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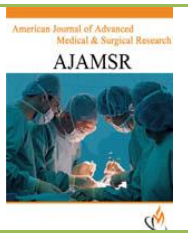

COMPARISON OF INCIDENCE OF ACUTE KIDNEY INJURY IN ON PUMP V/S OFF PUMP CORONARY ARTERY REVASCULARISATION SURGERY

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ABSTRACT
Off pump coronary artery bypass grafting (OPCAB) is worldwide acceptable as the preformed choice for myocardial revascularization. However, no definite data exist as to whether it is better than conventional coronary artery bypass grafting (CABG). We aimed to compare the incidence of acute kidney injury (AKI) and early outcomes between the conventional CABG and OPCAB. Between November 2014 to April 2015, 40 patients underwent ONCAB (group A) and another 40 patients had been subjected to OPCAB (group B). Analysis of preoperative, perioperative and postoperative courses related to AKI and clinical outcomes were performed. The perioperative data showed longer inotrope duration in ONCAB (46.85 ± 32.90hrs. vs. 26.42 ± 21.47 hrs, $P < 0.05$) as compared to OPCAB group, respectively. The incidence of pts. who need prolonged mechanical ventilation (>7 h), was also higher in ONCAB as compared to OPCAB group. Rise in serum creatinine as per our definition AKI practice guideline is comparable and non-significant in both the group (group A 6 no of patients vs group B 7 no of patients p =1.000). The choice of operative technique OPCAB versus ONCAB is not associated with reduced renal morbidity. But still OPCAB is more favorable with low ICU and hospital stay.

INTRODUCTION

Renal dysfunction after coronary artery bypass grafting (CABG) is independent risk factor for morbidity and mortality, as well as increased in length of ICU and hospital stay [1]. Although acute kidney injury (AKI) requiring replacement therapy occurs in less than 1% of cases, these patients could have a mortality rate up to 60% [2]. Major risk factor for postoperative AKI include advanced age, preoperative renal dysfunction (RD), diabetes mellitus, hypertension, history of nephrotoxic drug, congestive heart failure, prolonged cardiopulmonary bypass (CPB) time, and persistent low cardiac output states [3]. Among various theory, renal hypo perfusion, embolic loads to the renal vasculature and inflammatory damage secondary to CPB are widely recognised as the most important culprits [2, 4]. These all risk factors acts synergistically for the incidence of AKI following CABG [5,6]. Off-pump coronary artery bypass (OPCAB) surgery eliminates several risk factors associated with CPB that have been implicated in the development of postoperative AKI. OPCAB may therefore be the preferred technique for patients with multiple preoperative risk factors for AKI.

Early studies suggested decreased incidence of RD in OPCAB versus coronary artery bypass with CPB (ONCAB) patients assessed by early renal injury markers [7]. Others, however, contradicted these findings and found no differences in creatinine clearance between OPCAB and

ONCAB groups [8]. In our study we compared the incidence of AKI in OPCAB and ONCAB so that we could identify the risk factors for post-operative renal dysfunction and if possible avoid techniques that may cause post-operative renal dysfunction. We compared the incidence of AKI using the difference of postoperative to preoperative creatinine and postoperative urine output as a marker of AKI in ONCAB and OPCAB patients undergoing complete revascularization.

MATERIALS AND METHODS

Study design

Elective CABG patients who fulfilled the study criteria (age <80 years, no previous history of renal, liver disease, hypertension and diabetes mellitus) were recruited following informed consent. On the preoperative day, they were randomized into Group A: on pump coronary artery bypass (ONCAB) or Group B: off-pump coronary surgery (OPCAB). Study was approved by our institutional ethics committee. Study was done in the period of November 2014 to April 2015 at U.N. Mehta institute of cardiology and research centre, Ahmedabad. This study was a randomized controlled trial designed to know whether cardiopulmonary bypass increases chances of acute kidney injury in patients undergoing CABG or not. This prospective study enrolled 80 patients who underwent CABG. Research Randomizer online random number generator was used to create the randomization. All the patients were randomly divided in to two group. All surgery are done by a single surgeon trained in the OPCAB technique as well as on pump CABG technique with more than 10 year of experience and their conversion rate of OPCAB to on pump CABG is <5%.

