Renal Function In Off Pump Coronary Artery Bypass (Opcab) Surgeries: Effects Of Pentastarch And Tetrastarch: A Double Blind Randomised Trial

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Citation

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Abstract

Study Objective: To assess and compare the effect of pentastarch(HES 200/0.5) and tetrastarch(HES 130/0.4) on renal function during and after OPCAB surgeries.

Design: Randomized double blind prospective study

Setting: Operating theatre and intensive care unit[ICU] of an academic medical center

Interventions: 30 patients undergoing OPCAB surgery were randomly divided into two groups and were assigned to receive 500 ml of HES(200/0.5) –group H, or HES(130/0.4)-group V immediately after the induction of anesthesia.

Measurements And Results: Markers of glomerular as well as tubular functions were evaluated with blood and urine samples. Tetrastarch did not offer any advantage over pentastarch in patients with normal renal function after OPCAB. However the impact of each starch on postoperative renal functions was different. Tetrastarch did not significantly alter glomerular or tubular function while certain tubular markers like serum and urine sodium were elevated in the postoperative period after administration of pentastarch. However more specific markers like the fractional excretion of sodium and the renal failure index were not significantly changed in the postoperative period.

INSTITUTION WHERE THE STUDY WAS DONE

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INTRODUCTION

Renal dysfunction is a serious complication of coronary revascularisation with cardiopulmonary bypass [CPB] and results in increased mortality, morbidity and prolonged hospital and intensive care unit [ICU] stay. 1 The effects of cardiopulmonary bypass and the mediators of renal dysfunction have been studied extensively and well documented also. 12 The effects of colloids on renal function have also been documented when used for cardiopulmonary bypass(CPB). ³⁴ The course of patients in the early postoperative period is usually improved with OPCAB surgery compared with on-pump surgery. The duration of ventilatory support, intensive care unit [ICU] length of stay, and hospital length of stay are significantly diminished as shown in several studies. ⁵⁶

Given the number of hydroxyethyl starches in the market and the variances in their physicochemical properties, it is proven that the in vivo molecular weight and the plasma concentration decides the colloid osmotic power, pharmacokinetics, accumulation in tissues and the side effects on coagulation and renal function. It would seem that the best hydroxyethyl starch is the one with the lowest in vivo molecular weight above threshold of renal elimination. Legendre etal 7 reported 80% rate of 'osmotic nephrosis –like lesions '[vacoulisation of proximal tubular cells] in transplanted kidneys after routine administration of medium molecular weight [200 kD] hydroxyethyl starch. Hydroxy ethyl starch has been shown to reduce renal function in patients undergoing on pump coronary artery bypass grafting (CABG) and pentastarch has been shown to affect renal tubular function in the postoperative surgical unit. ⁸⁹ Our study assessed the effect of two starches of different physicochemical properties, with molecular weights above renal elimination threshold, on perioperative renal function, in off pump coronary artery bypass surgeries. We sought to find out if a smaller molecular weight starch would have less detrimental effects on renal function because of their less filtration across the glomerulus.

METHODS

After approval of the institutional review board and informed consent, we prospectively studied 30 patients scheduled for elective OPCAB surgery. Patients with a normal renal function as assessed by serum creatinine and normal urinalysis were included in the study. Patients with a history of renal impairment, diabetes mellitus, low cardiac output [EF<35%] or recent MI, hypertension, or unstable angina were excluded from the study. All patients were on beta-blockers, clopidogrel and isosorbide mononitrate preoperatively. None of the patients were on angiotensin converting enzyme inhibitors or diuretics. The patients were randomly assigned into two groups –group H, which received 500ml of pentastarch [HES 200/0.5] and group V that received 500 ml of tetra starch [HES 130/0.4] intraoperatively.

ANESTHETIC MANAGEMENT

Anesthesia was administered to a strict protocol. Premedication consisted of diazepam 10 mg on the night prior to and on the morning of surgery. Their routine betablocker, clopidogrel and isosrbide were continued till the morning of surgery. After insertion of peripheral venous and arterial cannulae under local analgesia, anesthesia was induced with fentanyl 2-4 mcg/kg,midazolam 0.05 mg/kg and propofol 1mg/kg intravenously. [Tracheal intubation was performed after administration of pancuronium bromide 0.1mg/kg and ventilated with O₂ A 7F triple lumen central venous catheter was inserted into right internal jugular vein and an indwelling bladder catheter was used for urine collection. Anesthesia was maintained with fentanyl and isoflurane. The patients were given 500 mls of pentastarch or tetrastarch immediately after induction, by a person totally blinded to the study and were maintained on Hartmanns

solution so as to maintain a mean arterial pressure [MAP] > 70 mm Hg and a central venous pressure[CVP] of about 6-8 mm Hg . Inotropic support, adrenaline [upto a dose of 0.05 mcg/kg], was started if MAP did not increase despite adequate filling pressures, defined as a CVP of 12, for the purposes of the study. Diuretics or mannitol were not used during this study.

