Original Research Article

A comparative evaluation of different types of hydroxy ethyl starch - on the blood sugar and serum electrolytes level

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Abstract

Background: Hydroxy Ethyl Starch (HES) is most commonly used volume expander in perioperative period. We planned this study to evaluate the effect of different generations Hydroxy Ethyl Starches and Ringer Lactate (RL) on the blood sugar level (BSL) and serum electrolytes in non-diabetic patient posted for gynaecological surgery under spinal anesthesia. **Material and method:** in a prospective, randomized, controlled trial, 150 female patients of ASA grade I and II, 18–70 years of age were included and randomly divided into 5 groups of 30 patients in each to receive either RL-Group 1, 6% HES 450 -Group 2, 6% HES 200 - Group 3, 3% HES 200 - Group 4, 6% HES 130 - Group 5. **Results:** Mean rise in BSL after 12 hours were 18.07±15.26, 37.57±9.73, 23.53±17.01, 26.33±19.64 and 26.20± 15.05 mg/dl in group 1,2,3,4,5 respectively. Mean change in serum sodium and chloride level ranged from -2.17±6.20 to 1.05±6.27 and -2.10 to-0.93 mEq/L respectively in all groups. There was a continuous decline in mean serum potassium level by 1.06, 0.83, 1.01, 0.80, 1.26 mEq/L and calcium level by 0.56, 0.72, 0.43, 0.55, 0.34 mg% in group 1,2,3,4 and 5 respectively. **Conclusion:** RL and HES produces a rise in BSL to a variable degree. There is no appreciable effect on serum sodium and chloride level while there is a marked drop in serum calcium and potassium which was evident even up to 12 hours. 3% HES 200 produces the least disturbances in serum calcium and serum potassium level.

Key Word: Hydroxy Ethyl Starch (HES), Pentastarch, Tetrastarch, Hetastarch, Ringer Lactate (RL), Blood Sugar Level (BSL), Serum Electrolyte Level.

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INTRODUCTION

Different generations of Hydroxyethylstarch (HES) are used perioperatively as a volume expander[1,2] and also in preloading prior to administration of spinal anesthesia. However there are some concern regarding use of HES in patients with sepsis and critically ill because of its association with the risk of renal injury and coagulation disturbances. High molecular weight HES (450/0.7) having prolonged terminal half life, may get deposited in reticuloendothelial system and can cause pruritus, increase in blood glucose level and altered biochemistry. Thus, there is a chance to induce or potentiate hyperglycemia and serum electrolyte imbalance particularly in patients with diminished ability to metabolize exogenous glucose i.e.in patients with Diabetes Mellitus or compramized renal status. There are various studies regarding HES and its pharmacokinetic and pharmacodynamics properties[3,4] and their effect on volume expansion[567], hemodynamics, blood sugar level[8,9,10,11], renal effect[5,12] and coagulation defect[3]. But the studies evaluating different generation saline based HES with blood glucose level and serum electrolytes are limited. Taking into consideration the hazardous effects of hyperglycemia and electrolyte imbalance in the perioperative period and the frequent use of HES as volume expander, the present study was aimed to examine the effects of 6% HES-450/0.7 (Hetastarch), 6% HES- 200/0.5 (Pentastarch), 3% HES- 200/0.5

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(Pentastarch), 6% HES- 130/0.4 (Tetrastarch) along with Ringer lactate (RL) as a control on the blood sugar level (BSL) and serum electrolytes (mainly Na^+, K^+, Cl^- and Ca^{++}) levels in non-diabetic patients undergoing gynaecological and perineal surgical procedures under spinal anesthesia.

MATERIAL AND METHODS

Study design: The study was designed as a prospective, open, randomized, comparative study. After approval from the institutional ethical committee, the study was conducted in the Department of Anaesthesiology, Zanana Hospital, SMS Medical College and Hospital, Jaipur on 150 female patients of 18-70 years age of ASA grade I or II who underwent major gynecological surgery under spinal anaesthesia. Exclusion Criteria of the study were patients with Diabetes Mellitus or any other biochemical derangement due to the disease, patients on drugs that cause hyperglycemia (acetaminophen, ascorbic acid, steroids), patients on drugs that cause hypoglycemia (Octreotide), patients with renal impairment, coagulopathy, low hematocrit value, patient refusal, patients who had a recent exposure to HES, blood or its components within past 2 weeks or allergy to HES. 2.2 Sample size: Sample size calculation was done based on a study done by Murthy *et al*[13] to see the effects of hydroxyl ethyl starches on blood sugar levels. They compared 6% Hetastarch 450 and 6% Pentastarch 200 with Ringer lactate as control. We have taken 30 patients in each group as per central limit theorem.

