

A Prospective, Randomized, Comparison Study on Effect of Perioperative Use of Chloride Liberal Intravenous Fluids versus Chloride Restricted Intravenous Fluids on Postoperative Acute Kidney Injury in Patients Undergoing Off-pump Coronary Artery Bypass Grafting Surgeries

Abstract

Context and Aims: Off-pump coronary artery bypass graft (OPCABG) is a form of CABG surgery. It is performed without the use of cardiopulmonary bypass machine as a surgical treatment for coronary heart disease. Acute kidney injury (AKI) is one of the common postoperative complications of OPCABG. Previous studies suggest important differences related to intravenous fluid (IVF) chloride content and renal function. We hypothesize that perioperative use of chloride restricted IVFs may decrease incidence and severity of postoperative AKI in patients undergoing OPCABG. **Methods:** Six hundred patients were randomly divided into two groups of 300 each. In Group A ($n = 300$), chloride liberal IVFs, namely, hydroxyethyl starch (130/0.4) in 0.9% normal saline (Voluven), 0.9% normal saline, and Ringer's lactate were used for perioperative fluid management. In Group B ($n = 300$), chloride-restricted IVFs, namely, hydroxyethyl starch (130/0.4) in balanced colloid solution (Volulyte) and balanced salt crystalloid solution (PlasmaLyte A), were used for perioperative fluid management. Serum creatinine values were taken preoperatively, postoperatively at 24 h and at 48 h. Postoperative AKI was determined by AKI network (AKIN) criteria. **Results:** In Group A, 9.2% patients and in Group B 4.6% patients developed Stage-I AKI determined by AKIN criteria which was statistically significant ($P < 0.05$). **Conclusion:** Perioperative use of chloride restricted IVF was found to decrease incidence of postoperative AKI. The use of chloride liberal IVF was associated with hyperchloremic metabolic acidosis.

Keywords: Acute kidney injury, hyperchloremic acidosis, off-pump coronary bypass grafting

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Introduction

Off-pump coronary artery bypass graft (OPCABG) surgery is done on beating heart without using extracorporeal circulation (heart-lung machine). OPCABG has benefits such as reduced systemic inflammatory response, lesser renal dysfunction, reduced incidence of stroke and cognitive problems, lesser coagulopathy and blood transfusion requirement, reduced morbidity and mortality, reduced length of intensive care and hospital stay.^[1,2] OPCABG has shown overall improved outcomes compared to on-pump CABG.^[3,4]

AKI is one of the serious postoperative complications of OPCABG.^[5] Such AKI may affect long-term kidney function, may increase hospital stay, adds extra financial

burden to the patients and increase overall morbidity and mortality.^[6]

We administer intravenous fluids (IVFs) routinely in the perioperative setting. Some of the IVFs such as normal saline, hydroxyethyl starch (130/0.4) in 0.9% normal saline (Voluven) have higher chloride content which may cause hyperchloremic metabolic acidosis.^[7] Hyperchloremic metabolic acidosis may cause renal vasoconstriction and decrease in glomerular filtration^[8] which may lead to renal dysfunction.^[9] Recent studies,^[10,11] review articles,^[12] and meta-analysis^[13] have shown the use of chloride-restricted IVFs has been associated with reduced risk of renal dysfunction in surgical and critically ill patients. Above findings suggest perioperative IVF choice could be an important consideration for better preservation of postoperative renal function.

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Methods

After approval of Institutional Ethics Committee, study was undertaken on total 600 patients. Written informed consent was obtained from all patients. In study Group A ($n = 300$) chloride-rich IVFs such as hydroxyethyl starch (130/0.4) in 0.9% normal saline (Voluven - Fresenius Kabi, Deutschland GmbH, Germany) and 0.9% normal saline (Claris Otsuka Private Limited, Village-Vasana-Chacharwadi, Tal-Sanand, Ahmedabad, India) and ringer lactate (Claris Otsuka Private Limited, Village-Vasana-Chacharwadi, Tal-Sanand, Ahmedabad, India) were used for perioperative fluid management. In Group B ($n = 300$) chloride restrictive IVFs such as hydroxyethyl starch (130/0.4) in balanced salt solution (Volulyte - Fresenius Kabi, Deutschland GmbH, Germany) and balanced salt crystalloids (PlasmaLyte A, Baxter private limited, Gurgaon, India) were used for perioperative fluid management.

