Original Article

Effect of Colloid versus Crystalloid Administration of Cardiopulmonary Bypass Prime Solution on Tissue and Organ Perfusion

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Background: We evaluated the effects of tissue and organ perfusion during and after coronary artery bypass graft surgery with either colloid (Voluven) or crystalloid (Lactated ringer's) as prime solution.
Methods: In this prospective randomized-controlled trial study, 70 patients undergoing on-pump coronary artery bypass graft surgery were randomly assigned to receive either colloid (Voluven) or crystalloid (Lactated ringer's) as prime solution, for initiation of cardiopulmonary bypass machine procedure. Tissue and organ perfusion markers including lactate, troponin I, liver and renal function tests and electrolytes were measured sequentially, before induction (T_1) to second days after surgery (T_5).
Results: With exception of chloride and potassium levels no significant differences detected in other measurements, and the laboratory results were entirely identical in both procedures.
Conclusion: There was no significant difference between Voluven® (hydroxyethyl starch, HES 130/0.4) and crystalloid (Lactated ringer's) as priming solution on the basis of organ and tissue perfusion tests assessment.

Key words: Prime, Colloid, Crystalloid, Lactate, Troponin, Hydroxyethyl Starch

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Introduction

Cardiopulmonary bypass (CPB) provides the extracorporeal maintenance of respiration and circulation at hypothermic and normothermic temperatures, despite its association with a number of profound physiological perturbations. The central nervous system, kidneys, gut, and heart are especially vulnerable to ischemic events associated with extracorporeal circulation.[1]

The heart-lung machine and the joined lines must be prepared before starting the cardiopulmonary bypass .Prime solutions are solutions which are used to prepare the extracorporeal perfusion line in cardiopulmonary bypass applications. Crystalloid (Ringer solution) as the base of prime solution is the classic method.[2]

The redistribution of circulation produces hypovolemia for which volume loading is necessary and which also takes advantage of the vasodilators by maintaining constant filling pressures. Colloid as well as crystalloid solutions are used for this purpose. As CPB is occasionally followed by capillary leaking, the qualities of the most preferable infusion solution are still being debated.[3]

Volume replacement is essential in the management of cardiac surgery patients. Different intravascular volume replacement regimens have been proposed for providing hemodynamic stability in this situation, including blood and its components (e.g., human albumin), synthetic colloidal (dextrans, gelatins, hydroxyethyl starch [HES]), or crystalloids (e.g.,Lactated Ringer's solution). Various modifications of approved HES have different molecular weights (MWs) (450 kd, 200–260 kd, and 70 kd) and degrees of substitution (DSs) (0.7, 0.62, and 0.5). HES with an intermediate MW (130 kd) and a very low DS (0.4) has been developed that has already been approved in several countries for treating hypovolemia.[4]

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Plasma volume expansion is essential during cardiac surgery. To achieve this main object, colloids may be preferred to crystalloids, because they more effectively increase blood volume and, subsequently, cardiac output.[5]

Hydroxyethyl starches (HES) have the advantage of a higher plasma-expanding effect and an infrequent incidence of allergic reactions, but they have more pronounced effects on hemostasis.[6]

Effects on hemostasis appear to be related to their specifications, a new HES with a lower in vivo molecular weight (HES 130/0.4) has been introduced. This new synthetic colloid appears to have fewer effects on hemostasis. HES with molecular weights (MWs)/degrees of substitution (DSs) of 130/0.4 up to 50 ml/kg were associated with blood loss in patients undergoing cardiac surgery with CPB. This may indicate that HES 130/0.4 should be preferred to HES 200/0.5 for plasma volume expansion in cardiac surgery patients [7], especially for use in priming solutions where we rarely need to add more than 20-25 ml/kg of fluids to circulatory system.

