



# ASSOCIATION OF POSITIVE INTRAOPERATIVE FLUID BALANCE WITH IN-HOSPITAL MORTALITY, IN DIABETIC PATIENTS UNDERGOING ELECTIVE CORONARY ARTERY REVASCULARIZATION; A RANDOMIZED CONTROLLED TRIAL

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## ABSTRACT

**OBJECTIVE:** To evaluate association of intra-operative fluid balance with in-hospital mortality in diabetic patients undergoing elective coronary artery revascularization.

**METHODS:** 100 diabetic patients, 35-65 years of age, undergoing coronary artery revascularization from December 2009 to December 2012 were included. They were divided into two groups, Group A had patients with positive fluid balance and Group B had patients with either normal or negative fluid balance. All operations were assisted by first two authors. These patients underwent cardiopulmonary bypass and their input output balance and Hct post CPB was measured along with any blood transfusions peri-operatively. In ICU patients were again monitored for transfusion of blood products. Patients were then divided into two groups, Group A received transfusion while Group B did not. P-values < 0.05 were considered as significant for all tests.

**RESULTS:** Out of hundred patients; (38%) patients had positive fluid balance, while (62%) had normal/negative fluid balance. Out of 38 positive fluid balance patients undergoing CABG twenty three patients were >61 years of age. The CPB time was >101 min in 35 patients, while cross clamp time was >101 min in 9 patients. Hct being >45% after CPB in 10 patients and found prolonged (>21 days) postoperative hospital stay in 32(84.2%) patients. The frequency of whole blood and packed cell volume were less in positive fluid balance group than normal/negative fluid balance group, showed insignificant association between blood transfusion and positive fluid balance as P-value < 0.05. A total of 10(26.3%) patients died during the study, only 2 belonged to the group of patients who were transfused. It was noted that all deaths were found in patients having positive fluid balance.

**CONCLUSION:** Positive fluid balance has high mortality rate in diabetic patients undergoing CABG.

**KEYWORD:** Coronary Artery Bypass, Positive Intraoperative Fluid Balance, Blood Transfusion

## INTRODUCTION:

Cardiac surgery is the largest consumer of blood products. Blood transfusion is associated with increased morbidity and mortality<sup>1,2</sup>. Reduction of blood transfusions is considered a relevant, important goal in cardiac surgery because of association of amount of transfusion and the adverse outcomes<sup>3</sup>.

Blood loss and red blood cell dilution due to positive fluid balance occur during CPB in cardiac surgery<sup>4</sup>. They result in steep drop in hematocrit and need for blood transfusion. Hemodilution has been identified as a major factor influencing the

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decision to transfuse. Likewise, several variables associated with total red cell mass, such as pre-operative anemia, female gender and small body size, advanced age, antiplatelet or antithrombotic drugs, complex procedures or emergency operations, and non cardiac patient co morbidities, are independent predictors of transfusion in cardiac surgery<sup>5-8</sup>. Existing guidelines depict the importance of limiting hemodilution, applying blood salvage techniques and using alternative therapies for transfusion and blood conservation<sup>7</sup>. Nevertheless despite its worldwide approval, the application of conservation or alternative therapies for transfusion has been slow<sup>9,10</sup>. It seems that in order to change practices, appropriately designed clinical trials are still needed to determine the relative effectiveness of different interventions<sup>11</sup>.

Unfortunately, data on the impact of intraopera-

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tive parenteral fluid administration on mortality in diabetic patients undergoing CABG are very limited. We designed this study because fluid balance is a modifiable variable, and secondly it is observed that when patients with diabetes are put on CPB the hematocrit reduces which is a risk factor for positive fluid balance. Thus the aim of the study was to evaluate the association of intraoperative fluid balance with mortality in diabetic patients undergoing elective coronary artery revascularization.

### **MATERIALS & METHODS:**

This prospective study was conducted at department of cardiac surgery, Punjab Institute of Cardiology from December 2009 to December 2012. One hundred consecutive diabetic patients age range 35-65 years, undergoing elective CABG on Cardiopulmonary bypass (CPB) were included in the study after informed consent. All operations were assisted by first two authors.

Exclusion criteria were emergency or re-do operations, recent administration of Streptokinase or other thrombolytic medications, pre-existing hematologic disease or coagulation abnormality, advanced cirrhosis, renal failure, preoperative blood product transfusion & combined cardiac and carotid surgery.

In our institute the preoperative blood component stocking and preparation for cardiac surgical patients is performed in such a way that the cross-matching of a large number (6 or more) of blood transfusion are done a day before the operation. Only two unit of whole blood are banked before the operation and the rest of blood donors are awaited till the need of transfusion arises.

All patients received routine anesthesia and intraoperative care, and were operated by the same team with CPB and cross clamping of ascending aorta. Acute normovolemic hemodilution and retrograde autologous priming of the CPB circuit were not used in any patient. No pharmacologic agent was used to decrease blood loss in cardiac surgery (such as aprotinin, aminocaproic acid or tranexamic acid). The aspirin clopidogrel were discontinued at least 72 hours before surgery in all cases.

