Efficacy of Pulsatile Perfusion Technique as a Renal Protection Strategy During Cardiopulmonary Bypass

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ABSTRACT

Introduction: Application of Pulsatile perfusion during conduct of cardio-pulmonary bypass (CPB) is believed to preserve the renal functions in patients undergoing cardiac surgery. But there has been lot of debate regarding its routine application. Renal impairment following cardiac surgery is a well-known fact. In present study, an attempt is made to justify the renal benefits of pulsatile perfusion over non-pulsatile perfusion technique applied during conduct of CPB in adult cardiac surgeries. Study aimed to compare post-operative Blood urea nitrogen, Sr. creatinine & creatinine clearance, Acute kidney injury (AKI) incidence, requirement of inotropic and mechanical cardiovascular support, renal replacement therapy, length of ICU stay, morbidity and mortality on application of pulsatile vs. non pulsatile flows during conduct of CPB.

Material and methods: 160 adult patients undergoing cardiac surgery requiring cardio-pulmonary bypass (CPB) with normal preoperative renal functions were randomly subjected to receive either Pulsatile perfusion ("PP" group, n=80) or Non-Pulsatile perfusion ("NPP" group, n=80) during conduct of CPB.

Results: Despite of significantly lower mean arterial pressure (MAP), post-operative Sr. Creatinine was significantly lower while Creatinine clearance was significantly higher in "PP" group compared to "NPP" group. Vasoactive inotropic score, Requirement of ventilatory and Mechanical cardiovascular support were significantly lower in "PP" group. There was no significant difference found in Length of ICU stay and all-cause Mortality in both the groups.

Conclusion: Pulsatile flows applied during conduct of cardiopulmonary bypass (CPB) offered renal protection despite of lower mean arterial pressures on CPB. The lesser requirement of post-operative inotropic, ventilatory and mechanical circulatory support in pulsatile group precisely defines better cardiac perfusion and protection offered by pulsatile perfusion technique.

Keywords: Cardio-pulmonary Bypass (CPB), Pulsatile Perfusion Technique, Blood Urea Nitrogen (BUN), Sr. Creatinine, Creatinine Clearance, Vasoactive Inotropic Score (VIS), Mechanical Cardiovascular Support, Intra-aortic Balloon Counter-pulsation (IABP), Acute Kidney Injury (AKI).

INTRODUCTION

Cardio-Pulmonary Bypass (CPB) circuit is used during cardiac surgery to provide circulatory and respiratory support during cardiovascular surgeries. It also manages the temperature of the patient to facilitate cooling and rewarming during surgery.[1] The cardioplegia delivery system incorporated into this CPB circuits aims to protect the heart during open heart surgeries.[1] The systemic cooling and cardioplegia offers organ protection during CPB, which perhaps the main purpose for which the extracorporeal circulation is invented. The major concern for cardiac surgeries performed on CPB is postoperative organ dysfunction.[2] The major organs which may get affected are kidneys, brain & heart itself.[1,2] Acute renal failure (ARF) following cardiac surgery develops in 1-30% of patients and is associated with a high mortality rate of 15-30%. Mortality is particularly high (50-80%) in the subset of patients having severe ARF requiring renal replacement therapy.[3] Existing cardiovascular disease, advanced age and baseline renal dysfunction, type of cardiac surgery, the duration of cardiopulmonary bypass and aortic cross-clamping are the major determinants of post-operative renal dysfunction.[3,4] The causes of this post CPB insult are multifactorial but, the pathogenesis of organ dysfunction is systemic inflammatory response (SIRS) initiated by exposure of patient's blood to the extracorporeal circulation and activation of complement system. The activation of coagulation system, fibrinolytic system and neurohumoral responses sets up SIRS and subsequent end organ dysfunction.[1,5] To minimize this untoward complication, conduct of cardio-pulmonary bypass has undergone many modifications in its circuitry and techniques. Use of miniaturized and heparin coated circuits, polypropylene membrane oxygenators are few circuit modifications for reducing the development of SIRS.[6] Pharmacological suppression of inflammation, use of optimal

