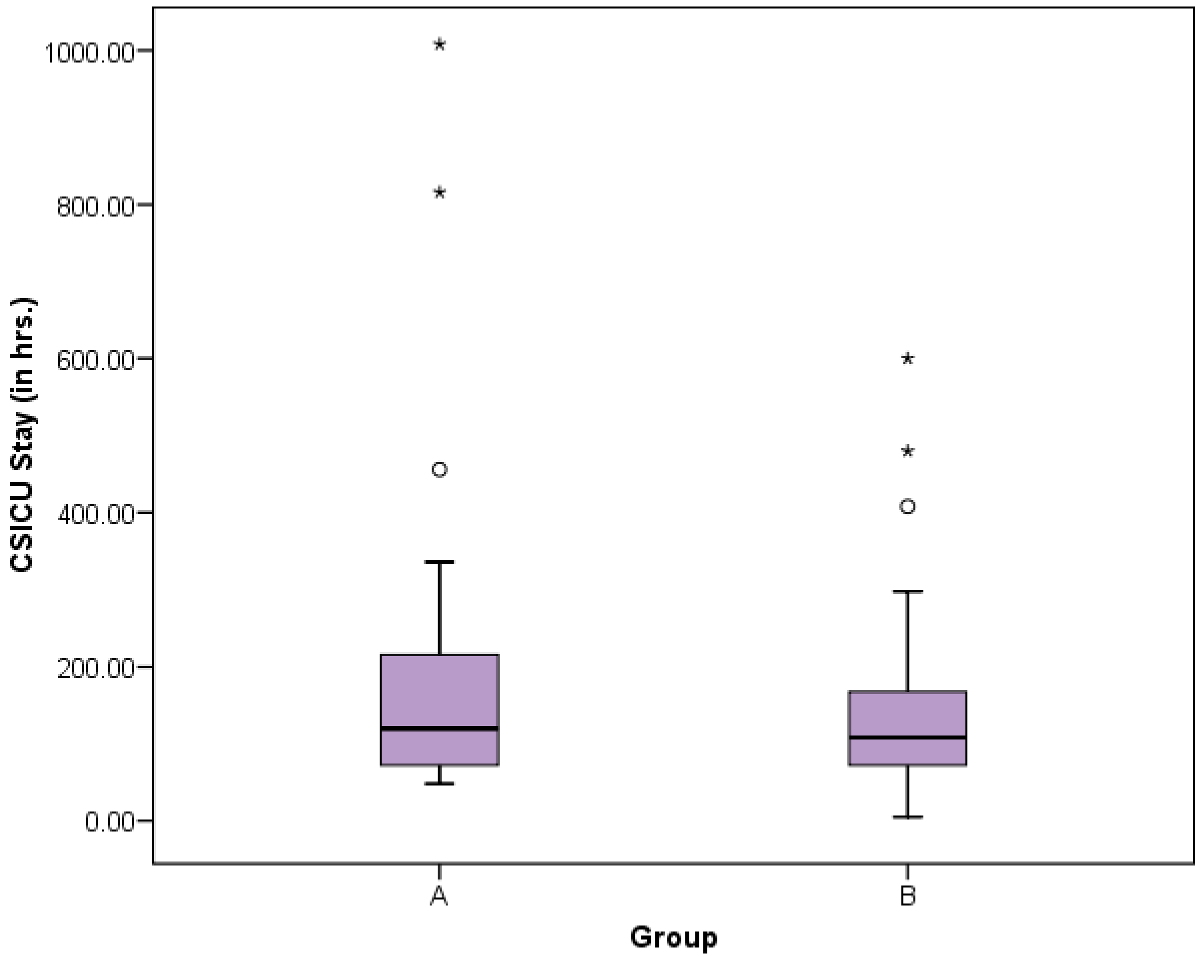

Figure 10 Shows the **CSI**CU stay of both the group**s** and according to statistical analysis p value of this variable is 0.146 which is statistically insignificant.