Groups: patients were divided into 5 groups of 30 each.

Group 1 - Control - Ringer Lactate (RL)- 15 ml/kg

Group 2 - 6% HES - 450/0.7(Hetastarch) - 15 ml/kg

Group 3 - 6% HES -200/0.5 (Pentastarch) - 15 ml/kg

Group 4 - 3% HES -200/0.5 (Pentastarch) - 15ml/kg

Group 5 - 6%HES -130/0.4 (Tetrastarch) - 15ml/kg

All types of hydroxyethyl starches were derived from waxy maize starch and containing normal saline as their carrier solution.

Protocols to be followed: Pre-anaesthetic checkup comprising thorough clinical examination, routine investigations for biochemical indices including fasting and postprandial (2hrs) blood sugar, serum electrolyte, serum calcium level etc. X-Ray chest, ECG and other special investigation if necessary. After overnight fasting confirmed and informed written consent was taken, the patient was taken into the OT and allocated to groups according to how they were received in OT i.e. 1st patient allocated to group 1, 2nd patient to group 2 and so on. An intravenous access was achieved with an 18G IV Cannula and a sample of blood was drawn and sent for blood sugar and serum electrolytes levels (Na^+, K^+, Cl^- and Ca^{++}). This reading was considered as basal or zero reading. Baseline parameters i.e. pulse, BP etc. were recorded and assigned intravenous fluid (Ringer Lactate, Hetastarch, Pentastarch or Tetrastarch) was started for preloading with the calculated dose (15 ml/kg) over 30 minutes. The spinal anaesthesia was given with inj. 0.5% Bupivacaine 3ml (Heavy). Patient was given oxygen @ 4L/minute through ventimask. All vitals have been recorded throughout the surgery. After preloading with assigned IV fluid the patients received Ringer Lactate as subsequent IV fluids @8ml/kg/hr intra and postoperatively till the final blood sugar reading is taken at the end of twelve hours from the basal reading. Blood sample for sugar and electrolyte level was taken after 60 minutes followed by two hourly (i.e.1, 3, 5, 7 and twelve hours) for next twelve hours. Further IV fluid and blood transfusion given as per blood loss and hemodynamic status. Urine output and any side effect were also recorded.

Statistical analysis: Data within the group was analysed using the paired t-test and between the groups was analysed using student t-test and ANOVA test. Data were presented as mean and standard deviation.

RESULTS

Demographic profile in regard to age, weight is comparable between groups. Maximum numbers of patients were between 36-50 years age group. Most of the patients were between 46-60 kg weight groups.

Table 1: Mean blood sugar level (± S.D.) in mg/dl at various time intervals in patients in different groups

Observation time(hrs)	Group 1 (RL)	Group-2 (6%HES450/0.7)	Group-3 (6%HES200/0.5)	Group-4 (3%HES200/0.5)	Group-5 (6%HES130/0.4)
	Mean± S.D.	Mean± S.D.	Mean± S.D.	Mean± S.D.	Mean± S.D.
Pre op	81.73±10.14[64-110]	80.77±13.61[60-119]	87.00±14.15[60-126]	79.67±14.04[60-119]	85.43±15.75[60-126]
0 (Basal)	94.57±12.69[50-117]	87.93±10.26[62-113]	95.83±12.22[77-124]	96.30±14.18[69-145]	94.17±11.11[77-120]
1	91.20±14.22[52-119]	88.40±8.81[72-109]	95.10±11.39[77-126]	92.30±12.8[71-130]	94.90±12.02[70-117]
3	98.83±18.94[56-150]	95.90±8.58[77-112]	97.40±13.20[75-134]	98.40±15.45[78-144]	101.97±14.05[85-139]
5	101.03±17.76[52-145]	101.20±10.29[78-129]	106.73±17.53[80-154]	100.77±14.07[78-132]	109.93±15.46[84-139]
7	105.67±17.14[46-137]	111.23±10.96[94-138]	118.33±23.96[70-179]	115.47±18.43[70-149]	117.00±17.89[82-147]
12	112.63±20.07[62-157]	125.50±9.79[110-149]	119.37±17.15[86-152]	122.63±19.43[78-148]	120.37±18.17[87-153]