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CPB flows (2.2 -2.5 lit/min/m2), maintenance of nadir haematocrit value to 24 % and mean arterial pressures of >70 mmHg (altogether called as "optimal" perfusion technique) is few of the adopted methods for minimizing the end organ damage during conduct of CPB.[6] In this context, whether the use of pulsatile perfusion technique over the non-pulsatile perfusion during conduct of cardiopulmonary bypass (CPB) minimizes the end organ damage has always been a debatable question.[6] Pulsatile perfusion is believed to be more similar to the body's circulatory mechanism and is considered superior in protecting end-organs with a disadvantage of increased haemolysis compared to non-pulsatile technique of perfusion.[7] Non-pulsatile flow is believed to cause increased systemic vascular resistance whilst the Pulsatile perfusion is rhythmic and similar to body's mechanism of circulation causes the reduction in systemic vascular resistance during CPB.[6,7,8] During CPB, Increased SVR occurs due to increased circulating catecholamines, vasopressin and activation of renin angiotensin system.[8] This vasoconstriction may lead to reduced visceral perfusion and after separation from CPB when left ventricle is already functionally compromised from the insult of the operative procedure may predispose to a low cardiac output syndrome and visceral organ damage.[7,8] Pulsatile flow applied during CPB is known to reduce systemic arterial vasoconstriction by reducing release of baroreceptor reflex hormones that occurs with non-pulsatile CPB.[7,8] The enhanced energy associated with pulsatile blood flow maintains microcirculation and increases renal, cerebral, pancreatic blood flow thus facilitates the aerobic metabolism and improves delivery of nutrients.[8,9] Pulsatile blood flow can enhance gas exchange within the membrane by generating secondary flows at the membrane–blood interface and also enhances the performance of the heat exchanger leading to improved heat transmission.[8,9] The modern CPB machines are equipped with occlusive twin roller pumps which generate pulsability by altering the speed of rotation of the rollers (a pulsatile module). The pulsatile flow is determined by pulse frequency, pulse width and base flows. Pulse frequency determines number of pulse cycles per minute. It has a high-speed phase and low-speed phase. An average speed of the two phases determines the set speed. Pulse width denotes the percent length of high-speed phase to total length of the pulse cycle. The base flow corresponds to the low-speed phase and is expressed as a percent of set speed.[9,10,11] The ideal settings for generation of pulsatile flow includes Pulse frequency of 60 cycles/min. pulse width of 40% and base flows of 40% of maximum achievable flows.[9,10,11] Data are either conflicting or insufficient to support recommendations for or against pulsatile perfusion to reduce the end organ injury resulting in increased incidence of mortality, MI, stroke, or renal failure.[6,9,11] Present study, our aim was to determine the efficacy of pulsatile perfusion applied during conduct CPB on post-operative renal function. The objective of the study was to compare the effect of Pulsatile vs Non pulsatile perfusion technique on post-operative renal function tests viz. BUN, Sr. creatinine & creatinine clearance. The secondary objective was to compare the inotropic requirements, mechanical cardiovascular support, need of renal replacement therapy, length of ICU stay, morbidity and mortality on application of pulsatile vs. non pulsatile flows during conduct of CPB.

MATERIAL AND METHODS

After clearance from institutional ethical committee & duly informed consent, the present study was conducted in tertiary care centre in northern Karnataka between August 2018 – April 2019. 160 adult patients of either sex between age 18-60 years having normal LV function and no or controlled diabetes coming for cardiac surgery, requiring cardiopulmonary bypass (CPB) were randomly divided to receive either pulsatile "PP group" or a non-pulsatile perfusion "NPP group" during conduct of CPB. The subjects with uncontrolled diabetes mellitus, pre-existing renal failure, history of pre-operative dialysis, use of contrast in less than 3 days, subjects with pre-existing acute heart failure and those with Sr Cr >1.2 mg/dl were excluded from the study. The demographic and clinical characteristics of study subjects were noted down for comparison and ensuring the two groups were similar in demographic and clinical characteristics. Variables like Type of surgery, Pre CPB haematocrit, Blood urea nitrogen, Sr. Creatinine, Creatinine clearance, pre-bypass mean arterial pressures (MAP), duration of CPB and aortic cross-clamp, flow rates and mean arterial pressures (MAP) during CPB were noted. Standard anaesthetic protocols were followed during induction of anaesthesia in both the group. Intravenous anaesthetic induction was done using inj. Midazolam 80 µcg/kg, Fentanyl 15 µcg/kg and inj. Propofol 0.5 mg/kg. the neuromuscular blockade was achieved using inj. Pancuronium 0.1 mg/kg. Anaesthesia was maintained using O2 60%, Air 40 %, isoflurane 1%, fentanyl and vecuronium. After sternotomy, systemic heparinization was achieved by giving inj. Heparin 4mg/kg to achieve ACT of > 480 seconds. The CPB circuit consisted of a Stöckert S5® or Stockert S3 heart–lung machine equipped with Primox® or Inspire 8® oxygenator (Sorin Group, Italy), an HVR Hard-shell reservoir (Sorin Group), a Sorin adult® tubing system, and a Stöckert Heater Cooler System 3T® (Stöckert Instrumente, Germany). The priming solution consisted of 1,200 ml (plsamalyte 600 ml, hydroxyethyl starch 500ml and Mannitol 100ml) and 10,000 IU heparin. After cannulation of Aorta, superior and inferior vena cava cardiopulmonary bypass was instituted. These machines are equipped with occlusive twin roller pumps which generate pulsability by altering the speed of rotation of the rollers (a pulsatile module). The pulsatile flow is determined by pulse frequency, pulse width and base flows. The BSA & flow rate were calculated using DuBois formula and flows were adjusted to achieve the cardiac index of 2.5 l/m2/min at room temperature 37 0 c. Pulsatile flows were initiated in "PP" group by settings pulse frequency at 60 cycles/min, pulse width at 40% and base flows at 40% of maximum flows achievable. The above settings were employed on the module to generate pulsatile flows. A Sorin inspire - 6 oxygenator was used for gaseous exchange; miniaturized circuits were employed so that less hydraulic energy