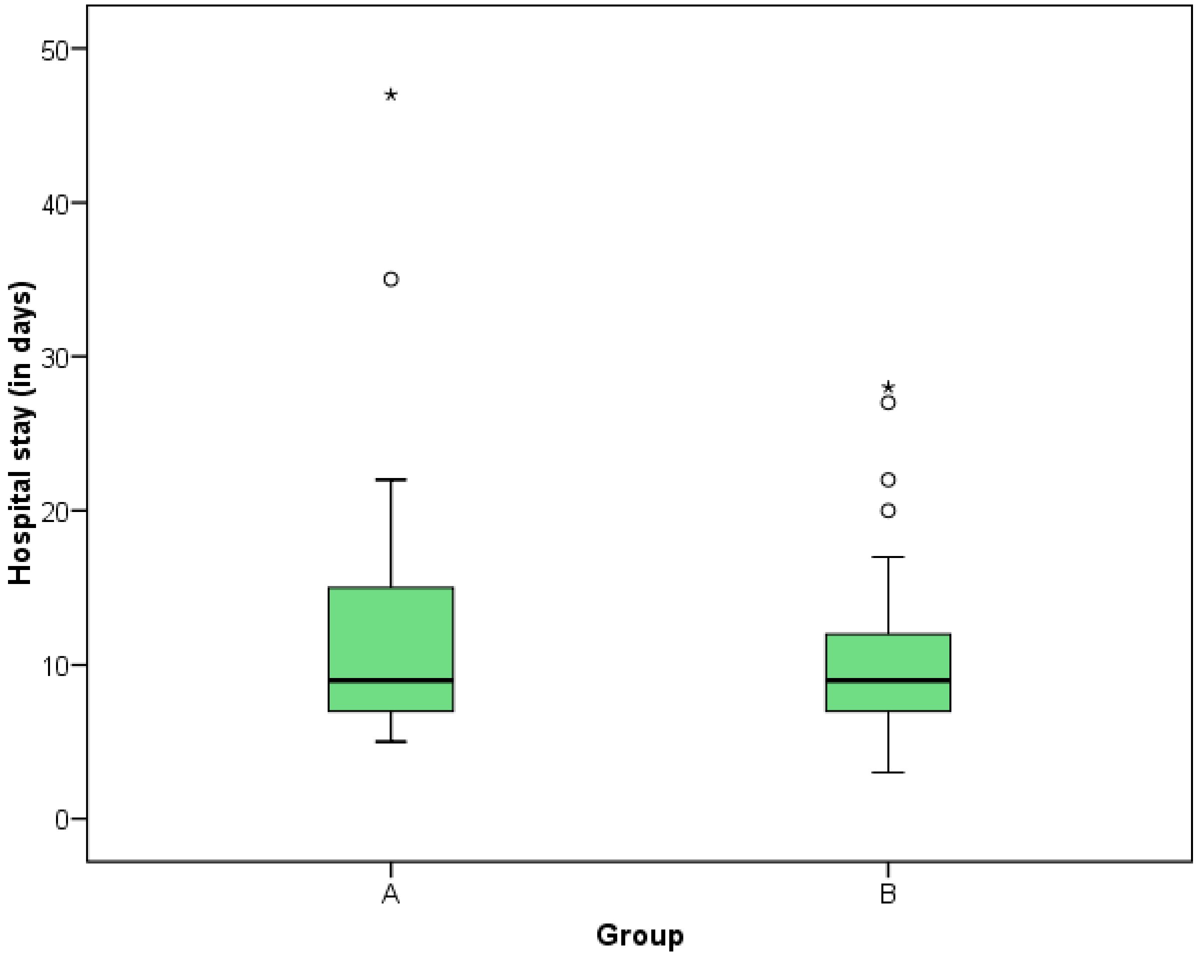

Figure 11 Shows the hospital stay of both the groups and according to statistical analysis p value of this variable is 0.138 which is statistically insignificant.