The serum creatinine, serum sodium, urine creatinine and urine sodium were calculated a] just before anesthetic induction and b] 24 hrs after the CABG. Urine output was calculated 24 hrs preoperatively and postoperatively for the purposes of calculation of creatinine clearance. Markers of glomerular function (glomerular filtration rate, creatinine clearance and serum creatinine) as well as tubular function (fractional excretion of sodium, serum and urinary sodium and renal failure index) were then evaluated by a person totally blinded to the study.

RENAL MARKERS

The renal function of these patients was evaluated by measuring both the glomerular markers and tubular markers. The glomerular markers included creatinine clearance [CrCl], serum creatinine [s.Cr] and the glomerular filtration rate. ₃ Creatinine clearance was calculated using the formula

CrCl = u.Cr*UoP/sCr*1440 where u.Cr represents urinary concentration of creatinine and UoP the urine output respectively.

The glomerular filtration rate [GFR] was calculated using the Gault- Crockford formulla, which can be written as

GFR =[140 - age] * wt/s.Cr * 72

The tubular function was also assessed and the parameters measured included urinary sodium [u.Na], serum sodium[s.Na], renal failure index[RFI] and the fractional excretion of sodium[FeNa]. 3

The fractional excretion of sodium [FeNa] was calculated as

 $FeNa = u.Na^* s.Cr^*100/s.Na^*u.Cr.$

The renal failure index[RFI] was calculated as:

RFI = u.Na*s.Cr/u.Cr

STATISTICAL ANALYSIS

Assuming a power of 90% and type I error of 5%, the minimum sample size required for the study as determined

by power analysis, was 13 patients per group. A slightly larger sample of 15 patients per group was chosen. The markers of renal function, the hemodynamic parameters and the demographic data for statistical analysis were evaluated for statistical significance. The results are expressed as mean +/- standard deviation unless stated otherwise. The results were analyzed using the paired and unpaired t tests and statistical significance was accepted as p<0.05.

RESULTS

The demographic profile of both the groups are given in the table 1 and are comparable. The duration of the surgery and the number of grafts were almost identical in all the patients.

Figure 1

Table 1: DEMOGRAPHIC PROFILE GROUP H vs GROUP V NS – not significant

	Group - H	Group - V	
Age[yrs]	55.9±10.7	59.5±10.4	NS
Weight [kg]	66±8.9	64.33±7.5	NS
Height [cms]	152.2± 11.2	154.3±10.9	NS
Ejection fraction [%]	54±2.8	55±2.6	NS
Male: Female	13:2	13:2	NS
Duration of surgery [hrs]	3.2±1.1	3.4±1.3	NS
No. of grafts	2.2	2.4	NS

The intraoperative and postoperative hemodynamic variables are given in Table 2. 9 patients required perioperative inotropic support to maintain a MAP >70 and the inotropes were weaned off in the postoperative ICU within 12 hours. None of the patients required blood or blood products and their blood loss was comparable as well. The mean duration of ventilation and ICU stay was not significant between the groups.

Figure 2

Table 2: HEMODYNAMIC PARAMETERS IN THEPERIOPERATIVE PERIOD NS – not significant

	GROUP H	GROUP V	
Total iv fluid given in L in 24 hrs[including the colloid]	2.3±0.32	2.1 ± 0.38	NS
Patients with inotropic support at the end of surgery	4	5	
Blood or blood products	NIL	NIL	
Re-exploration	NIL	NIL	
Duration of ventilation [hrs]	8.8±1.3	9.1±1.4	NS
Duration of ICU stay [days]	1.8± 0.7	1.7±0.8	NS
Postoperative drainage [ml]	388±66	351±61	NS

The glomerular and tubular functions in each group were assessed preoperatively and the impact of administration of the starches on the renal functions was calculated separately for each groups and compared as well. The baseline renal parameters were comparable between Group H and Group V and are given in Tables 3,4 below.