was wasted. Prime solutions were adjusted to maintain a circulatory HCT of at least 24-25 %. Appropriately sized aortic cannulas were used to have least resistance. A pulse pressure of 12-15 mmHg was maintained during perfusion. The speed of roller pump was kept constant for both pulsatile and non-pulsatile flows. Stockert 3t and Cincinnati sub-zero haemotherm were used to cool and later rewarm the patients perioperatively. Conventional ultrafiltration (CUF) was avoided on CPB. Patients in which CUF was done, were excluded from study. Del-nido cardioplegia was used if required during the cardiac surgical procedure. Use of loop-diuretics and albumin was avoided during CPB. After the desired surgical procedure was accomplished and once the de-airing was done and cardiac rhythm was established, the cross-clamp was released subjects were weaned off CPB once the criteria for weaning was fulfilled. The heparin was antagonized using protamine sulphate in the ratio of 1:1. The use of antifibrinolytics was avoided as they may lead to renal impairment in post-operative period.[12] Inotropic requirement after weaning off CPB was noted. After closure of sternum and surgical incisions, the patient was shifted to post-operative ICU. Vasoactive inotropic Score of first 24 hours inotropic requirement was calculated (VIS) using formula;

VIS = Dopamine (µcg/kg/min) + Dobutamine (µcg/kg/min) + [Milrinone (µcg/kg/min) x 10] + [Epinephrine (µcg/kg/min) x100] + [Norepinephrine (µcg/kg/min) x 100] + [Vasopressin (units/hr) x10000] + [50×levosimendan dose [µcg/ kg/min].[13]

Insertion of Intra-aortic balloon counter pulsations (IABP) pump as a mechanical cardiovascular support was Indicated in those subjects who had an evidence of Low cardiac output despite of increasing inotropic requirements and ventricular dysfunction causing hemodynamic instability during or after weaning off CPB. Primary outcome variables i.e., Blood urea nitrogen, Sr. Creatinine, Creatinine clearance and urine output were recorded 24th and 96th hours post-surgery. Secondary outcome variables, i.e., Duration of ICU Stay in days, untoward events like acute kidney injury (AKI) (defined as Stage 1: -1.5–1.9 times increase in serum creatinine from baseline or ≥0.3 mg/dL absolute increase in sr. Creatinine or Urine volume <0.5 mL/kg/h for 6–12 hours, Stage 2:- sr. Creatinine ≥2.0–2.9 times from baseline or urine volume <0.5 mL/kg/h for ≥12 hours, Stage 3:- Increase in sr. Creatinine to ≥4.0 mg/dL or Initiation of renal replacement therapy or urine volume <0.3 mL/kg/h for ≥24 hours or anuria for ≥12 hours)(KIDGO Criteria)[14] requiring haemodialysis, sepsis, multiorgan dysfunction (MODS), respiratory failure, morbidities and all-cause mortality were also noted. Later the intergroup and intragroup pre to post comparison of study variables was done to determine the efficacy of both the perfusion techniques as renal protective strategies and to know their effect on outcome of surgery.

Quantitative study variables following normal distribution were expressed in terms of mean ± standard deviation (SD). Qualitative variables were expressed in terms of percentage. The intergroup and intra-group pre to post procedure comparison of study variables was done and analysed using "z test". P value of <0.05 was considered as significant. P <0.001 was considered as highly significant. P >0.05 was considered non-significant.