Adult patients of either gender aged between 40 and 70 years with estimated glomerular filtration rate (eGFR) of more than 60 mL/min/1.73 m², patients with triple vessel coronary heart disease, and the American Society of Anesthesiologist – II - III physical status were included in the surgery.

Patients with serum creatinine higher than 1.20 mg/dl in males and higher than 0.8 in females, emergency surgery, preoperative resting hypoxia (room air oxygen saturation [SpO₂] <90%), preoperative mechanical ventilation, body mass index (BMI) <18 or >30, age <40 or >70 years, ejection fraction < 45%, comorbid disease other than hypertension (HTN) and diabetes mellitus (DM), cardiovascular instability requiring cardiac support to maintain hemodynamic parameters within 20% of baseline perioperatively, intraoperative or postoperative respiratory dysfunction leading to partial pressure of carbon dioxide (PaCO₂) >45 mmg or requiring noninvasive ventilation, not able to maintain intraoperative or postoperative haemodynamic parameters within 20% of baseline, intraoperative or postoperative demise of patient due to other than renal function deterioration, preexisting known kidney disease or previous nephrectomy or previous renal transplantation were excluded from the study.

Sample size was calculated with two-tailed distribution. A total of 180 cases in each arm were required for effect size of 0.3 level of significance at 5%, power of 80%, and allocation ratio of 1:1. In our study, we had taken 300 patients in each arm. The sample size calculation was derived using software G* power 3.1.9.2. Continuous variables were assessed for the normality using Shapiro–Wilk test. If the variables were normally distributed, they were expressed as mean ± standard deviation otherwise median (interquartile range). All the categorical variables were expressed either percentage or proportion. Comparison of all the normally distributed variables was done by *t*-test or ANOVA. Comparison of

all the non-normally distributed continuous variables was done by Mann–Whitney U-test or Kruskal–Wallis H test. Categorical comparisons were done by either Chi-square test or Fisher’s exact test based on number of observations. Data analysis was carried out by Windows SPSS ver. 16.0. All $P < 0.05$ was considered as statistically significant.

All the patients were subjected to thorough preanesthetic check-up and written informed consent was taken from all patients. All the patients were premedicated with intramuscular morphine 0.1 mg/kg and promethazine 0.25 mg/kg. Under local anesthesia, 16G wide bore intravenous (IV) cannula and arterial line were inserted. General anesthesia induced with IV thiopental 5 mg/kg, IV fentanyl 5µg/kg and 50% nitrous oxide, and 1% sevoflurane in oxygen. Tracheal intubation was facilitated by IV rocuronium 1 mg/kg. After induction, all patients were secured with central venous line. Anesthesia was maintained with nitrous oxide and sevoflurane in oxygen, IV fentanyl infusion 2µg/kg/h, IV propofol infusion 1 mg/kg/h and muscle paralysis with IV rocuronium infusion 6µg/kg/min. Supplemental doses of IV midazolam 2.5 mg boluses were given accordingly. OPCABG was performed with median sternotomy and cardiac stabilization using myocardial stabilizer (Octopus II). IV heparin 2 mg/kg (100U = 1 mg) given at the beginning of graft harvesting and activated clotting time was maintained around 350s throughout the surgical procedure. After completion of anastomosis of all coronary grafts, heparin was reversed with IV protamine 1 mg for 1 mg of heparin by IV infusion. After the procedure, all patients were shifted to cardiothoracic intensive care unit for the further care and monitoring.