TABLE 3,4 BASELINE RENAL PARAMETERS IN GROUP H AND GROUP V

GFR-Glomerular Filtration Rate, CRCL- Creatinine clearance, S Na –serum sodium

FeNa-fractional excretion of sodium, U Na- urinary sodium,

RFI - renal failure index

NS - not significant

Figure 3

Table 3: Baseline glomerular function

	Pre operative Group H	Pre operative Group V	t	Significance
GFR[ml/min]	79.36 ± 24.5	72.67 ±3.9	1.04	NS
CRCL[I/min]	0.07±0.03	0.08±0.07	0.5	NS
S. Creatinine [mg%]	1±0.19	1.05 ± 0.23	0.72	NS

Figure 4

Table 4: Baseline tubular function

	Pre operative Group H	Pre operative Group V	t	Significance
SNa+[meq/l]	142± 3.4	140.2± 3.9	1.35	NS
FeNa+	3.03 ± 2.61	2.99 ± 2.17	0.13	NS
U.Na+ [meq/l]	140.7± 25.9	152.4 ±13.8	1.5	NS
RFI	4.31±3.74	4.08±3.1	0.18	NS

The post operative glomerular and tubular functions were comparable between the groups and were not statistically significant.(TABLE 5,6)

TABLE 5,6 POST OPERATIVE RENAL FUNCTIONS GROUP H VS GROUP V

GFR-Glomerular Filtration Rate, CRCL- Creatinine clearance, S Na –serum sodium

FeNa-fractional excretion of sodium, U Na- urinary sodium,

RFI - renal failure index

NS - not significant

Figure 5

Table 5: Glomerular function

	Post operative Group H	Post operative Group V	t	Significance	
GFR [ml/min]	77.29 ± 29.4	70.24 ± 18.4	1.04	NS	
CRCL [l/min]	0.07 ± 0.04	0.08 ± 0.05	0.5	NS	
S. Creatinine [mg%]	1.08±0.29	1.05±0.19	0.72	NS	

Figure 6

Table 6: Tubular function

	Post operative Group H	Post operative Group V	t	Significance
SNa+[meq/l]	144.8 ± 5.52	145 ± 4.19	0.11	NS
FeNa+	3.1 ± 2.01	2.77 ± 1.36	0.55	NS
U.Na+ [meq/l]	164.7 ± 19.2	152.5 ± 16.7	0.07	NS
RFI	4.5 ±2.95	3.62±1.33	1.05	NS

The impact of administration of pentastarch and tetrastach on the renal function in the postoperative period was also studied. It was noted that though the glomerular function was not altered much, pentastarch elevated non specific tubular markers like S.Na and U Na significantly while more specific markers like the FeNa and RFI did not change significantly. The tetrastarch did not affect the glomerular or tubular function in the postoperative period in a significant way(TABLES 7,8). Though the glomerular filtration rate declined in the postoperative period in both the groups and serum creatinine increased in group H, the results were not statistically significant. The renal failure index showed a marginal increase in group H in the postoperative period and there was a tendency for the index to decrease in group V, though the observed values were insignificant statistically.

Figure 7

Table 7: IMPACT ON POSTOPERATIVE RENALFUNCTION IN GROUP H

	GFR [ml/min]	CRCL [l/min]	S. Creatinine [mg%]	S Na (meq/l)	U.Na Meq/I	Fe Na	RFI
Pre	79.36±	0.07 ±	1+019	142±	140.7±	3.03 ±	4 31+3 74
operative	24.5	0.03	120.00	3.4	25.9	2.61	1.0120.11
Post	77.29 ±	0.07±	1.08 + 0.29	145 ±	164.7±	3.1 ±	45+2.95
operative	29.4	0.04	1.001 0.10	5.2	19.2	2.01	1.0 22.00
t	0.4	0.7	1	2.15*	4.45*	0.93	0.2

GFR-Glomerular Filtration Rate, CRCL- Creatinine clearance, S Na –serum sodium

FeNa-fractional excretion of sodium, U Na- urinary sodium,

RFI - renal failure index

NS - not significant

*-Statistically significant, p< 0.05

Figure 8

Table 8: IMPACT ON POSTOPERATIVE RENAL FUNCTION IN GROUP V

	GFR [ml/min]	CRCL [L/min]	S. Creatinine [mg%]	S Na [meq/l]	U.Na Meq/I	Fe Na	RFI
Pre	72.67	0.08 ±	105+022	140.2±	152.4	2.99±	4 0.0+2 1
operative	±3.9	0.07	1.05 ± 0.25	3.9	±13.8	2.17	4.0013.1
Post	70.24 ±	0.08 ±	1.05 + 0.19	145 ±	152.5±	2.77 ±	3.62
operative	18.4	0.05	1.00 1 0.10	4.19	16.7	1.36	±1.33
t	0.7	0.5	0.5	0.75	0.1	0.78	0.68

DISCUSSION

This is the first study to compare the differences in renal function between pentastarch and tetrastarch in off pump CABG patients. The glomerular as well as tubular functions were assessed separately and we concluded that tetrastarch and pentastarch were comparable in terms of glomerular and tubular function postoperatively. Administration of tetrastarch did not offer any advantage over pentastarch in patients with normal renal function undergoing OPCAB.