On the other hand, Verheij and colleagues demonstrated that in acute lung injury (ALI) saline or colloids, do not affect permeability, provided that fluid overloading is avoided, except for HES which may prevent increased permeability.[8]

Further investigations demonstrated, in vitro and in vivo, that hemodilution with 0.9% saline and other crystalloid solutions caused enhanced coagulations as measured using thrombelastograph analysis and routine coagulation studies. Their finding showed a hypercoagulable state after surgery in the control (saline) group, and insignificant change in the Hydroxyethyl starch group, given that patients undergoing vascular surgery may be at an increased risk of coagulations especially intra-arterial coagulation. Crystalloids for rapid fluid loading in vasculopathic patients undergoing surgery is improper.[9]

The technique of cardiopulmonary bypass is important to maintain systemic perfusion and oxygenation during coronary artery bypass grafting and open heart operations. Nevertheless the effect of cardioplegic arrest, hypothermia, aortic cross clump, reperfusion state and stress responses are complex and not fully elucidated.[10]

Tissue perfusion and oxygenation during CPB is achieved by adjusting flow rate, temperature, gas flow, priming content and hemoglobin to maintain oxygen delivery.

The elevated blood lactate levels associated with metabolic acidosis are common among critically ill patients with systemic hypoperfusion and tissue hypoxia. Lactate production results from cellular metabolism of pyruvate into lactate under anaerobic condition. Therefore, blood lactate level in type A lactic acidosis is related to the total oxygen debt and the magnitude of tissue hypoperfusion.[10, 11]

Global or regional alterations in the metabolic status of the myocardium occur during cross-clamp time and reperfusion.[12]

One of the most sensitive markers of inadequate preservation of the myocardium is the creation of myocardial tissue acidosis and increment of lactate level of serum.[13] Therefore, the evaluation of myocardial metabolism during cardiac surgery allows the investigator to quantify the degree of physiologic impairment.

Likewise, incomplete myocardial protection is responsible for blood elevation of troponin I. Troponin I has been shown to be a specific marker of myocardial damage, with a higher sensitivity and specificity; moreover, recent reports have defined postoperative troponin I as a sensitive marker of the quality of myocardial protection and of prognostic value for cardiovascular events at follow-up.[12]

Also the next strong predictor of cardiovascular events and death is the estimated glomerular filtration rate (eGFR). Renal dysfunction, even when relatively mild, is an important determinant of outcome after CABG and that discriminatory measures such as eGFR may be of particular value in risk stratification.[14] This collation was done considering that HES, compared to albumin and fresh frozen plasma (FFP) is the best colloid at lowest prices and its ability to modify hypercoagulable state. In addition it diminishes effect on permeability in acute lung injury.

Also this study assessed whether substitution of other priming fluid for HES (130/0.4) significantly affects postoperative perfusion of tissue and major organs by determination of lactate, Troponin, hepatic and renal function tests.

Patients and Methods

This study was carried out after approval by the Anesthesiaology Research Center of Shiraz University of Medical Sciences and obtaining written consent from the patients under study. This was a randomized prospective investigation and included seventy patients younger than 75 years of age. The patients scheduled for elective CABG surgery by using CPB and those with renal or hepatic insufficiency (serum createnin>1.3mg/dl,

ASTandALT>2.5×normal), low ejection fraction (EF<25%) and reoperation were excluded. The patient with autoimmune diseases, cardiogenic shock, cardiac arrest and myocardial infarction during 10 days before operation were also excluded. The patients who needed DC shock or intraaortic ballon and whose pump time took more than 80 minutes were also excluded from the study.