Monitoring consists of heart rate, invasive arterial pressure, SpO₂, 5 lead electrocardiogram, end-tidal carbon dioxide, central venous pressure, temperature, minimum alveolar concentration and end-tidal concentration of anesthetic gases, blood loss, and urine output. With above monitoring, hemodynamic parameters were maintained within 20% of baseline by titration of vasoactive drugs such as nitroglycerin, adrenaline, dobutamine, and noradrenaline infusion. There were brief periods of hypotension during positioning of the heart for grafting, which were reversed after repositioning of heart. Arterial blood gas analysis was done preoperatively 1 day before surgery, twice intraoperatively one after heparin injection as an anticoagulant agent in the beginning of surgery, and one after protamine injection for heparin reversal after the surgical procedure was over and postoperatively every 4th hourly as per hospital protocol. Serum creatinine concentration was determined at 24 h and 48 h postoperatively. All patients were electively ventilated 6–12 h postoperatively. They were extubated after they met extubation criteria. All the patients were given supplemental oxygen postoperatively through Hudson face mask.

Preoperatively, eGFR values were calculated by modification of diet in renal disease equation^[14]

$186 \times (\text{serum creatinine}/88.4)^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female})$.

We have taken serum creatinine values preoperatively, postoperatively at 24 h, and at 48 h of surgery. Perioperative change in kidney function assessed by acute kidney injury network (AKIN) criteria^[15] and compared between the study groups.

Acute kidney injury network classification

Stage 1 – increase creatinine 1.5 times from baseline or increase of >0.3 mg/dl within 48 h. Stage 2 – increase creatinine 2 times from baseline. Stage 3 – increase in creatinine 3 times from baseline or creatinine >4 mg/dl with an acute increase >0.5 mg/dl within 48 h or new-onset renal replacement therapy. We did not consider urine output as it may alter with use of diuretics.

Hyperchloremic metabolic acidosis was assessed from arterial blood gases (ABGs) taken preoperatively 1 day before surgery, intraoperatively two ABGs – one after heparin injection and one after protamine injection and postoperative ABGs at 24 h and 48 h. Hyperchloremic metabolic acidosis was assessed by reduction in serum bicarbonate (HCO_3^-) matched by an approximately equivalent increase in the serum chloride (Cl^-) concentration and by calculating strong ion difference (SID).^[16] SID was calculated from following simple formula, which is sufficient for practical purpose^[16]

$$\text{SID} = \text{serum sodium (Na}^+) + \text{serum potassium (K}^+) - \text{Cl}^-$$

Decrease in SID below 40 indicates acidosis. Perioperative changes in pH, PaCO_2 , HCO_3^- , base excess (BE), Na^+ , K^+ , lactate, and SID were compared between the study groups.

Results

Study groups were comparable in terms of sample size, age, gender, BMI [Table 1], and comorbidities (HTN and DM) [Table 2]. Study groups were comparable preoperatively with respect to serum creatinine, eGFR, pH, PCO_2 , HCO_3^- , BE, Cl^- , Na^+ , K^+ , lactate, and SID [Table 3].

The mean postoperative serum creatinine in Group A at 24 h was 1.093 and in Group B at 24 h was 0.846 with a $P = 0.004$. Moreover, the mean postoperative serum creatinine in Group A at 48 h was 0.974 and in Group B at 48 h was 0.832 with a $P = 0.032$ [Table 4]. Moreover, there was statistically significant difference in postoperative serum creatinine at all-time points ($P < 0.05$).

In Group A, 9.2% patients and Group B 4.6% patients developed Stage-I AKI determined by AKIN criteria which were statistically significant ($P < 0.05$). No patients had Stage II or III AKI postoperatively [Table 5]. No patients were on renal replacement therapy during study period.

In Group A, intraoperative and postoperative ABGs showed statistically significant difference in pH [Graph 1], HCO_3^- [Graph 2], BE, Cl^- , and SID in all time points ($P < 0.05$).

