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A study to observe the effects of infusion of 6% hydroxyethyl starch (130/0.4) on renal function in cardiac surgical patients

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ABSTRACT

Background: The possibility of nephrotoxic effect caused by hydroxy ethyl starch (HES) used as volume therapy in this particular setting is of major clinical concern. We conducted this retrospective study to look for the possible nephrotoxic effects and other systemic adverse effects if any, of 6% HES 130 kD, 0.4 DS used as intraoperative volume expander in the cardiac surgery setting. **Aims and Objectives:** This study aims to determine whether the infusion of 6% hydroxyethyl starch (130/0.4) harms renal function in cardiac surgical patients. **Materials and Methods:** The present study was a retrospective study. Sixty-six patients who received crystalloids with hydroxyethyl starch and a matched control of 66 patients based on age and sex and other baseline parameters who received crystalloids only were part of the study. The data extracted from the electronic medical record include patient demographics, details for additive EURO score, and pre-operative data that include details of comorbid illnesses, namely, hypertension and diabetes, plasma hemoglobin, serum creatinine, and eGFR. **Results:** There is no statistically significant difference in serum creatinine and incidence of post-operative renal dysfunction between the study groups. There was a higher rate of re-exploration and duration of intensive care unit, and hospital stay. **Conclusion:** In our study, HES 130/0.4 in the dose used as a plasma expander did not adversely affect renal function in cardiac surgical patients undergoing CABG. The study recommends further detailed studies in this area involving multiple centers.

Key words: Renal function; Harmful effects; Cardiac surgery

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INTRODUCTION

The maintenance of cardiac output in cardiac surgery includes maintenance of preload, afterload, contractility, and heart rate. Colloids, particularly hydroxy ethyl starch (HES), may be used for rapid sustained volume expansion intraoperatively. The present study is aimed to determine alteration in renal function, if any, with infusion of HES using serum creatinine up to the time of discharge following surgery. Intravenous fluid therapy is a vital component of the management of patients undergoing surgery and in critical care units, the choice of intravenous fluid is dictated by underlying clinical scenario, pathophysiological mechanism of disease, the physicochemical characteristics, and safety profile of the fluid. Colloids such as HES, albumin, and gelatins have been used to maintain circulating blood volume, cardiac output, and tissue perfusion in hypovolemic patients. The colloid-crystalloid controversy is at least 30 years old. If crystalloids are given, 3–4 times, the quantity has to be administered, for example, for a volume benefit of 250 ml, we have to administer close to 1000 ml of crystalloid. Crystalloids stay in the circulation for a short time as half-life is extremely short and lead to third-spacing and tissue edema. HES is classified by molecular weight (MW) and degree of substitution into high MW, medium MW, and low MW. About 6% HES (130/0.4) has beneficial role over the larger molecule HES (200/0.5) in cardiac surgeries as it is associated with

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less coagulopathy. Obviously, low MW-HES such as HES (130/0.4) proposed to be used in the study, has lesser side effects, and is safer. The maximum dose of HES (130/0.4) as per manufacturer's literature is 50 mL/kg/day. The fears concerning the use of HES may be related to interference with coagulation, accumulation of HES in phagocytes of liver, skin, muscle and gut, anaphylactoid reactions (<0.06%), and renal dysfunction. Acute kidney injury (AKI) is one of the most serious complications occurring after cardiac surgery. When severe enough to require dialysis, mortality and morbidity are markedly increased, despite modern techniques of extrarenal epuration and supportive intensive care.[1] It is generally accepted that several factors lie at the origin of AKI after cardiac surgery. Advanced age, pre-operative disturbed renal function, duration of cardiopulmonary bypass (CPB), type of surgery, and post-operative hemodynamic instability can be important factors compromising renal function.[2] The possibility of nephrotoxic effect caused by HES used as volume therapy in this particular setting is of major clinical concern. We conducted this retrospective study to look for the possible nephrotoxic effects and other systemic adverse effects if any, of 6% HES 130 kD, 0.4 DS used as intraoperative volume expander in the cardiac surgery setting.

Aim and objectives

This study aims to determine whether infusion of 6% hydroxyethyl starch (130/0.4) harms renal function in cardiac surgical patients.

MATERIALS AND METHODS

Study design

This was a retrospective study.

Study setting

Great Eastern Medical School and Hospital, Srikakulam, Andhra Pradesh, India.

Study participants

Sixty-six patients who received crystalloids with hydroxyethyl starch and a matched control of 66 patients based on age and sex and other baseline parameters who received crystalloids only were part of the study. The study was approved by the institutional human ethical committee. The participants were recruited using the following criteria.