Patients were pretreated with intra muscular morphine (0.05-0.1 mg/kg) 1 h before anesthesia. Upon arrival in the operating room five leads ECG were attached, and leads II and V5 were continuously monitored. A 20 G radial artery catheter was inserted for continuous monitoring of arterial pressure. Central venous pressure catheter (ARROW® –Germany) was inserted into the right internal jugular vein before induction of anesthesia. Nasopharyngeal temperature probe was inserted (mode of monitor: DATEX.OHMEDA®S/5-Finland). A standardized anesthesia protocol was used for all patients. The anesthetic drug doses were calculated according to body weight, and anesthesia was induced with midazolam 0.03-0.05 mg/kg, sufentanil 1.5-2.0 mcg/kg , and sodium thiopental 1-2mg/kg. Pancruniom bromide 0.15 mg/kg was administered to facilitate tracheal intubation. Anesthesia was maintained by continuous infusion of propofol 50-150 mcg/kg/min and remifentanil 0.1-1.0 mcg/kg/min.

All patients underwent standard median sternotomy. Heparin (300U/kg) was given for anticoagulation before CPB. CPB was introduced by arterial cannulation from the ascending aorta and by two stage venous cannulation from the auricle of the right atrium. Cardioplegia cannula was positioned into the root of the aorta and cardioplegia was given to all the patients through antegrade way. To begin the CPB of 35 patients, by using a computer-generated randomization method, 1500 ml Ringer solution plus 200 ml mannitol 10% and 60 ml sodium bicarbonate 5%, containing 150 IU/kg heparin was used as the prime solution. On the other hand, to begin the CPB on the second group of 35 subjects , 1500 ml HES 130-0,4 , 200 ml mannitol 10% , 60 ml sodium bicarbonate 5% and 150 IU/kg heparin was used as the prime solution. At moderate hypothermia (32° to 34°C rectal temperature), pump flows on CPB were adjusted to maintain a mean arterial pressure of more than 50 mm Hg and a flow rate of 2.2 L/min/m^2 body surface area. Intravascular volume replacement was managed with equivalent amount of crystalloid and colloid solutions to maintain a central venous pressure of 8-16 mmHg according to baseline values. There were no patients extubated in the operating room or within the first several hours after operation.

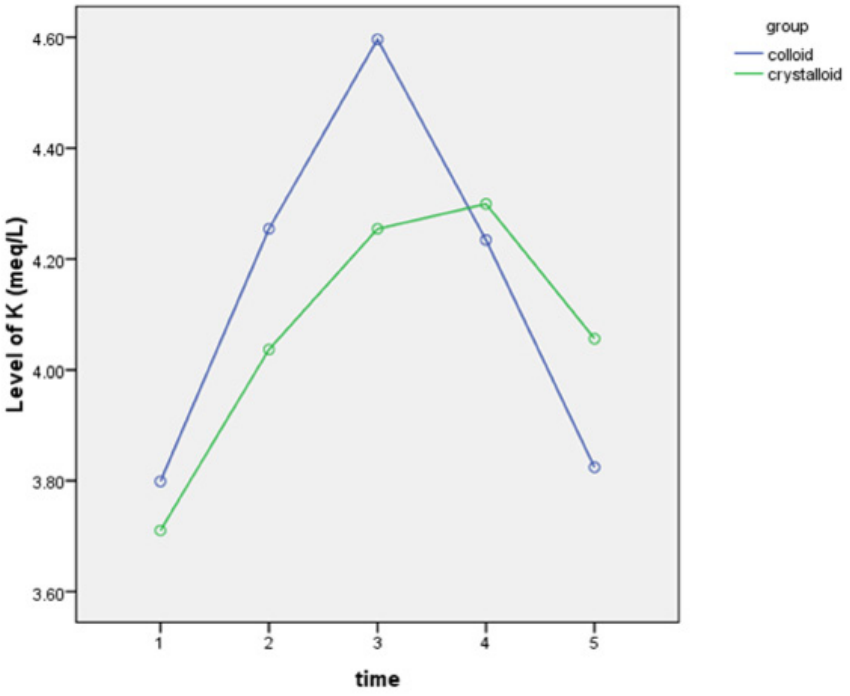

Figure 1. Trend of potassium level at different times of pre and post- intervention in the two groups of study