Table 1: Comparison of mean age, gender, mean body mass index, mean duration of surgery

	Group A (n=300)	Group B (n=300)	P
Mean age (years)	59.40±7.017	58.18±6.30	0.378
Gender (female/male)	86/214	91/209	0.833
Mean BMI (kg/m ²)	28.9±1.28	29.4±1.35	0.496
Mean duration of surgery (min)	379±50.624	374±49.898	0.751

BMI: Body mass index

Table 2: Comparison of comorbidities (hypertension and diabetes mellitus) between the study groups

Comorbidities	Mean (%)		P
	Group A	Group B	
HTN	15.4	13.8	0.452
DM	40	30.8	
Both HTN and DM	44.6	55.4	

HTN: Hypertension, DM: Diabetes mellitus

Table 3: Comparison of preoperative mean serum creatinine, mean estimated glomerular filtration rate, mean pH, mean PCO_2 , mean bicarbonate, mean base excess, mean serum chloride, mean serum sodium, mean serum potassium, mean lactate, and mean strong ion difference

	Group A	Group B	P
Serum creatinine	0.940±0.161	0.866±0.142	0.306
eGFR	85.03±13.861	85.59±11.167	0.119
pH	7.404±0.24	7.410±0.235	0.181
PCO_2	39.584±2.265	39.427±2.607	0.644
HCO_3^-	24.513±0.676	24.429±0.433	0.387
BE	0.426±0.564	0.393±0.517	0.624
Cl^-	102.323±2.773	102.276±3.520	0.512
Na^+	139.661±3.058	139.523±2.716	0.875
K^+	4.181±0.375	4.138±0.374	0.205
Lactate-	1.4286±0.256	1.391±0.247	0.283
Strong ion difference	41.520±3.065	41.400±4.348	0.140

eGFR: Estimated glomerular filtration rate, HCO_3^- : Bicarbonate, BE: Base excess, SID: Strong ion difference, Na^+ : Serum sodium, K^+ : Serum potassium, Cl^- : Serum chloride

Table 4: Comparison of mean serum creatinine preoperatively, postoperatively at 24 h and postoperatively at 48 h between the study groups

Creatinine	Group A	Group B	P
Preoperative serum creatinine	0.940±0.161	0.901±0.142	0.306
Postoperative serum creatinine at 24 h	1.093±0.133	0.846±0.118	0.004
Postoperative serum creatinine at 48 h	0.974±0.100	0.832±0.113	0.032

Mean base excess [Graph 3], mean serum chloride [Graph 4] and mean serum SID [Graph 5] in Group A in comparison

Table 5: Acute kidney injury network criteria stage-group cross tabulation

AKIN stage	Group		P
	Group A (n=300)	Group B (n=300)	
None			0.0044
Count	274	286	
Percentage within AKIN stage	48.8	51.2	
Percentage within group	90.8	95.4	
Stage I			
Count	24	14	
Percentage within AKIN stage	66.7	33.3	
Percentage within group	9.2	4.6	

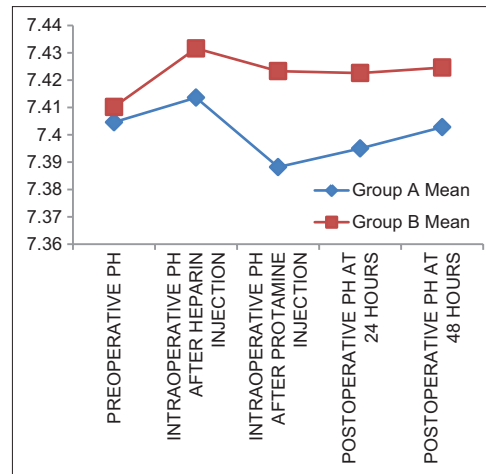
AKIN: Acute kidney injury network criteria

to Group B and there was no statistically significant difference in PCO₂, Na⁺, K⁺, and lactate ($P > 0.05$) thus proving that Group A had significant hyperchloremic acidosis.