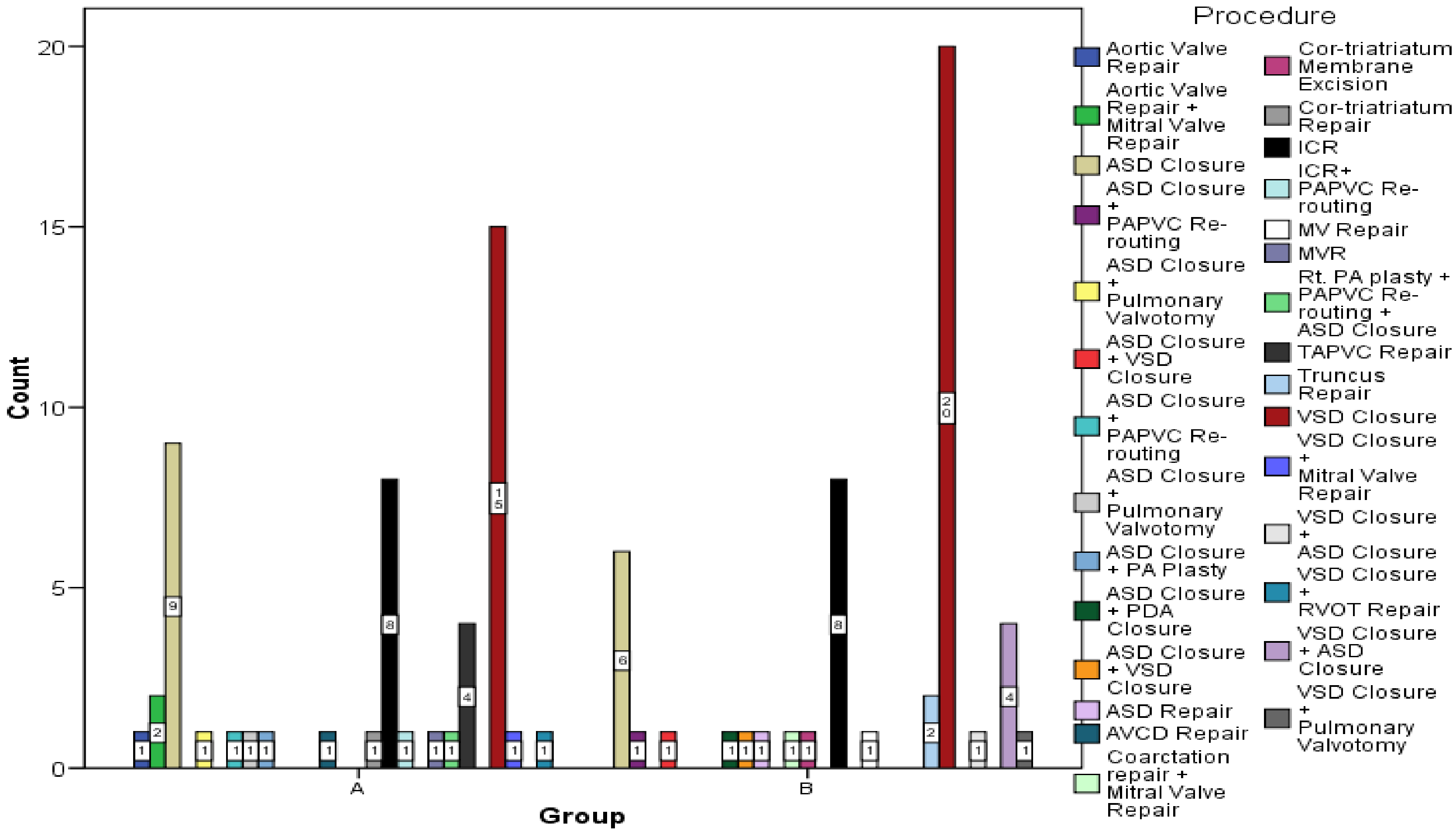

Figure 12 Number of patients and various procedures allocated in both the groups.

4. Discussion

During cardiopulmonary bypass (CPB) procedures, both solid and gaseous microemboli (GME) present significant challenges by potentially transitioning from venous to systemic circulation, potentially leading to embolic complications. To mitigate this risk, arterial line filters (ALFs) have been widely adopted, earning a Class 1, Level A endorsement according to European guidelines, underscoring their critical role in enhancing post-operative safety.[8]

Historically, the efficacy of ALFs in cardiac surgeries was illuminated by Åberg et al. in 1974, highlighting their pivotal role in reducing postoperative cognitive impairments among patients. This seminal study revealed that patients with ALF integration exhibited normal cognitive functions within two months post-surgery, a stark contrast to the minimal improvement seen in the non-ALF group, marking a significant milestone in CPB practice.[9]

In the United States, the incorporation of ALFs alongside CPB has been standardized, reflecting a commitment to surgical safety.[10,11] A comprehensive review from 2006 placed ALFs at the pinnacle of evidence-based practice, although it's important to note that these conclusions were drawn from studies conducted in the 1980s, a time when bubble oxygenation was prevalent.[12] The subsequent research by Pugsley et al. in 1994 further substantiated the benefits of ALFs in significantly reducing cerebral microemboli and associated neuropsychological deficits.[12] However, the evolution of CPB technology, including the advent of membrane oxygenators and circuit miniaturization, calls for updated clinical trials to reassess the necessity and efficacy of ALFs within modern CPB protocols.

In Europe, Johagen and Svenmarker's survey revealed a widespread adoption of ALFs, primarily to thwart arterial embolization, indicating a global consensus on their utility as a preventative tool against GME.[13] The introduction of integrated arterial filters with oxygenators has spurred a new wave of research, examining their impact on CPB outcomes. Sathianathan et al.'s in-vitro evaluation of neonatal CPB circuits highlighted the benefits of circuit miniaturization in reducing hemodilution and inflammatory responses, despite the potential for GME to cause undetected long-term neurological damage during complex cardiac surgeries.[14] Salavitabar et al. praised the hemodynamic superiority of the QUADROX-i Neonatal Oxygenator with an integrated arterial filter, especially in its ability to maintain low-pressure drops and high GME capture rates at reduced flow rates.[15]