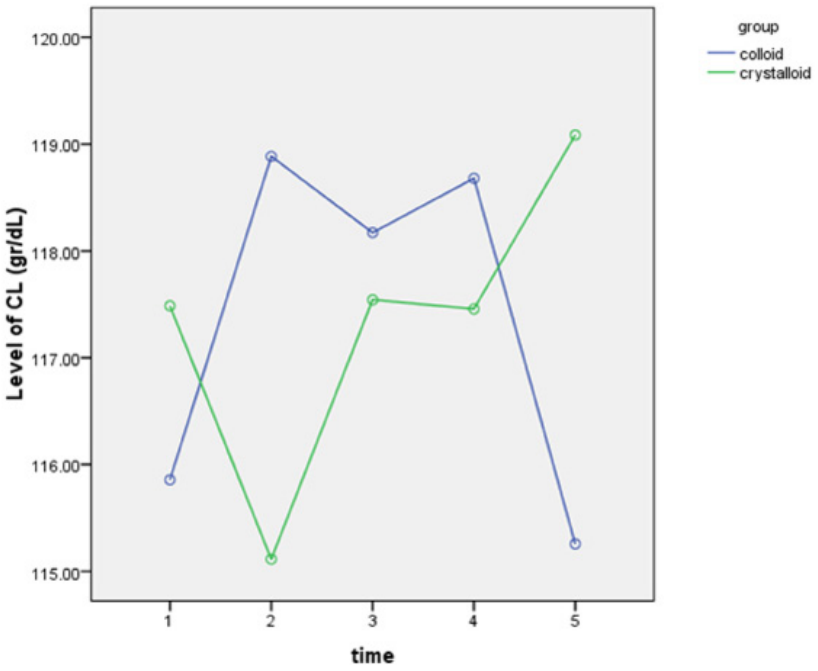

Figure 2. Trend of chloride level at different times of pre and post -intervention in the two groups of study

Level of lactate were determined before induction of anesthesia(T_1), 4hr (T_2), 12hr(T_3), 24hr(T_4), 48hr(T_5) after operation as a marker of tissue perfusion. In this manner serum levels of glucose, HCO3, Na, K, Cl, Ca and pH, were measured at these times (biosensor assay GEM Premier -3000-5700-US).

The Troponin-I (cTnI) level an index of myocardial ischemia were measured at T_1, T_2, T_3 and T_5 (by Troponin-I enzyme immunoassay test kit DP-10109), and level of SGOT, SGPT,PT, PTT, BUN and Createnine as indicators of hepatic and renal perfusion and coagulation state were determined at T_1, T_4, T_5 (by autoanalyzer–Response® 910 Germany) and Createnine clearance at T_1, and T_5. All samples were obtained through the arterial line and prepared immediately for biochemistry assays.

Statistical Analysis

Nominal data including sex, use of inotrop in operation room and intensive care unit, DM, chronic obstructive pulmonary disease (COPD), hyperlipidemia and hypertension for comparing between two groups were statistically analyzed using Chi- square test. The comparison of continuous data between groups (age, Body mass index, Ejection fraction, aortic clump time, CPB time, operation time, drainage of chest tube, and intubation time) were done with student's t- test (considering of variance equality with Leven test) and mann-whitney U test (for variables of blood transfusion in operation and ICU, and graft number that have not normal distribution). Experimental results are presented as arithmetic mean ± SD for continuous variables, and count and

Table 1. Distribution of demographic data in two groups of patients

Parameter		Colloid	Crystalloid	P value
Sex	F	9 (25.7%)	14 (40%)	0.203
	M	26 (74.3%)	21 (60%)	
DM	Y	9 (25.7%)	9 (25.7%)	0.999
	N	26 (74.3%)	26 (74.3%)	
COPD	Y	11 (31.4%)	12 (34.3)	0.799
	N	24 (68.6%)	23 (65.7%)	
Hyper-lipidemia	Y	26 (74.3%)	26 (74.3%)	0.999
	N	9 (25.7%)	9 (25.7%)	
HTN	Y	17 (48.6%)	15 (42.9%)	0.631
	N	18 (51.4%)	20 (57.1%)	
Age		57.4±9.3	57.6±9.0	0.917
BMI		24.4±3.9	25.3±3.4	0.306
EF		48.4±10.6	51.9±7.4	0.114

DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease; HTN: hypertension; BMI: body mass index; EF: ejection fraction

Table 2. Distribution of operative data in two groups of patients

Parameter		Colloid	Crystalloid	P value
Inotrop need (OR)	Y	22(62.9%)	21(60%)	0.806
	N	13(37.1%)	14(40%)	
Inotrop need (ICU)	Y	23(65.7%)	25(71.4%)	0.607
	N	12(34.3%)	10(28.6%)	
Clump time (minute)		34.86±7.67	37.05±9.41	0.288
CPB time (minute)		64.69±15.99	65.63±19.93	0.828
Operation time (hour)		3.64±0.48	3.69±0.63	0.75
ICU stay (day)		3.04±0.84	2.94±1.32	0.707
Hospital stay (day)		5.23±0.94	5.43±1.79	0.56
Intubation time (hour)		11±1.75	11.17±1.71	0.679
Graft number (median)		3	3	0.94[3]
Drainage (mL)		934.9±591.0	853.4±552.5	0.554

OR: operation room; ICU: intensive care unit

percent for nominal variables. Normal distribution of parameters was evaluated with one sample kolmogrov-smirnov test. Hemodynamic and inflammatory indices were analyzed according to repeated measurements. The tests of within-subject contrasts were done for break down the main effect and interaction. Contrasts were compared at each level of post-operation time (T2, T3, T4, and T5) to before operation (T1) across colloid or crystalloid therapy groups. Assumption of sphericity was violated in muchly test (P< 0.05) for levels of lactate, glucose, HCO3, Na, Cl, Ca, pH, SGPT, SGOT, BUN, Troponin and thus after adjustment of degree of freedom by correlation coefficient of Greenhouse . Gisser and Huynh- Feldt, average p-value of foregoing assumptions was reported. Such assumption was met for other independent variables. Statistical analyses were performed using SPSS version 16 software.

Results

In this study 70 patients (35 patients in colloid group and 35 subjects in crystalloid group) were assessed. Demographic and operative data of them are shown in Tables1 and 2. There were no statistical differences between groups regarding of measured parameters.

Table 3. Blood electrolyte levels at different times of pre and post- intervention in two groups of patients

Parameter		Time					P value
		T_1	T_2	T_3	T_4	T_5	
HCO3	Colloid	24.4±1.9	20.1±2.2	20.6±3.3	23.8±3.5	25.3±4.2	0.174
	Crystalloid	23.6±2.4	19.0±2.2	20.1±4.3	23.9±2.9	26.5±3.2	
Na	Colloid	136.4±3.1	138.1±3.1	138.8±5.7	140.1±4.8	138.2±4.9	0.127
	Crystalloid	137.0±2.6	139.0±3.7	141.4±5.9	140.3±5.3	137.3±5.4	
K	Colloid	3.8.±0.6	4.3±0.7	4.6±0.7	4.2±0.6	4.8±0.6	0.016
	Crystalloid	3.7±0.5	4.0±0.6	4.3±0.6	4.3±0.6	4.1±0.5	
Cl	Colloid	115.9±4.4	118.9±11.9	118.2±8.4	118.7±8.4	115.3±4.3	0.026
	Crystalloid	117.5±8.1	115.1±3.7	117.5±4.8	117.5±4.4	119.1±15.4	
Ca	Colloid	4.2±0.8	3.9±0.6	3.5±1.3	4.0±0.7	3.1±1.2	0.529
	Crystalloid	3.9±1.3	3.9±1.0	3.4±1.2	3.5±1.5	3.2±1.3	
pH	Colloid	7.5±0.1	7.4±0.1	7.4±0.1	7.3±0.5	7.5±0.1	0.279
	Crystalloid	7.5±0.1	7.4±0.1	7.3±0.1	7.4±0.1	7.4±0.1	
Glucose	Colloid	113.8±53.5	210.9±90.0	231.9±90.3	203.1±90.5	151.2±51.5	0.668
	Crystalloid	117.0±60.6	209.7±73.5	254.3±103.2	210.6±84.0	156.8±51.5	