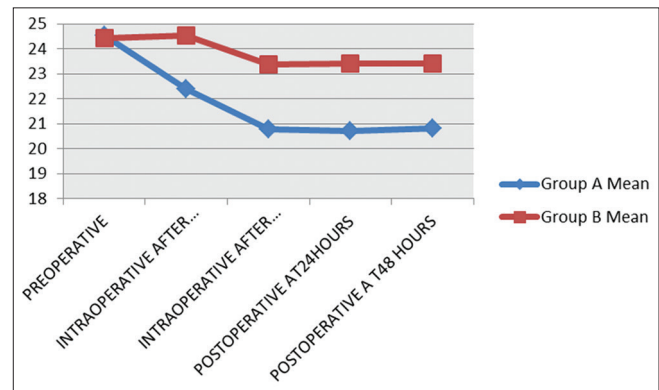
Discussion

Our present study shows, perioperatively use of chloride-restricted IVFs was associated with statistically significant lower incidence AKI Stage - I postoperatively. Use of chloride liberal IVFs perioperatively was associated with hyperchloremic acidosis and increased incidence of AKI Stage-I postoperative AKI. None of the patients in the study groups developed AKI Stage II or Stage III.

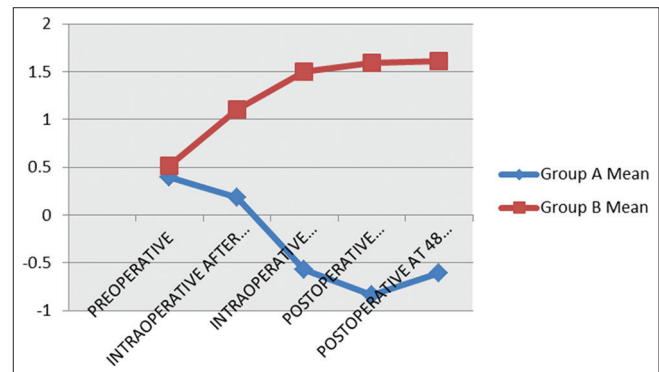
Our study indicates that IVFs chloride content can affect renal function after OPCABG. Like our study, previous studies also have found a significant association between hyperchloremic acidosis and AKI with the use of chloride liberal IVFs compared to chloride restricted IVFs. In 2015, article by Kim *et al.* reveal that the incidence of severe AKI and persistent AKI after OPCAB were significantly lower and the postoperative extubation time and duration of hospital stay were significantly shorter with the use of balanced solutions.^[17] In 2015 Yunos *et al.* found that liberal chloride therapy remains associated with a greater risk of kidney disease.^[11] In 2014, review article by Lobo and Awad argue that chloride-rich crystalloids such as 0.9% saline should be replaced with balanced crystalloids as the mainstay of fluid resuscitation to prevent “prerenal” acute kidney injury (AKI).^[9] In 2011, Meyera in their study found that the Cl⁻ level was lower ($P < 0.05$ at the end of surgery), and arterial pH was higher in the balanced group at all-time points except baseline, and BE was less negative at all-time points after baseline ($P < 0.01$).^[12] McCluskey *et al.*, in 2013,^[18] Shaw *et al.*, in 2014^[19] and Young JB *et al.*, in 2012^[20] found that increased morbidity and mortality after noncardiac surgery was independently associated with hyperchloremia.^[15-17] These findings strongly support the notion that perioperative use of chloride-restricted IVFs is associated with a decreased incidence of postoperative AKI.