Inclusion criteria

Patients who underwent elective coronary artery bypass graft surgery either ON PUMP or OFF PUMP, during January 2020–December 2022 were included in the study.

Exclusion criteria

The following criteria were excluded from the study:

1. Patients with pre-operative renal dysfunction.
2. Patients undergoing cardiac surgeries other than CABG and procedures combined with CABG.

After the Institutional Review Board approval, the perioperative database for the period January 2015–December 2016 identified all adult cardiac surgeries during that period. Consent from the patients is deemed not necessary as this will be a retrospective data analysis.

HES group

Sixty-six patients received crystalloids and 6% HES (130/0.4) intraoperatively.

Crystalloid group

Sixty-six patients received only crystalloids as intraoperative intravenous fluid.

Methods

The data extracted from the electronic medical record include patient demographics, details for additive EURO score, and pre-operative data that include details of comorbid illnesses, namely, hypertension and diabetes, plasma hemoglobin, serum creatinine, and eGFR.

Ethical considerations

The present study protocol was approved by the institutional human ethical committee.

Statistical analysis

The data collected were scored and analyzed, continues variables were presented as means with standard deviation (SD), and categorical variables were presented as frequency and percentages. Student's t-test was used for testing the significance of all the variables mean and SD in groups. The Chi-square test was used to compare proportions. All the statistical results were considered significant at $P \leq 0.05$.

RESULTS

Table 1 presents the age-wise distribution of the participants. Table 2 presents the gender-wise distribution of the participants. Table 3 compares the standard/additive EuroSCORE between the groups. These scores were not significantly different between the groups. Table 4 presents the comparison of pre-operative hypertension between the study groups showing no significant differences. Table 5 presents the comparison of pre-operative diabetes between the study groups showing no significant difference. Table 6 presents the pre-operative hemoglobin between the study groups showing no significant difference. Table 7

Table 1: Demographic data – age-wise distribution of participants

Age group	Study group							
	Hydroxyethyl				Crystalloids			
	Male		Female		Male		Female	
	No.	%	No.	%	No.	%	No.	%
34–43	4	6.56	0	0	4	6.67	0	0
44–53	9	14.75	2	40.00	14	23.33	2	33.33
54–63	27	44.26	1	20.00	23	38.33	3	50.00
64–73	19	31.15	2	40.00	18	30.00	1	16.67
≥74	2	3.28	0	0	4	6.67	0	0
Total	61	100	5	100	60	100	6	100
Mean	54.48				58.29			
SD	8.76				9.10			
t-value	0.13							
p-value	0.90							
Significant	Not significant							

Table 2: Demographic data – gender-wise distribution of the participants

Gender	Study group			
	Hydroxyethyl		Crystalloids	
	No.	%	No.	%
Male	61	92.42	60	90.91
Female	5	7.58	6	9.09
Total	66	100	66	100
Chi-square	0.10			
P-value	0.75			
Significant	Not significant			

Table 3: Pre-operative standard/additive EuroSCORE between the groups

Statistics	Study group	
	Hydroxyethyl, N=66	Crystalloids, N=66
Mean	1.97	2.18
SD	1.74	1.69
t-value	0.72	
P-value	0.47	
Significant	Not significant	

Table 4: Pre-operative hypertension between the groups

Hypertension	Study group			
	Hydroxyethyl		Crystalloids	
	No.	%	No.	%
Yes	54	81.82	53	80.30
No	12	18.18	13	19.70
Total	66	100	66	100
Chi-square	0.05			
P-value	0.82			
Significant	Not significant			

presents the pre-operative estimated GFR between the study groups showing no significant difference. Table 8 presents pre-operative serum creatinine levels and Table 9 presents post-operative serum creatinine levels in the study groups. Table 10 presents post-operative renal

Table 5: Pre-operative diabetes between the groups

Diabetes	Study group			
	Hydroxyethyl		Crystalloids	
	No.	%	No.	%
Yes	31	46.97	26	39.39
No	35	53.03	40	60.61
Total	66	100	66	100
Chi-square	0.77			
P-value	0.38			
Significant	Not significant			

Table 6: Pre-operative plasma hemoglobin (gm/dl) between the groups

Statistics	Study group	
	Hydroxyethyl, N=66	Crystalloids, N=66
Mean	13.56	13.53
SD	1.36	1.19
t-value	0.11	
p-value	0.91	
Significant	Not significant	

Table 7: Pre-operative GFR between the groups

Statistics	Study group	
	Hydroxyethyl, N=66	Crystalloids, N=66
Mean	75.56	74.65
SD	20.26	14.92
t-value	0.29	
P-value	0.77	
Significant	Not significant	