The CPB pump and circuit were primed depending on patient height and weight. Anticoagulation level was achieved with heparin 3IU/ml of primed solution and CPB was started when the ACT reached > 400 sec. Pump flow was maintained at 1.8-2.5 liter/min/m<sup>2</sup>. Patients were operated under hypothermia down to 28-32°C.

In order to monitor patients fluid balance status, monitoring was performed with CBC, ABGs, Hct, Hb% and Oxygen saturation. All patients received intermittent antegrade cold blood cardioplegia. The cardioplegia solution is made from the patients' blood received in CPB. After preparation the cardioplegic solution is handed over to Anesthetist in pneumatic pressurized infusion bag for delivery during aortic cross clamp.

After grafting and then weaning from CPB, protamine 3 mg/kg was given intravenously to neutralize the total dose of heparin. Remaining CPB circuit blood together with blood saved from the operation field was re-transfused, if needed.

After weaning from CPB and re-transfusion of salvaged blood, patients were transfused for hematocrit  $\leq 24\%$ , for hemostasis or on surgeon's decision. In the ICU, patients were transfused for hematocrit  $\leq 24\%$ , while transfusion decisions for hematocrit values between 24-30% were evaluated in a multimodal manner.

Postoperatively all patients were admitted to the ICU. The input / output status, post CPB hematocrit and patients weight on 1st postoperative day, were taken as predictors of positive fluid balance. Patients were categorized on the basis of any of following positive findings; > 500ml positive fluid balance in last 24 hours, HCT < 26 and change in weight of > 2kg. Patients were transferred to the ward when their clinical condition and laboratory findings were acceptable. Except for the two authors, the surgeons, their assistants, perfusionists and ICU personnels were not informed about the study. At the end of study date, all data was divided into two groups viz Group A (positive fluid balance) and Group B (normal/negative fluid balance) respectively.

Group Data was analyzed using SPSS (Statistical Package for Social Sciences) Version 20.0 for Window. Frequencies and percentages were given for qualitative variables. Chi square test and Fisher exact test (if cell frequency was less than 5) was applied to observe the association of the qualitative variables with both groups (positive fluid balance verses normal/negative fluid balance), while for quantitative variable independent t test was applied. P-value  $\leq 5\%$  was considered as significant. All tests applied were two tailed.

### **RESULTS:**

The study included 100 patients who underwent isolated coronary artery bypass graft surgery, (38%) patients had positive fluid balance, while (62%) had



**Table-I: Descriptive and Inferential statistics of the patient characteristics with respect to Positive fluid balance.**

Variables		Fluid Balance		p-value
		Positive (n=38)	Normal/negative (n=62)	
Age (yrs)	40-50	3(7.9%)	23(37.1%)	0.001
	51-60	12(31.6%)	39(62.9%)	
	>61	23(60.5%)	0	
Weight (Kg)	50-70	3(7.9%)	17(27.4%)	0.048
	71-90	13(34.2%)	17(27.4%)	
	91-100	19(50%)	22(35.5%)	
	>101	3(7.9%)	6(9.7%)	
Flow Rate (L/Min/m <sup>2</sup> )	<1.8	0	27(43.5%)	0.001
	1.81-2.2	28(73.7%)	21(33.9%)	
	>2.3	10(26.3%)	14(22.6%)	
CPB Time (min)	1-30	0	1(1.6%)	0.001
	31-60	0	22(35.5%)	
	61-100	3(7.9%)	15(24.2%)	
	101-150	20(52.6%)	17(27.4%)	
	>151	15(39.5%)	7(11.3%)	
Cross Clamp time (min)	1-20	0	15(24.2%)	0.001
	21-40	0	11(17.7%)	
	41-60	20(52.6%)	24(38.7%)	
	61-100	9(23.7%)	2(3.2%)	
	>101	9(23.7%)	10(16.1%)	
HCT at-terCPB	21-26%	0	12(19.4%)	
	27-35%	4(10.5%)	35(56.5%)	
	36-45%	24(63.2%)	10(16.1%)	
	>45%	10(26.3%)	5(8.1%)	
Hospital Stay (days)	<5	0	19(30.6%)	0.001
	5-10	0	19(30.6%)	
	11-20	6(15.8%)	18(29%)	
	>21	32(84.2%)	6(9.7%)	
Transfusion	Transfused	14(36.8%)	36(58.1%)	0.039
	Not Transfused	24(63.2%)	26(41.9%)	
Transfusion (types)	whole blood	8(21.1%)	28(45.2%)	0.007
	Packed Cell volume	0	5(8.1%)	
	Plasma	6(15.8%)	3(4.8%)	
	Not Transfused	24(63.2%)	26(41.9%)	
Units transfused		0.79±1.255	1.31±1.275	0.051
Mortality		10(26.3%)	0	0.001

normal/negative fluid balance.(Table-1)

Positive fluid balance patients were found to be older (more than 60 years of age) as 23(60.5%), were more likely to be over weight (more than 90 kg) as 19(50%). Cardiopulmonary bypass time and aortic cross-clamp time (more than 100 minutes) were found to be higher in positive fluid balance patients and found prolong (>21 days) postoperative hospital stay in 32(84.2%) patients. The frequency of whole blood and packed cell volume were less in positive fluid balance group than normal/negative fluid balance group. while Postoperative mortality was found to be higher in (group A) positive fluid balance as compared to

(group B) normal/negative fluid balance group as (26.3% vs. 0%).