Anaesthesia and conduct of CPB

A standardized protocol was followed for induction and maintenance of anesthesia. Anesthetic administration of anxiolytics, narcotics, and muscle relaxants was similar in both groups. No patient in either group received regional anesthesia. Each patient had continuous perioperative monitoring of central venous, systemic arterial pressures, SpO2, ECG and nasopharyngeal temperature.

In ONCAB patients, a standard adult extracorporeal tubing set was used incorporating a 40 µm arterial line filter in conjunction with a Trillium Affinity NT Hollow Fiber Oxygenator (Medtronic Ltd, USA). The circuit was primed with 1500 ml of ringer lactate, 50 ml 20% Mannitol, 50 ml Sodium bicarbonate, and 7000 IU of sodium heparin. An S3 roller pump (Sto¨ckert Instrumente GmbH, Munich, Germany) controlled no pulsatile flow which was maintained at or above 2.5 l/min per m2. The mean perfusion pressure was titrated between 60 to 70 mmHg with a combination of phenylephrine and sevoflurane. Alpha-stat management of acid-base status was used during CPB.

In OPCAB patients, Haemodynamic stability with a target mean arterial pressure of 65 mmHg was achieved with a combination of preload management (intravenous fluid and autotransfusion with the Trendelenberg posture), external pacing, meticulous thermoregulation (head wrap, forced air warming, warmed transfusion and elevated ambient temperature) and Inotropic support if required.

Surgical procedure

Group A:

CABG was performed with the help of cardio pulmonary bypass. In CPB blood is drained through a single two-stage venous 36/51 fr cannula (Medtronic DLP, Medtronic UK Ltd.) inserted into the right atrium/ inferior vena cava and arterial return via a curved metal tip cannula (Medtronic DLP, Medtronic UK Ltd.) placed in the ascending aorta. The procedure was conducted under mild hypothermia (34 C) with myocardial protection provided by intermittent ante grade cold blood cardioplegia (4 C). The cardioplegic mixture consisted of St. Thomas solution. Diastolic cardiac arrest was induced with 20ml/kg of cardioplegic infusion supplemented at 20 min intervals by further doses. Aortic anastomoses of vein grafts were performed on a reperfused heart following cross-clamp removal.

Group B:

In the off pump CABG group, the heart was exposed through a median sternotomy and pericardiectomy. Multiple traction suture placed along cut edges and posterior aspect of pericardium to facilitate exposure of the heart during coronary anastomoses. Systemic heparin was administered at 1 mg/kg to prolong the activated clotting time to approximately 250 s. For improved exposure of the target coronary vessel a suction-based mechanical stabilizer (Octapus II, Medtronic Ltd., Watford, UK) used prior to arteriotomy. An intraluminal shunt (Biovascular Inc., Minnesota, USA) was used during distal anastomoses for distal myocardial perfusion and preservation. Aortic anastomoses of vein grafts were performed using a partial-occlusion clamp in the standard fashion.

Assessment of renal function

Blood samples were collected from each patient preoperatively and until postoperative day 3. Changes in renal function were assessed by measuring blood urea and serum creatinine(Cr). Urine output is also measured hourly until day 3. Demographic variables and perioperative characteristics were also collected. Inotropic duration, ventilation duration, ICU and hospital stay also measured. Blood product requirement also calculated from OR.

Definition of RD/AKI

We have excluded patients with preoperative serum creatinine (Cr-Pre) values > 1.5 mg/dL, those on hemodialysis, taking nephrotoxic drugs, and patients whose

OPCAB converted to CPB. The analysis also excluded patients with CAG performed within 72 hour prior to surgery.