Graph 1: Comparison of mean pH at different time points



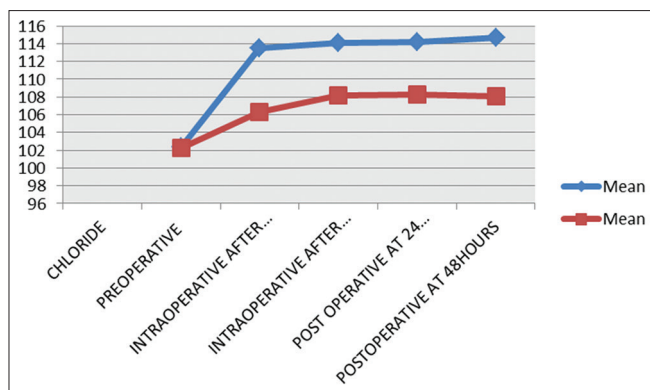
Graph 2: Comparison of mean bicarbonate at different time points



Graph 3: Comparison of mean base excess at different time points

Another pertinent result of our present study was development of statistically significant hyperchloremic metabolic acidosis, which can be avoided using chloride-restricted IVFs. These findings were in accordance with previous studies^[7,21] that is development of hyperchloremic metabolic acidosis after administration of chloride liberal fluids.

Our study has several limitations. The sample size was small despite a sufficient number of subjects as per result of power of analysis. Only patients with



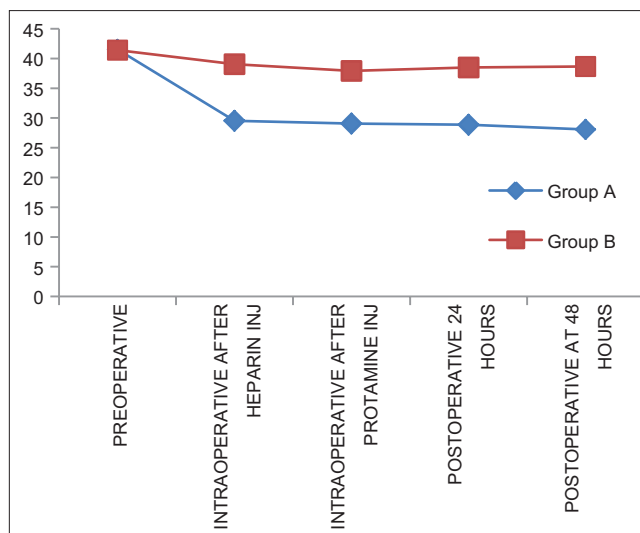
Graph 4: Comparison of mean serum chloride at different time points

eGFR >60 ml/min/1.73 m² were considered. Simple SID was calculated using only Na⁺, K⁺, and Cl⁻ values. OPCABG surgery *per se* is a major surgery involves various derangements and many factors can alter acid-base status. We did not consider volume of perioperative IVF administered, perioperative blood loss and perioperative volume of blood products administered. Study period was limited up to postoperative 48 h only.

Furthermore, few previously published studies did not show a significant association between hyperchloremic acidosis and AKI with the use of chloride liberal IVFs compared to chloride restricted IVFs. In meta-analysis published in 2015 by Krajewski *et al.* found that there is only weak association with higher chloride content and unfavorable outcomes, but mortality was unaffected by chloride content.^[13] Guidet *et al.*, in 2010, in their extensive review on balanced solutions say that, hyperchloremic acidosis is a moderate and relatively transient side effect, minimized or avoided by limiting chloride liberal IVF administration.^[22] In 1994, McFarlane and Lee compared plasmalyte 148 versus saline 0.9% for intraoperative fluid replacement on 30 patients undergoing major hepatobiliary or pancreatic surgery, those receiving saline had significantly increased chloride concentrations, decreased HCO₃ concentrations, and increased base deficit compared with those receiving Plasma-Lyte, there were no significant changes in plasma sodium, potassium, or lactate concentrations in either group. They concluded that the exclusive use of 0.9% saline intraoperatively produced a temporary hyperchloremic acidosis and use of a balanced salt solution such as Plasma-Lyte148 may avoid this complication.^[21] Accordingly, our present results should be interpreted with caution, and further randomized larger multicenter trials are needed.

Conclusion

From our study, we conclude that hyperchloremic acidosis developed after infusion of chloride liberal IVFs was found to be detrimental to kidney function postoperatively.



Graph 5: Comparison of mean strong ion difference at different time points

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Conflicts of interest

There are no conflicts of interest.

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