Table4. Values of hepatic and renal perfusion markers at different times of pre and post-intervention in two groups of study

Parameter		Time					P value
		T_1	T_2	T_3	T_4	T_5	
Lactate	Colloid	1.13±0.59	3.47±2.22	4.61±3.23	3.89±3.22	3.89±3.22	0.506
	Crystalloid	0.91±0.53	2.86±1.64	4.57±3.16	2.86±1.95	1.84±0.98	
SGPT	Colloid	32.2±18.1	----------	----------	30.8±15.8	31.9±15.8	0.516
	Crystalloid	31.5±16.9	----------	----------	28.7±14.3	27±12.4	
SGOT	Colloid	29.9±14.5	----------	----------	50.3±23.8	48.4±24.9	0.731
	Crystalloid	28.9±15.8	----------	----------	53.8±38.7	51.3±36.0	
PT	Colloid	12.8±1.1	----------	----------	13.4±1.1	13.1±1.1	0.132
	Crystalloid	12.8±1.3	----------	----------	13.6±1.4	13.7±1.2	
PTT	Colloid	34.6±6.4	----------	----------	45.4±13.0	40.4±151	0.557
	Crystalloid	34.9±5.8	----------	----------	38.7±10.0	37.9±7.6	
Troponine	Colloid	0.04±0.08	0.45±0.58	1.89±4.3	----------	1.61±2.37	0.741
	Crystalloid	0.01±0.04	0.40±0.61	1.33±2.52	----------	1.35±2.71	
Createnine	Colloid	0.96±0.18	----------	----------	1.25±0.35	1.15±0.37	0.168
	Crystalloid	1±0.15	----------	----------	1.15±0.37	1.21±0.45	
BUN	Colloid	15.6±6.3	----------	----------	18.3±6.7	22.5±8.3	0.544
	Crystalloid	19.0±6.8	----------	----------	19.9±6.9	24.1±10.1	
Createnine Clearance	Colloid	81.7±25.9	----------	----------	----------	70.8±26.2	0.706
	Crystalloid	73.3±17.9	----------	----------	----------	64.2±21.8	

Post-operative data Intention-to-treat analysis for length of stay in ICU (P=0.707) and hospitalization (P= 0.506) showed no significant differences between the colloid and crystalloid treatment groups (Table 2).

As shown in Table 3, there was a significant difference between the kind of fluid therapy and potassium levels of patients (P= 0.016). Also the mean differences in T5 and T1 differed significantly between the two groups (P=0.032) (Fig. 1).

Chloride level of patients was also affected by the kind of fluid therapy (P= 0.026), and as demonstrated in Table 3, the mean differences between T2 and T1 were significantly different between the two groups (P= 0.04) (Fig. 2).

However, there were no significant differences in the kind of fluid therapy between the levels of other independent variables (Table 4).

The values of T1 and T5 for createnin clearances in crystalloid and colloid group were 18.05±3.06 and 9.07±3.64 respectively, which were not significantly different (P=0.706) between the two groups (Table 4).

Discussion

The type of fluids used for priming solution is still a topic of much debate.