We considered AKI when patients serum creatinine was raised ≥ 0.3 mg/dl within 48 hours or increase in serum creatinine ≥ 1.5 times baseline which is known or presumed to have occurred within prior 7 days or urine volume < 0.5 ml/kg/hr for 6 hours according to KDIGO ,AKI practice guideline [9].

RESULTS

Total eighty patients were randomly allocated to either on-pump surgery or off pump surgery (40 patients each). Baseline demographic and preoperative clinical characteristics were statistically non-significant in both groups (Table 1). Number of grafts was comparable in both the group. The Postop complications were statistically non-significant in both the group, including serum creatinine, creatinine clearance, urine output, and left ventricular ejection fraction. Rise in serum creatinine as per our definition as per AKI practice guideline is comparable and non-significant in both the group (group A 6 no of patients vs. group B 7 no of patients p =1.000). In off pump coronary bypass grafting the blood product requirement is less compare to coronary artery bypass grafting using CPB machine which is statistically significant (group A 30 unit vs. group B 12 unit p =0.0001) (Table 2).

Patients undergoing CABG with CPB more often arrived at the intensive care unit receiving inotropic support compared with those having OPCAB (group A 46.85 ± 32.90 vs. group B 26.42 ± 21.47 p = 0.002); however, inotrope use after operation did not associate with AKI. Post-operative ventilation hours, ICU stay and hospital stay were less in OPCABG patients compare to CABG patients using CPB machine (Table 3). No significant difference in serum Cr or blood urea were detected between the groups during the study period with both parameters staying within the normal range throughout (Table 3).Table 4 displays serum creatinine data and its comparison with preop and post op and its percentage increase which was statistically non-significant.

Table 1. Demographic and preoperative findings

Variables	ONCABG (N=40) 1	OPCAB (N=40) 0	p value
Age (year)	58.25 ± 8.05	55.55 ± 9.81	0.183
Sex	M=31 F=9	M=35 F=05	
Height (cm.)	161.75 ± 7.42	161.05 ± 7.76	0.942
Weight (kg)	61.65 ± 9.46	60.75 ± 9.69	0.676
DM (no of pts.)	15	15	0.817
HTN (no of pts.)	18	16	0.821
BSA (m^2)	1.63 ± 0.155	1.64 ± 0.159	0.783
Pre op Creatinine (mg/dl)	1.0± 0.25	0.90 ± 0.17	0.53
Pre op Creatinine Clearance (ml/min)	71.91 ± 20.60	78.40 ± 22.11	0.179
Pre op Urea (mg/dl)	30.42 ± 17.79	26.57 ± 9.42	0.230
Pre op LVEF (%)	43 ± 7.82	42.87 ± 7.91	0.944

DM: Diabetes Mellitus, HTN: Hypertension, BSA: Body surface area, LVEF: Left ventricular ejection fraction

Table 2. Operative and postoperative parameters

Variables	ONCAB (N=40) Mean ± SD	OPCAB (N=40) Mean ± SD	p value
Blood products (/unit)	30	12	0.0001
Graft	3.17 ± 0.71	2.9 ± 0.63	0.074
Post op serum Creatinine (mg/dl)	1.17 ± 0.31	1.07 ± 0.26	0.125
Post op serum Creatinine clearance (ml/min)	62.81 ± 21.47	67.31 ± 20.44	0.340
Post of LVEF (%)	44.75 ± 7.75	44.37 ± 6.99	0.821
Post op Urine output (ml/kg/hr)	1.11 ± 0.38	1.02 ± 0.36	0.277

LVEF: Left ventricular ejection fraction

Table 3. Postoperative parameters

Variables	ONCAB (N=40) Mean ± SD	OPCAB (N=40) Mean ± SD	p value
Post op serum creatinine (mg/dl)			
Post op day1	1 ± 0.24	0.90 ± 0.19	0.058