Table 8: Pre-operative serum creatinine between the groups

Statistics	Study group	
	Hydroxyethyl, N=66	Crystalloids, N=66
Mean	1.06	1.05
SD	0.22	0.22
t-value	0.24	
P-value	0.81	
Significant	Not significant	

Table 9: Post-operative serum creatinine between the groups

Day	Hydroxyethyl			Crystalloids			Statistics		
	N	Mean	SD	N	Mean	SD	t-value	P-value	SIGN.
Day 1	66	1.11	0.30	66	1.06	0.22	1.18	0.24	NS
Day 2	66	1.15	0.31	66	1.07	0.21	1.78	0.08	NS
Day 3	64	1.17	0.43	64	1.07	0.20	1.69	0.10	NS
Day 4	47	1.23	0.54	52	1.10	0.25	1.51	0.14	NS
Day 5	22	1.25	0.78	20	1.22	0.17	0.18	0.86	NS

Table 10: Post-operative renal dysfunction between the groups

Statistics	Study group			
	Hydroxyethyl		Crystalloids	
	No.	%	No.	%
Yes	4	6.06	1	1.52
No	62	93.94	65	98.48
Total	66	100	66	100
Chi-square	1.87			
P-value	0.17			
Significant	Not significant			

dysfunction between the groups. No significant difference was observed.

DISCUSSION

Reliable data of renal damage after HES treatment in cardiac surgical setting are lacking. This study is to compare the effect of 6% HES 130/0.4 (Voluven) versus crystalloid on the renal function in patients who underwent CABG over a period of 2 years. Incidence of post-operative AKI is determined by serum creatinine values and compared between the study groups. Other post-operative morbidities, intensive care unit stay, and LOHS are also compared. This is a retrospective study conducted in 132 patients who underwent CABG either ON PUMP or OFF PUMP over a period of 2 years. Patients grouped as HES group with 66 patients and crystalloid group with 66 patients. Serum creatinine estimated at periodic intervals in the post-operative period was recorded. AKI determined with AKIN criteria. Other associated post-operative morbidities were also compared between groups. Thus regarding our primary objective, there is no statistically significant difference in serum creatinine and incidence of post-operative renal dysfunction between the study groups. In secondary objectives, we found higher rate of re-exploration and duration of ICU and hospital stay.

Patients in both groups are comparable regarding demographic and pre-operative data. Cardiac surgery patients are at risk of developing post-operative renal failure. Indeed, the risk of developing renal dysfunction after cardiac surgery is rather high, ranging from 5% to 30%. Severe ARF requiring dialysis develops in 1–5% of cardiac surgery patients.[3] AKIN classification was used to characterize post-operative AKI. This classification relies on urine output and change in serum creatinine over 48 h time window, which seems appropriate to assess the potential impact of intraoperative use of HES on post-operative renal function. We used pre-operative serum creatinine and serum creatinine levels measured in the post-operative days to establish the AKIN stage. In our study, the time course of serum creatinine and urine output did not differ significantly between the study groups. This is comparable to the study conducted by Datzmann et al.,[4]Gurbuz et al.,[5] Yanartas et al.,[6] and Hanz et al.[7]

Post-operative urine output in both groups is similar but serum creatinine is higher in the HES group. The reasons given in the study are (a) significant longer ischemic and CPB times in the HES group, (b) potato-derived balanced HES 130/0.4 (Tetraspan) was used in the study rather than non-balanced corn-derived HES (Voluven), (c) greater blood and blood product transfusion in the HES group. Earlier studies.,[8,9,10] post-operative 12th h serum creatinine is similar between the study groups but 24th h serum creatinine is higher in the HES group. Similarly, results were observed by the Skhirtladze[4] et al. and other recent recent studies.[11,12]

Limitations of the study

The dose of HES used for intravenous fluid therapy was limited to 500 mL. This represents the average dose of 6.6 mL/kg for a 75 kg patient and it is possible that the use of a larger amount would have led to a different conclusion.

CONCLUSION

In our study, HES 130/0.4 in the dose used as a plasma expander did not result in adverse effects on renal function in cardiac surgical patients undergoing CABG. The study recommends further detailed studies in this area involving multiple centers.

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PKD- Concept and design of the study, results interpretation, review of the literature, and preparing the first draft of the manuscript. **BK-** Concept and design of the study, results interpretation, review of the literature, and preparing the first draft of the manuscript. **DVK** and **RRS-** Concept and design of the study, statistical analysis and interpretation, and revision of the manuscript.

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