RESULTS

Intergroup comparison of demographic and clinical study variables shown no significant difference in age (47.20±5.12 vs. 49.09±13.60, p>0.05) years, body surface area (1.55±0.18 vs. 1.59±0.25, p>0.05) kg/m^2, pre-CPB haematocrit (40.98±5.61 vs. 41.70±5.11, p>0.05)%, pre-CPB urine output (183.48±137.07 vs. 213.57±160.24, p>0.05) ml, CPB flow rates (3.80±0.47 vs. 3.88±0.64, p>0.05) lit/min , duration of CPB (99.76±30.23 vs. 88.51±32.10, p >0.05) minutes and Duration of cross clamp (53.04±38.47 vs. 69.46±36.20,p>0.05) minutes in "NPP" group vs. "PP" group. There was no statistically significant difference found in baseline renal function tests viz. Blood urea nitrogen (28.43±12.05 vs. 25.34±8.67, p >0.05) mg/dl, sr. creatinine (0.96±0.25 vs. 0.86±0.27, p>0.05) mg/dl, creatinine clearance (82.41±28.43 vs. 109.69±34.46, p >0.05) ml/kg/ m^2, Mean arterial pressure on CPB (77.81±14.39 vs. 79.59±10.81, p>0.05) mmHg and nadir haematocrit on CPB (24.44+1.67 vs. 23.81±1.64, p>0.05) % in "NPP" group vs. "PP" group. (Table.1). Primary outcome variables i.e., sr. creatinine (1.22±0.35 vs. 0.75±0.25, p<0.001) was significantly lower and creatinine clearance (62.77±22.91 vs. 109.27±67.56, p<0.05) was significantly higher 96 hours after surgery in "PP" group compared to "NPP" group despite of statistically non-significant difference in mean arterial pressures (84.00±10.78 vs. 79.65±9.40, p>0.05) mmHg between two groups. No significant difference found in 24 hours Urine output (2563.43±654.31 vs. 2720.30±600.54, p>0.05) ml and Blood urea nitrogen (30.29±10.06 vs. 26.79±10.13, p>0.05) between two groups. Secondary outcome variables like Duration of mechanical ventilation (24.05±11.21 vs. 19.04±9.73, p<0.05) hours, vasoactive inotropic requirement score (VIS) (15.0±3.07 vs. 11.95±3.32, p<0.001) and duration of ITU stay in days (5.35±2.04 vs. 4.54±1.19, p< 0.05) were significantly lower in pulsatile perfusion group. There was no significant difference seen in IABP requirement (7 (8.75%) vs. 4 (5%), p>0.05), all-cause mortality (1 (1.25%) vs.1 (1.25%), >0.05) between two groups. (Table.2), (Graph.1). Single death in each group was attributed to low cardiac output and post-operative sepsis. KDIGO "stage 1" of Acute Kidney Injury (rise in sr. creatinine >/= 0.3 mg/dl or 1.5-1.9 times increase from baseline) was seen in 29 (36.25%) subjects in "NPP" group and only in 8(10%) subjects in "PP" group (p=0.0017) while KDIGO stage 2 AKI (rise in sr. creatinine >/=2.0 – 2.9 times increase from baseline) was seen in 5(6.25%) subjects in "NPP" group and only in 1(1.25%) subject in "PP" group (p=0.2). AKI requiring renal replacement therapy was not seen in either of the groups.

Intra-group Pre-post comparison in "NPP" group revealed significantly dysregulated postoperative Blood urea nitrogen, (22.99±8.42 vs. 30.61±10.66, p<0.001) mg/dl, Sr. Creatinine (0.86±0.27vs.1.21±0.36, p<0.001) mg/dl and creatinine

clearance (106.21±11.84 vs. 63.27±22.43, p<0.001) ml/kg/m2 from the respective baseline values in spite of comparable post-operative Mean arterial pressures (79.81±10.75 vs. 83.85±10.39, p>0.05). Post-operative Haematocrit was lower (41.70±5.11 vs. 35.64±5.85%, p<0.001) than the baseline value. (Table.3) (Graph.2).

Intra-group Pre-post comparison in "PP" group showed significantly improved Sr. Creatinine (0.98±0.25vs.0.75±0.25, p<0.05) and creatinine clearance (82.41±23.54 vs. 109.27±37.56, p<0.05) compared to baseline values in spite of non-significant increase in mean arterial pressure (77.81±14.39 vs. 79.65±9.40, p>0.05). No

Study characteristics	"NPP" Group [Mean ± SD (SE)]	"PP" Group [Mean ± SD (SE)]	"Z" Score	"P" value (Significance)
Age (Years)	47.20±5.12 (1.69)	49.09±13.60 (1.52)	-0.66	0.51(NS)
Sex	Male =53 (66.25%)	Male =43 (53.75%)	1.54	0.12(NS)
	Female=27(33.75%)	Female=37(46.25%)	-1.76	0.78(NS)
BSA (M^2)	1.55±0.18 (0.02)	1.59±0.25 (0.03)	-1.91	0.58(NS)
Hypertension	18 (22.5%)	14 (17.5%)	0.75	0.45(NS)
Diabetes Type (II)	12 (15%)	8 (10%)	0.87	0.38(NS)
Type of Surgery	CABG = 42 (52.5%)	CABG =32 (40%)	1.49	0.14(NS)
	Valve Replacement Surgery = 28(35%)	Valve Replacement Surgery = 36 (45%)	-1.38	0.17(NS)
	Miscellaneous=10(12.5%)	Miscellaneous=12(15%)	-0.23	0.82(NS)
CPB Flow Rates (lit/min)	3.80±0.47 (0.05)	3.88±0.64 (0.07)	-1.39	0.16(NS)
Duration of CPB (min)	99.76±30.23 (3.38)	88.51±32.10 (3.59)	0.69	0.49(NS)
Duration of Aortic 'Cross Clamp' (min)	53.04±38.47 (4.30)	69.46±36.20 (5.80)	-0.79	0.43(NS)
Duration of Surgery (hrs.)	4.65±1.11 (0.12)	3.70±1.00 (0.11)	6.95	0.00001(HS)
Pre CPB-Haematocrit (%)	40.98±5.61 (0.63)	41.70±5.11 (0.57)	-0.76	0.45(NS)
Pre CPB-BUN (mg/dl)	28.43±12.05 (1.35)	25.34±8.67 (0.09)	1.33	0.18(NS)
Pre CPB-Sr. Creatinine (mg/dl)	0.96±0.25 (0.03)	0.86±0.27 (0.03)	1.72	0.08(NS)
Pre CPB-Creatinine Clearance (ml/min)	82.41±28.43 (3.18)	109.69±34.46 (3.85)	-1.52	0.13(NS)
MAP On CPB (mmHg)	77.81±14.39 (1.61)	79.59±10.81 (1.29)	-0.58	0.56(NS)
Nadir Haematocrit on CPB (%)	24.44±1.67 (0.19)	23.81±1.64 (0.18)	1.70	0.09(NS)
Pre - CPB Urine Output (ml)	183.48±137.07 (15.33)	213.57±160.24 (19.15)	-0.09	0.93(NS)
CPB Urine Output (ml)	1735.71±536.93(64.18)	1914.13±289.91(32.41)	-1.93	0.053(NS)