Comparative studies, such as the one conducted by Gursu et al., have begun to explore the distinctions between integrated and non-integrated arterial filter oxygenators, noting the advantages of integrated systems in reducing prime volume requirements, maintaining intraoperative hematocrit levels, and potentially lowering postoperative transfusion needs and inflammatory markers.[16] Myers et al. affirmed the reliability and efficiency of oxygenators with integrated arterial filters, eliminating complications associated with external filters.[17] Furthermore, Ghazwan et al.'s comparison of integrated and non-integrated oxygenator-filter combinations showcased the superior emboli removal efficiency of newer integrated systems.[18]

This study aimed to delve into the performance of the Terumo Capiox RX 05 and FX 05 oxygenators, with a particular focus on their impact on neurocognitive outcomes as measured by the FOUR score. While

Taggart and Westaby have linked macro and microembolisms to a spectrum of postoperative cognitive issues, our findings indicate comparable neurocognitive outcomes between integrated and external filter systems, highlighting the integrated system's advantages in reducing circuit complexity and priming volumes.[19]

The interplay between blood and non-endothelial surfaces during CPB can trigger a systemic inflammatory response, ranging from subclinical to severe, potentially leading to multiorgan dysfunction or death. Innovations such as biocompatible surface coatings and circuit miniaturization represent non-pharmacological strategies to attenuate this response.[20,21] The integration of arterial filters within oxygenators exemplifies a significant advancement in reducing the synthetic material-blood interface, thereby minimizing system priming volumes and potentially enhancing patient recovery, although further research is necessary to conclusively determine its impact on postoperative outcomes, including mechanical ventilation times and hospital stays.

Limitations

There are few limitations in our study. This study was a single-centre study and all the patient population were operated by single pediatric cardio-thoracic surgeon which provides concordance among interventions.

Our study was conducted with the non-pulsatile flow while pulsatile flow may increase the incidence of GME. Hence the use of pulsatile flow should be considered to evaluate the efficacy of an integrated arterial filter. We have not considered change in temperature and flow rates during this study. It has been demonstrated in few studies that arterial line emboli increases with an increase in temperature and flowrate. Incoming emboli load was not standardized in our study. The use of transcranial doppler during CPB to detect GME could have added benefits which could have been co-related with the FOUR score results for neurocognitive indices. Near-infrared spectroscopy (NIRS) system which is highly effective to detect CNS function was not used.

In this study various non-integrated oxygenators viz. SORIN (Dideco D-901, Dideco D-902), Medtronic Affinity (Pixie), Capiox RX15, EUROSETS (Trilly) in group A were used due to unavailability of Capiox Baby RX 05 globally as transportation system was affected by Russia-Ukraine war.

5. Conclusion

The integration of arterial filters with CPB circuit miniaturization has shown promise in reducing hemodilution, systemic inflammatory responses, and the risks associated with gaseous microemboli (GME), which are known to potentially impair neurological function over the long term. Our study utilized the FOUR score method to evaluate neurological outcomes, revealing no significant differences between patients using external versus integrated arterial filters, suggesting both approaches are effective in mitigating GME-related neurological risks.

Secondary outcomes, including mechanical ventilation time and the duration of stays in the CSICU and hospital, did not show significant differences between the two groups, although there was a trend towards improved outcomes with integrated filters. Aortic cross-clamp and CPB times were found to be significant in influencing clinical outcomes.

Our findings indicate that the integrated arterial filter oxygenator, particularly the Capiox FX05, could serve as a viable replacement for external arterial filters, potentially enhancing patient safety and clinical outcomes in pediatric CHD patients. However, further research with a larger sample size and additional neurological assessment tools is recommended to validate these preliminary findings.

Key Clinical Message

Advancements in cardiopulmonary bypass (CPB) technology have led to the creation of novel configurations that incorporate surface-coating techniques, blood filtration, and device miniaturization. This study focused on evaluating the differences between patients undergoing CPB surgery with integrated versus non-integrated arterial line filters, examining both perioperative and postoperative clinical outcomes as well as neurocognitive performance.

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Annexure-I

FOUR score			
1.Eye response (E)	**Points**	**2.Motor response (M)**	**Points**
4= eyelids open or opened, tracking, or blinking to command 3= eyelids open but not tracking 2= eyelids closed but open to loud voice 1= eyelids closed but open to pain 0= eyelids remain closed with pain		4= Thumbs-up, fist, or peace sign 3= Localizing to pain 2= Flexion response to pain 1= Extension response to pain 0= No response to pain or generalized myoclonus status	
3.Brainstem reflexes (B)	**Points**	**4.Respiration (R)**	**Points**
4= Pupil and corneal reflexes present 3= One pupil wide and fixed 2= Pupil or corneal reflexes absent 1= Pupil and corneal reflexes absent 0= Absent pupil, corneal, and cough reflex		4= Not intubated, regular breathing pattern 3= Not intubated, Cheyne-Stokes breathing pattern 2= Not intubated, irregular breathing 1= breathes above ventilator rate 0= Breathes at ventilator rate or apnea	

E	M	B	R	TOTAL