Post op day 2	1.09 ± 0.31	0.98 ± 0.24	0.093
Post op day 3	1.03 ± 0.34	0.94 ± 0.26	0.193
Post op urea (mg/dl)			
Post op day1	34.63 ± 13.67	29.32 ± 12.55	0.075
Post op day 2	46.0 ± 32.85	35.27 ± 15.75	0.065
Post op day 3	40.92 ± 18.55	33.69 ± 14.26	0.054
Inotrope duration (hrs.)	46.85 ± 32.90	26.42 ± 21.47	0.002
Ventilation (hrs.)	13.70 ± 17.93	6.35 ± 3.53	0.013
ICU stay (days)	4.57 ± 1.94	3.90 ± 1.21	0.067
Postop hospital stay (days)	8.85 ± 4.24	7.27 ± 1.90	0.035

Table 4. Serum Creatinine Concentration in Patients with Renal Dysfunction

Variables	ONCAB (N=40) Mean ± SD	OPCAB (N=40) Mean ± SD	p value
Pre op Creatinine (mg/dl)	1.00 ± 0.25	0.90 ± 0.17	0.53
Post op serum creatinine (mg/dl)	1.17 ± 0.31	1.07 ± 0.26	0.125
Differences	0.168 ± 0.29	0.16 ± 0.25	0.926
Percentage increase	26.71 ± 21.45	24.16 ± 22.63	0.125
Incidence of AKI (no. of pts.)	6	7	1.00

AKI: Acute kidney injury

DISCUSSION

Choice of operative technique in CABG is very much important in view of postoperative AKI. Our study fail to demonstrate superiority of beating CABG compared to on pump CABG in view of AKI. Our analysis supports that in a low-risk population, CABG via ONCAB is not associated with increased incidence of postop AKI as defined by markers of AKI. Several trials have demonstrated a change in surrogate markers of RD such as creatinine clearance, fractional excretion of sodium, microalbuminuria, and N-acetyl glucosaminidase activity in favour of OPCAB versus ONCAB [7, 10]. We have not measured surrogate markers but we have concentrated more on increase in postoperative s. cr > 1.5 times baseline or o.3mg increase in 48 hour. Using this definition, however, the present study did not reveal a benefit of OPCAB over ONCAB with respect to postoperative renal function.

Major contributing factor to the development of postoperative AKI is perioperative renal ischemia. The association between markers of compromised renal perfusion and adverse renal outcome has been well demonstrated in the literature and in clinical practice [6, 11, 12]. AKI may occur due to imbalance of the medullary oxygen supply-demand relationship. This asymptomatic "renal ischemia" may be elicited during the course of CABG and other major surgical procedures.

An observational study by Nanette *et al.,* [13]. suggest that choice of operative technique (OPCAB versus CABG) is not associated with reduced renal morbidity. The ONCAB group comprised 119 patients and the OPCAB group 220 patients total of 339 patient. In this study 18 (8.2%) of 220 OPCAB patients versus 12 (10%) of 119 ONCAB patients (p = 0.55) developed postoperative RD. So type of operation did not associate with the presence of postoperative RD.

An observational study by Ascione *et al* [14] of patients with preoperative renal insufficiency (preoperative creatinine >1.7 mg/dL) shown a statistically significant increase in isolated 12-hour postoperative serum creatinine in 3250 ONCAB when compared with 51 OPCAB patients. The reasons those results differ from the current results may include differences in the Cr-Pre, the small sample size of OPCAB compared to ONCAB and potential differences in European and Indian populations.

Results of the current study deserve particular attention because of good sample size, randomize controlled trial and all patients received complete revascularization by single proficient and experienced surgeon and population studied is representative of Indian tertiary care hospital.

In another small randomized trial of 40 low-risk patients [15] found similar increases in sensitive indicators of renal tubular injury and glomerular dysfunction, after both OPCAB and CABG. Although none of these randomized low-risk patients developed postoperative creatinine abnormalities. Data in the current study confirm the results of Tang *et al*. [15] and suggest that of CPB does not increase renal morbidity for patients with normal preoperative renal function undergoing CABG.