Table-1: Intergroup comparison of baseline clinical, demographic and study variables.

Study outcome variable	"NPP" Group [Mean ± SD(SE)]	"PP" GROUP [Mean ± SD(SE)]	"Z" Value	"P" Value (significance)
Hematocrit (HCT) (%)	35.86±6.08 (0.68)	40.97±7.60 (0.85)	-3.34	0.0084(S)
Blood Urea Nitrogen(mg/dl)	30.29±10.06 (1.12)	26.79±10.13 (1.13)	1.55	0.121(NS)
Sr. Creatinine (Sr. Cr) (mg/dl)	1.22±0.35 (0.04)	0.75±0.25 (0.03)	7.01	0.00001(HS)
Creatinine Clearance (ml/min)	62.77±22.91 (2.56)	109.27±67.56(7.55)	-4.6	0.00001(HS)
Mean Arterial Pressure (mmHg)	84.00±10.78 (1.29)	79.65±9.40 (1.05)	1.93	0.054(NS)
Post CPB Urine Output (ml)	2563.43±654.31 (73.15)	2720.30±600.54(67.14)	-1.12	0.26(NS)
Duration of Mech Ventilation(hr)	24.05±11.21 (1.25)	19.04 ±9.73 (1.09)	2.14	0.032(S)
Vasoactive Inotropic Score (VIS)	15.05 ± 3.07 (0.69)	11.95 ± 3.32 (0.37)	4.34	0.00017(HS)
Requirement of IABP	7 (8.75%)	4 (5%)	0.83	0.406(NS)
Post-Operative AKI (Stage 1) KDIGO	29 (36.25%)	8 (10%)	3.14	0.0017(S)
Post-Operative AKI (Stage 2) KDIGO	5 (6.25%)	1(1.25%)	1.29	0.2(NS)
ITU stay (days)	5.35±2.04 (0.23)	4.54±1.19 (0.14)	2.24	0.025(NS)
Mortality (All-Cause)	1 (1.25%)	1 (1.25%)	0	1(NS)

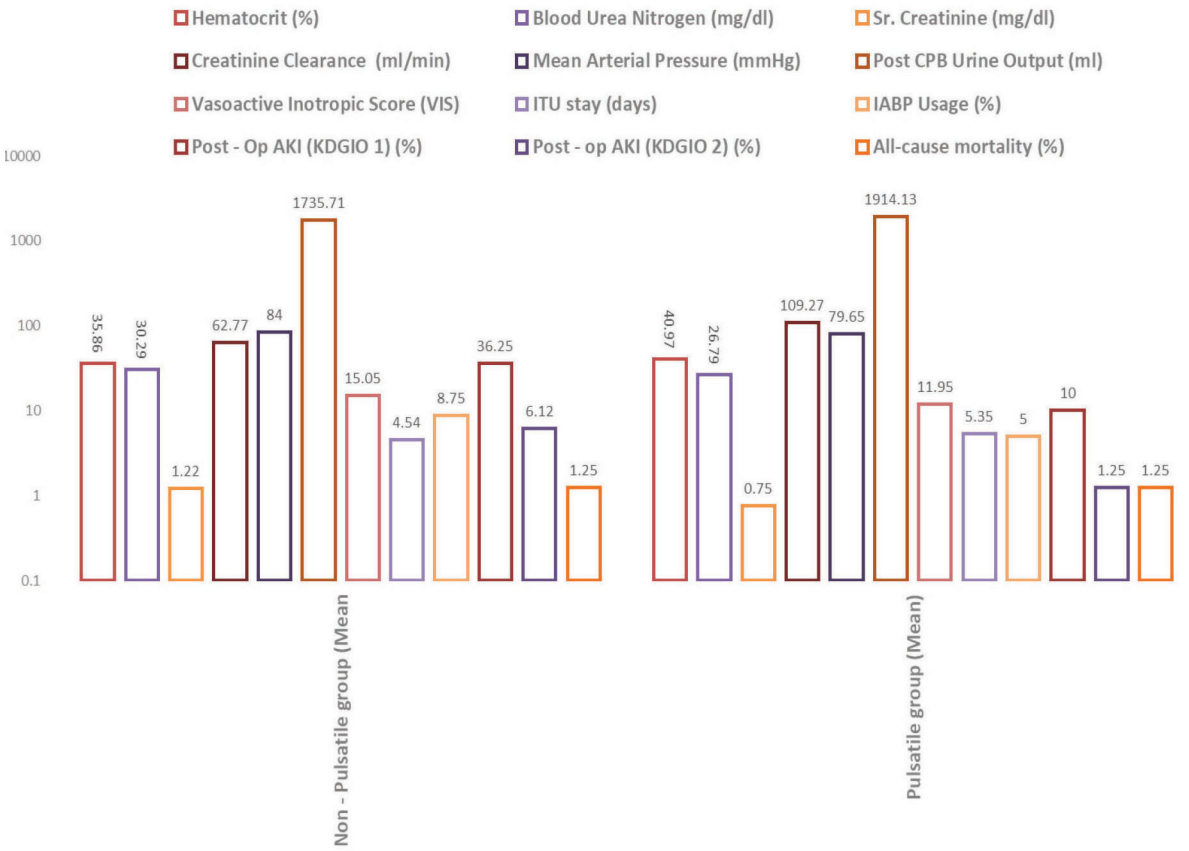
Table-2: Intergroup comparison of primary and secondary outcome variables.