Volume replacement with colloids is considerably more expensive than with crystalloids. Clinical studies demonstrated that colloids and crystalloids have different effects on physiological measurments. The use of hypo-oncotic priming solution causes myocardial edema, and crystalloid volume loading may lead to a vicious cycle as lowered compliance necessitate higher filling pressure to preserve the same function. On the other hand hyper-oncotic colloid solution may have dried the patients' extracellular spaces to an extent that causes considerable vasopressin secretion.[3] The high molecular weight of gelatine solution remains largely intravascular, in contrast to the crystalloid fluids, which are mostly distributed in the interstitium, resulting in tissue swelling.

Progressive tissue edema which results in impairment of tissue oxygenation may be consequence of volume replacement with lactated Ringer's solution to maintain intravascular volume and cardiac output.

Capillary perfusion and tissue oxygenation were significantly depressed in lactated Ringer's haemodiluted animals, as a result of interstitial edema.[15] We hypothesized that persistent anaerobic metabolism, is a marker of inadequate intraoperative myocardial protection and may predict early post-

operative left ventricular dysfunction.[16] It is important to emphasize that the significance of lactate determination may be misinterpreted, especially when evaluated as an isolated parameter. However, when interpreted, in the context presented herein, in terms of sequential hemodynamic and oxygen transport data, lactate determination may be very useful both in assessing the degree of accumulated oxygen deficit, and in titrating therapy to support the necessary physiological compensations.[17] Epinephrine and other potent ß-adrenergic agonists may cause lactic acidosis and anaerobic glycolytic enzymes may be responsible.[18] For these reasons we also decided to test the predictive value of troponin I, because this is a relatively new available means of detecting myocardial ischemia. Troponin I, being superior to lactate, may allow investigators to quantify the degree of myocardial impairment immediately, especially during the reperfusion time. Isoform I of the troponins is only of cardiac origin. Intraoperative troponin I correlating with peripheral measurements at 12, 24, 48, and 72 hours, notifies the surgeon about the postoperative myocardial function.[12]

A worse outcome also has been reported in patients with renal dysfunction not requiring dialysis. These studies have concentrated on patients with moderately to severely elevated serum creatinine who were dichotomized on the basis of an arbitrary cutoff level. Serum creatinine now is generally accepted to be an insensitive indicator of renal function. In contrast, glomerular filtration rate (GFR), a more accurate measure, is recommended for this purpose and identifies patients with mild renal impairment despite normal or nearly normal creatinine levels.[14]

Recent data demonstrate that estimated GFR (eGFR) is a very powerful predictor of outcome in patients with acute myocardial infarction and is more useful in this respect than serum creatinine [14] We therefore, used eGFR in addition to net value of creatinine and blood urea nitrogen levels.

However, in this study same parameters were utilized for comparison of voluven as a colloid and lactated ringer as a crystalloid in priming solution.

The results obtained were entirely identical in the two groups with two exceptions: First, in contrast to the crystalloid group, there was an increase in chloride level at T_2 in relation to T_1. In the colloid group which may be important and due to high concentration of chloride in voluven solution (154 mMol/L).

We noticed obvious potassium level increment at T_5 in relation to T_1 in crystalloid group that may be due to presence of potassium compound in lactated ringer solution (0.030gnd, s/100ml).

When using a specific solution for resuscitation, one has to consider the possible side effects such as anaphylactic reactions, elevated bleeding tendency, increased tissue edema, alterations in immune function or renal dysfunction, which have all been reported for colloid solutions.[15] The use of voluven as colloid priming agent in the present study, did not result in such side effects.

The present study suffered from several limitations such as lactated Ringer's solution which contains lactate and metabolized by normal liver function.[15] In our study we cannot exclude some derangement of hepatic function leading to a decrease in lactate metabolism and to a secondary increase in lactate levels. Although performing the study in a single center is an additional limitation of our experiment, it provides uniformity in the peri-operative handling of the patient population throughout this investigation.

In summary, we conclude that HES (130/0.4) solution is an alternative colloidal priming agent in patients undergoing on-pump CABG. We believe that crystalloid and other expensive colloids can substitute for HES (130-0.4) solution without any detrimental effect on tissue and organ perfusion.

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