## DISCUSSION:

Perioperative edema has long been linked with increased mortality and can result in injury to many organs, including the heart, lungs, and brain. Edema acquired during CPB may contribute to this mortality. Similarly the blood and its products are frequently transfused in patients undergoing cardiac surgery of all varieties, adding to the positive fluid balance. Coronary revascularization is the most frequent cardiac surgical operation and the mean number of transfusion in CABG ranges from 0 to 6.3 units per patient, and the frequency of transfusion ranges from 16% to 100%<sup>12</sup>. However, reduction of blood transfusions calls an important achievement for every surgical procedure recently and so is true in the domain of cardiac surgery. Transfusion practices vary between institutions and surgeons<sup>7</sup>.

Looking at other side of picture, low haematocrit level on CPB (<24%), is independently associated with stroke, myocardial infarction (MI), renal failure, prolonged ventilation, sepsis, reoperation due to bleeding<sup>6,13,14</sup>. Knowing these morbidity and mortality risk factors the surgeons usually have lesser threshold for transfusion<sup>15-17</sup>. To compensate this there should be certain methods and techniques which can lead to a decrease of haemodilution aiming at fewer transfusions in such operations. Considering volume load as modifiable factor, a number of efforts have been made to reduce the resulting positive fluid balance under CPB, like miniaturizing the circuit size, aspirating mediastinal blood and transfusing residual CPB blood back to patients circulation<sup>18-20</sup>. The fluid balance on CPB should be carefully monitored and measured and the Anaesthetist, Cardiac perfusionist and surgeons, should strive to achieve a zero or negative fluid balance without reaching on the native reservoir fluid. This goal is achievable in majority of cases. A positive fluid balance should be avoided if possible until it is beneficial in specific situations. However, a positive fluid balance may mark a decreased cardiac function leading to an increased mortality.

Toraman F et al<sup>21</sup> found that hypertension, diabetes, chronic obstructive pulmonary disease, New York Heart Association (NYHA) Class III-IV, use of angiotensin converting enzyme (ACE) inhibitors, chronic renal failure, and female gender were the significant preoperative risk factors for



increased volume replacement during CPB. This study suggests that intraoperative volume overload increases blood transfusion and length of hospital stay in patients undergoing CABG. Our study was conducted purely on diabetic patients undergoing CABG on pump. However it supported the notion of Toraman F et al<sup>21</sup>, as there was increased hospital stay, increased blood transfusion requirements and increased mortality linked to Group A.

Both our study and that conducted by Grist<sup>22</sup> suggested that positive fluid balanced patients are more likely to be in higher risk categories, weighed more, and had longer pump times ( $p < .05$ ) with an adjusted odds ratio for mortality of 1.73 (1.01 - 2.96, 95% confidence interval). Grist et al<sup>22</sup> stated that circulatory failure during the weaning process demands substantial fluid resuscitation to wean from CPB, resulting in a positive fluid balance and thus correlated to an increased mortality rate. This supports our finding of maximum mortality in patients who had developed positive fluid balance post CPB.

Vretzakis G et al<sup>11</sup> published a randomized controlled trial involving 130 patients operated for CABG under CPB supported by reinfusion of washed shed blood from thoracic cavities, and reported significant reduction of intraoperative packed red cells transfusions with a restrictive parenteral fluid protocol. Patients in Group B, in

our study, were similarly dealt and were not given transfusion of blood products, thereby decreasing shift in fluid balance and thus mortality.

Scott et al<sup>23</sup> transfusion was used in 72.5% of on-pump patients compared with 45.7% of off-pump patients. Use of CPB, preoperative hematocrit  $< 35\%$ , female gender, increasing age ( $\geq 65$  years), and decreased body weight ( $\leq 83$  Kg) were significant predictors of transfusion. In our study, prolonged CPB time, and increasing age and increased weight were associated with the increased transfusion requirements and mortality.

In conclusion, our study depicts that the fluid overload perioperatively is associated with higher mortality rate in diabetic patients who undergo Conventional on-pump CABG.

The limitations of this study were related to its non-standard blinding (no formal blinding, different anesthesiologists and perfusionist and primary surgeons, in different cases). The open nature of the operative area and use of sterile drapes and other spillage make the exact quantification of irrigation and blood loss difficult. In addition, lack of standardization with regards to intravenous fluid administration in group B (liberal fluids) is also a limitation.

#### **CONCLUSION:**

Patients with positive fluid balance had high mortality rate in diabetic patients undergoing CABG.



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