Study variable	PRE- CPB [Mean ± SD (SE)]	Post – CPB [Mean ± SD (SE)]	"Z "Value	"P "Value (Significance)	%Change in Means
Hematocrit (%)	41.70 ± 5.11 (0.57)	35.64±5.85(0.65)	4.95	0.0001(HS)	-14.54
Blood Urea Nitrogen (mg/dl)	22.99 ± 8.42(0.94)	30.61±10.66(1.19)	-3.57	0.00035(HS)	33.17
Sr. Creatinine (mg/dl)	0.86 ± 0.27(0.03)	1.22± 0.35(0.04)	-5.54	0.00001(HS)	48.45
Creatinine Clearance(ml/min)	106.21 ±11.84 (1.32)	63.27±22.43(2.51)	11.21	0.00001(HS)	-40.43
Mean Arterial Pressure (mmHg)	79.81 ±10.75 (1.20)	83.85±10.39(1.16)	1.71	0.087(NS)	5.06

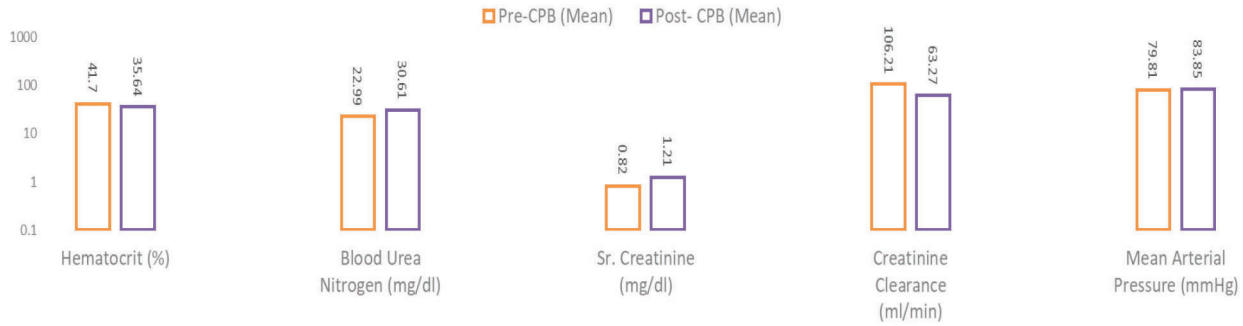
Table-3: Intra group pre to post comparison of study variables in non- pulsatile perfusion (NPP) group.

Study variable	PRE-CPB [Mean ±SD (SE)]	POST–CPB [Mean±SD (SE)]	"Z" Value	"P" Value (Significance)	%Change in means
Hematocrit (%)	40.98±5.61(0.63)	40.97±7.60(0.85)	0.01	0.99 (NS)	-0.02
Blood Urea Nitrogen (mg/dl)	28.43±2.05(1.35)	26.79±10.13(1.13)	0.66	0.51(NS)	-5.76
Sr. Creatinine (mg/dl)	0.98 ± 0.25(0.03)	0.75 ± 0.25 (0.03)	2.94	0.003(S)	-23.10
Creatinine Clearance (ml/min)	82.41±23.54(2.63)	109.27 ± 37.56 (4.2)	3.93	0.00008(HS)	32.59
Mean Arterial Pressure (mmHg)	77.81±14.39(1.61)	79.65 ± 9.40 (1.05)	-0.69	0.49(NS)	2.36

Table-4: Intra group pre to post comparison of study variables in pulsatile perfusion (PP) group.