Pros and Cons

It is well known fact that Cardiopulmonary bypass activate inflammatory responses including the complement, coagulation, fibrinolytic, and kallicrein cascades. This will lead to increased capillary permeability, accumulation of interstitial fluid, leukocytosis, and organ dysfunction [16, 17, 18]. Free plasma hemoglobin, elastase and endothelin, and free radicals including superoxide, hydrogen peroxide, and the hydroxyl radicals may be generated during CPB

and may determine injury in the renal brush-border membrane. Nonpulsatile flow, inadequaterenal cell perfusion, hypothermia and duration of CPB are also thought to have adverse effects on renal function [19, 20, 21].

Although there is some beneficial effect of hemodilution on blood viscosity and improved renal plasma flow following pump priming [22] and the use of mannitol in the prime in the on-pump group. This will help to maintain glomerular capillary pressure and prevent tubular obstruction, protect against free radical induced injury to kidney, decrease ischemia-induced protein leakage across kidney vessel walls, and reduce plasma hydrogen peroxide free radicals [23].

OPCAB is beneficial due to its constant pulsatile perfusion causing less inflammation and decrease embolic load. Although CPB is a state of controlled shock, OPCAB is not exception to this. There are transient but frequent and significant periods of low cardiac output and global hypoperfusion during OPCAB. It is well established that cardiac output and thus organ perfusion can be temporarily compromised with different manoeuvres employed to optimize exposure of target vessels on a beating heart [24]. The 'vertical heart Position'adopted for grafting the obtuse marginal and distal circumflex territory in particular can cause a significant decrease in cardiac output. Therapeutic steps such as increasing preload with intravenous fluid or autotransfusion (Trendelenberg posture) and inotropic and vasoconstrictor support can be taken to prevent major cardiovascular downturns and maintain haemodynamic stability. Overall effects of these brief and otherwise insignificant episodes of hypoperfusion may result in ischaemic renal injury comparable in magnitude to that produced by CPB. These factors may attenuate any benefits of avoiding CPB. Demonstration of this effect would require a continuous cardiac output monitoring device with real-time measurement capability with thermodilution pulmonary artery catheters which was not done in our study. Alternatively, each technique either OPCAB or ONCAB may cause AKI by its unique mechanism, with resultant similar aggregate rates.

Though incidence of AKI is similar in both the groups there are some variable which differ. Inotrope support duration is longer in on pump CABG group. The ischemia imposed by aortic cross-clamping can result in considerable myocardial stunning, which is a condition of prolonged reversible postischemic ventricular dysfunction of viable myocardium that follows reperfusion and which may exacerbate preexisting irreversible ventricular dysfunction [25]. Several factors, including microemboli, reperfusion injury, chest closure, incomplete rewarming, and hemodilution, have been suggested to explain the observed decline in cardiac function postoperatively. In an analysis of data from several previous studies, Royster [26] presented an interesting composite figure that showed a decline in ventricular function immediately after CPB as compared with preoperative values with a consistent early (after CPB) improvement in systolic myocardial performance, reaching the preoperative level 1 to 2 hours after CPB.CPB can lead to excessive fibrinolysis persisting for up to 2 hours after surgery. Hypothermia and prolonged pump time were also considered to aggravate hyperfibrinolysis [27-30]. Hemodilution causes platelet counts to decrease rapidly to about 50% of preoperative levels soon after starting CPB. Platelet dysfunction appears to be dependent on contact of platelets with the synthetic surfaces CPB circuit. Within minutes after starting CPB, the bleeding time (BT) is prolonged significantly and platelet aggregation to adenosine diphosphate (ADP) or collagen is impaired [31-33]. This all factor cause increase in consumption of blood product in ONCAB surgery. Even ventilation hour, ICU and hospital stay is longer in ONCAB compared to OPCAB because of above factor.

CONCLUSION

The choice of operative technique OPCAB versus ONCABG is not associated with reduced renal morbidity. But still OPCAB is more favorable with low ICU and hospital stay.

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