However, the impact of each starch on postoperative renal functions was different. The postoperative renal functions, both glomerular and tubular, were not significantly changed after administration of tetrastarch. Certain tubular markers like serum sodium and urine sodium were significantly elevated after pentastarch administration, but more specific markers like the fractional excretion of sodium and the renal failure index were comparable in the postoperative period. The elevation of these tubular markers in normal subjects even with a relatively small volume raises questions regarding their safety in patients with mild to moderate renal impairment. Dehne etal reported changes in tubular function after administration of HES 200/0.5 in a group of postsurgical ICU patients. Patients undergoing HES therapy showed increased excretion of alpha 1-microglobulin, Tamm-Horsfall-protein and of brush border enzyme acetylbeta-glucosaminidase. There was no change in the glomerular function in their group of patients.

The spectrum of postoperative renal dysfunction ranges from mild sub clinical renal dysfunction to overt oliguric renal failure needing dialysis. The consensus on the gold standard marker or the yardstick for the study of acute postoperative renal failure is lacking and crude measurements like urine output correlates poorly with renal vitality. As such the glomerular and tubular function have to be evaluated in terms of specific markers and indices.

Winkelmeyer etal showed that exposure to hydroxyethylstarches during on pump coronary artery bypass grafting may be associated with a decrement in postoperative renal function independent of the renal function values at baseline. Administration of HES [600/0.75] was associated with reductions in GFR in the post operative period in the ICU. ₉ We used two starches of lesser molecular weight and molar substitution ratio in OPCAB surgeries and the glomerular function was not significantly altered in the postoperative period.

Studies have shown that baseline renal function is a known major risk factor for postoperative renal dysfunction. Boldt J etal compared HES 130/0.4 and HES 200/0.5 in first time elective cardiac surgery patients using extracorporeal circulation and found out that the renal function was without group differences till the first postoperative day. ⁴ When HES 130/0.4 was compared with gelatin especially in elderly patients above 70 yrs undergoing cardiopulmonary bypass, Boldt J etal reported elevated kidney proteins in both the groups, which returned to normal on second postoperative day. ¹⁰

Jungenheich etal studied the pharmacokinetics of HES in patients with mild to moderate renal impairment and found that the concentration of HES in plasma was greater in patients with creatinine clearance < 50 ml/min. The plasma half life was prolonged by impaired renal function and was common in old age. ¹¹ The mechanism of renal insult following colloid administration has been entitled as acute hyperoncotic renal failure syndrome and it has been attributed to the elevated colloid osmotic pressure, which offsets the hydrostatic glomerular function pressure, leading to reduced urine output. It is more with colloids having high molecular weight and high degree of substitution. [[[11.12]]]

The study has several limitations. The use of a relatively small dose of 500 ml of colloids could be a major limitation of the study. This was in conjunction with the institutional protocol of using only a maximum of 500 ml of colloids in OPCAB surgeries and using crystalloids for the rest of the replacement during the perioperative period. However both the groups received the same amount of colloids and the subtle, significant increase in the tubular markers it has caused even in normal subjects raises queries regarding the safety of starches in mild to moderate renal impairment, where it has been proven to be safe. It should be interesting to find out if higher volumes of starches had a more significant impact on renal function in OPCAB surgeries. Again the data does not seem to suggest whether these changes are reversible or not. The long-term consequences of hydroxyethyl starches on renal function need to be addressed in a well-controlled trial. The volume status of the patient preoperatively might also a confounding variable. Though all our patients were fasted overnight on the day before surgery there was no direct measurement of the intravascular volume that might have had an impact on the renal perfusion pressure. All patients had good urine output 24 hours prior to the surgery though this is only an indirect measurement of the volume status. We could not exclude the fact that any other confounding factor could have remained unaccounted for in our analysis.

The derangement of certain tubular markers even in patients with normal renal function raises concern regarding the safety of pentastarch in OPCAB surgeries. Hence assessment of specific tubular markers like N-acetyl- -D-glucosaminidase and glutathione transferase will throw more light into the extent of tubular dysfunction. Recent studies have shown the superiority of serum cystatin C to serum creatinine in detecting minor reductions of glomerular filtration rate. It has a greater ability to detect subclinical renal dysfunction than serum creatinine ₁₃. It seems necessary to conduct a sufficiently large randomized controlled trial to confirm these findings, to describe long-term effects, and to identify patients who are particularly vulnerable to this potentially important side effect of hydroxyethyl starch use.

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