Graph-1: Intergroup comparison of primary & secondary outcome variables

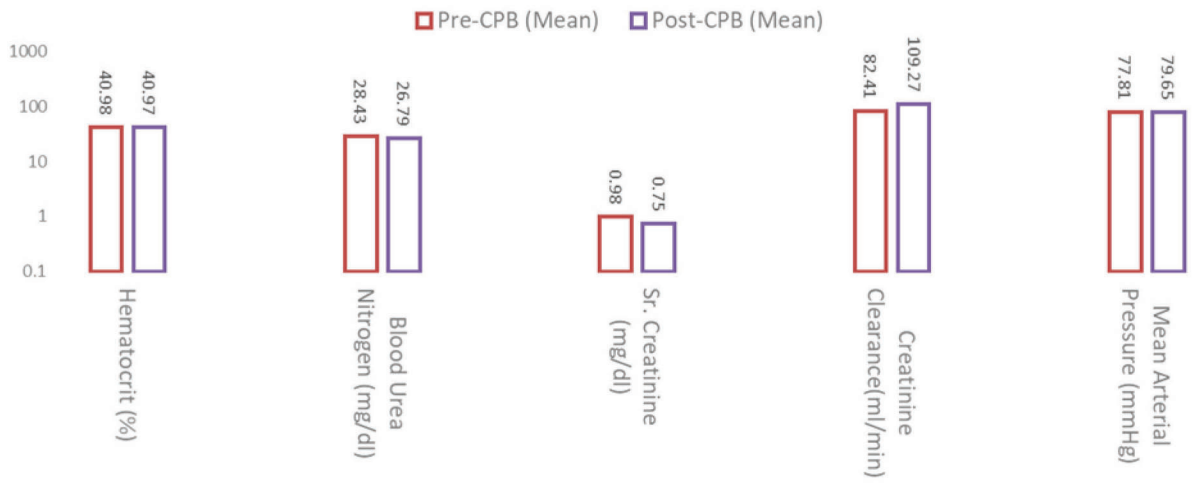


Graph-2: Intra-group Pre to post comparison of study variables in Non pulsatile (NPP) group

statistically significant difference observed in Haematocrit (40.98±5.61 vs. 40.97±7.60, p>0.05) and blood urea nitrogen (28.43±12.05 vs. 26.79±10.13, p>0.05) from their respective baseline values. (Table.4) (Graph.3)

DISSCUSSION

In present study, post-operative creatinine clearance and Sr. Creatinine were better regulated when a pulsatile perfusion was applied during CPB. The non-pulsatile flows on CPB caused dysregulation of creatinine clearance and Sr. creatinine. This reno-protective effect of Pulsatile flows on CPB can be attributable to resemblance of pulsatile flows to body's rhythmic flow and physiological circulatory mechanism.[7] This reno-protective effect was observed in spite of lower mean arterial pressures on CPB and similar duration of CBP, aortic cross clamp, and CPB flow rates in



Graph-3: Intra-group pre to post comparison of study variables in Pulsatile perfusion (PP) group

pulsatile compared to non-pulsatile perfusion group. Better flow dynamics & generation of optimal kinetic energy leading to improved RBC transit, capillary perfusion and lymphatic drainage during pulsatile flows, may be the reason behind better perfusion offered to kidneys.[7] Lower mean arterial pressures in pulsatile group in post – operative period denotes lesser SVR compared to non-pulsatile group. our findings were similar to Poswal & Mehta et al who compared pulsatile flows with non-pulsatile in 60 adults undergoing cardiac surgery on CPB. The creatinine clearance in pulsatile flow group on the 2nd post-operative day was significantly higher against depressed Cr. Cl in non- pulsatile group. SVR was significantly lower in pulsatile group which lead to improved microcirculation and enhanced cell diffusion.[15] 80 adult patients requiring cardiac surgery on CPB studied by Mohammad Zadeh et al showed more dysregulated values of Blood urea nitrogen and Sr. Creatinine in non-pulsatile group compared to the pulsatile group. Our study showed similar results in context to BUN and Sr. Creatinine.[16] Milano et al applied short-term pulsatile perfusion in 40 elderly subjects undergoing aortic valve replacement to determine the renal benefits of Pulsatile cardiopulmonary bypass and observed significant perioperative decline in renal function in non-pulsatile group. Even this short-term Pulsatile perfusion proved its efficacy in maintenance of glomerular filtration and causing lower renal tissue injury. They attributed this observation to higher haemodynamic energy with lower mean systemic vascular resistance during CPB in pulsatile group.[17] Similarly, in present study, we observed renal function was better preserved in pulsatile group. Immediate post-operative haematocrit was better maintained in pulsatile group. This observation can be attributed to maintained rheology of blood flow reducing transit time for blood and large scale and exponential activation of coagulation system, fibrinolytic system.[18] The pulsatile CPB using roller pumps results in a greater extent of haemolysis, which has failed to prove its clinical significance.[18] Inotropic and vasoconstrictor drug infusion requirement score (VIS) for first 24 hours for maintaining hemodynamic stability was significantly lower in pulsatile group. Lesser chances of perioperative myocardial injury and subsequent prevention of cardiac dysfunction in pulsatile CPB may be a reason behind the lesser inotropic requirement in pulsatile perfusion group[19] Jung et al demonstrated that the non-pulsatile pump may require 25%–28% higher pump flow than the pulsatile pump to maintain equivalent coronary blood flow in an experimental study.[20] The length of ICU stay in days was significantly lower in pulsatile group. Lesser inotropic requirements and use of mechanical cardiovascular support, early weaning off from mechanical ventilation were the attributes for shorter ICU stay in this group.[21] The all-cause mortality was similar in both groups. Similar study with bigger sample size is required to make a justifiable comment on mortality and morbidity. Postoperative renal dialysis was not required in any of the groups. Taylor & Bain et al. concluded that pulsatile perfusion offered significant haemodynamic advantages over non-pulsatile perfusion in terms of total mortality attributed to post-perfusion low cardiac output ,requirement of mechanical (intra-aortic balloon) or drug circulatory support in 350 patients who received either pulsatile or non- pulsatile perfusion.[21] Literature review of 228 articles by Undar A et al. to clarify the truths and dispel the myths regarding the mode of perfusion used during open-heart surgery in paediatric and adult patients points in favour of pulsatile flow which improved blood flow of the vital organs including brain, heart, liver and pancreas, reduced the systemic inflammatory response syndrome and decreased the incidence of post-operative deaths in paediatric and adult patients. Vital organ recovery in several types of animal models were better in pulsatile than non-pulsatile perfusion. Pulsatile flow generated more hemodynamic energy which maintains better microcirculation compared to non-pulsatile flow.[22] Alkan T, Undar A et al. demonstrated paediatric cardiac surgical patients receiving pulsatile perfusion required less inotropic support, shorter intubation period, shorter duration of intensive care unit (ICU) and hospital stay. Use of pulsatile flow resulted in improved patient outcomes in terms of preserving better cardiac and pulmonary functions in the early post-CPB period.[23] In our study, performed on adult subset, we found similar results.

Haines N, Wang S et al. has provided evidence of better cardiac, renal, and pulmonary outcomes in patients receiving pulsatile perfusion owing to better cytokine, endothelin, and hormone levels and a higher respiratory index pulsatile perfusion mode compared with non-pulsatile perfusion.[24] Tim G C and Mc Philimey E et al. Retrospectively analysed 2,489 cardiac surgical patients receiving either pulsatile or non-pulsatile flows and concluded that the incidence of AKI, Stages of AKI and mortality was similar in two groups.[25] In contrast, our study, KDIGO "stage 1" of Acute Kidney Injury (rise in sr. creatinine >/= 0.3 mg/dl or 1.5-1.9 times increase from baseline) was seen in 29 (36.25%) subjects in "NPP" group and only in 8(10%) subjects in "PP" group (p=0.0017) while KDIGO stage 2 AKI (rise in sr. creatinine >/=2.0 – 2.9 times increase from baseline) was seen in 5(6.25%) subjects in "NPP" group and only in 1(1.25%) subject in "PP" group (p=0.2) Though, AKI requiring renal replacement therapy was not seen in either of the groups, incidence of stage 1 AKI was significantly higher in Non pulsatile perfusion group . Attributable causes for this observation are likely to be more liberal definition of AKI stage 1 in KDIGO classification i.e., >/= 0.3 mg/dl increase in sr. creatinine from baseline) and the lower baseline values of sr. creatinine (below <0.5 mg/dl) to begin with. Furthermore, KDGIO criteria may lead to misdiagnosis of AKI as it relies on smaller change in serum creatinine.[26] More justifiable explanation on this observation can only be given after studying a larger sample population.

Limitations

1. Present study was primarily aimed to observe the effects of pulsatile perfusion on renal bk biochemical markers. For justifiable statement on requirement of haemodialysis or renal replacement therapy, acute kidney injury, renal failure and all-cause mortality in perioperative period, larger sample size was required.
2. Systemic vascular response (SVR) during CPB was not taken in consideration. It would have shown a good correlation between SVR on CPB and post-operative renal function.[25]
3. Creatinine clearance (Cr. Cl) was determined by Cockcroft-Gault equation as Cr. Cl = [(140 − age) × body weight]/ (plasma creatinine × 72) for males & (× 0.85 if female). This method is not the gold standard for creatinine clearance estimation and standardization for body surface area (BSA) is needed as its largely influenced by BSA.[27]
4. Cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), IL-18 and kidney injury molecule-1 (KIM-1) which better quantify the extent of acute ischemic and/or tubular injury were not investigated.[28]

CONCLUSION

Pulsatile perfusion during cardiopulmonary bypass (CPB) offers renal protection despite of lower mean arterial pressures on CPB compared to non-pulsatile perfusion. Improved post-operative Blood urea nitrogen, Serum Creatinine and Creatinine clearance in pulsatile perfusion group against the worsened values in non-pulsatile group surrogates better renal protection offered by pulsatile flows during CPB. Significantly lesser requirement of inotropic, mechanical circulatory and ventilatory support in pulsatile group precisely defines better cardiac perfusion and protection offered by pulsatile perfusion technique. The better preservation of peri-operative haematocrit may also have attributed to renal protection in pulsatile perfusion group. Authors recommend the use of pulsatile flows over a non-pulsatile during conduct of cardio-pulmonary bypass.

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