Observation	Group-1	Group-2	Group-3	Group-4	Group-5
Mean Age	41.13±	40.13±	42.03±	43.27±	43.43±
(± S.D.)	10.94	10.03	10.95	10.74	10.71
Mean Weight	52.20±	48.97±	48.77±	50.93±	50.10±
(± S.D.)	8.89	9.56	6.88	9.96	12.81

In group 1, maximal blood sugar level increased from basal value of 94.57±12.69 mg/dl to 112.63±20.07mg/dl at the end of twelve hours (an increase of 18.07±15.26mg/dl; P value <0.001) which was statistically highly significant. In group 2, the blood sugar level increased from the basal value of 87.93±10.26 mg/dl to 125.50±9.79 mg/dl at the end of 12 hours (an increase of 37.57±9.73 mg/dl; P value <0.001). In group 3, maximal blood sugar level was observed at 12 hours (119.37±17.15mg/dl; P value <0.001) which was similar to group 1and2. In group 4 there was a significant increase in BSL from basal value 7th hour onward. The maximal blood sugar level was observed at 12 hours (122.63±19.43mg/dl; ↑26.33±19.64mg/dl i.e. 27.35% from basal value; P value <0.001) which was similar to group 1, 2and 3. Similarly in group 5, maximal blood sugar level was observed at 12 hours (120.37±18.17mg/dl; an increase of 26.20±15.05mg/dl i.e. 27.82% from basal value; P value <0.001) which was similar to group 1, 2, 3 and 4.

Table 2: Mean change in blood sugar level (± S.D.) in mg/dl from the baseline (0hrs)

Observation time (Hrs)	Group 1 (RL)		Group-2 (6%HES450/0.7)		Group-3 (6%HES200/0.5)		Group-4 (3%HES200/0.5)		Group-5 (6%HES130/0.4)	
	Mean change± S.D.(% variation)	P value (sig.)	Mean change ± S.D. (% variation)	P value (sig.)	Mean change ± S.D.(% variation)	P value (sig.)	Mean change ± S.D.(% variation)	P value (sig.)	Mean change ± S.D.(% variation)	P value (sig.)
1	-3.37±8.56 [-3.56%]	0.0398	0.47±9.64 [0.53%]	0.7927	-0.73±11.50 [-0.77%]	0.7294	-4.00±12.17 [-4.15%]	0.0823	0.73±11.99 [0.78%]	0.7399
3	4.27±13.99 [4.51%]	0.1055	7.97±9.18 [9.06%]	0.0001	1.57±14.50 [1.63%]	0.5585	2.10±14.85 [2.18%]	0.4449	7.80±12.95 [8.28%]	0.0026
5	6.47±13.47 [6.84%]	0.0135	13.27±9.22 [15.09%]	<0.001	10.90±18.12 [11.37%]	0.0026	4.47±14.44 [4.64%]	0.1009	15.77±12.95 [16.74%]	<0.001
7	11.10±11.70 [11.74%]	<0.001	23.30±11.15 [26.50%]	<0.001	22.50±24.40 [23.48%]	<0.001	19.17±21.24 [19.90%]	<0.001	22.83±14.56 [24.25%]	<0.001
12	18.07±15.26 [19.10%]	<0.001	37.57±9.73 [42.72%]	<0.001	23.53±17.01 [24.56%]	<0.001	26.33±19.64 [27.35%]	<0.001	26.20±15.05 [27.82%]	<0.001

Table 3: Mean serum sodium level (± S.D.) and minimum and maximum value in mEq/L at various time intervals in patient in different groups

Observation time(hrs)	Group 1 (RL)	Group-2 (6%HES450/0.7)	Group-3 (6%HES200/0.5)	Group-4 (3%HES200/0.5)	Group-5 (6%HES130/0.4)
	Mean± S.D.	Mean± S.D.	Mean± S.D.	Mean± S.D.	Mean± S.D.
Pre op	137.85±4.01 [129.4-148]	138.46±3.05 [130.5-145.3]	138.51±4.49 [129-149]	138.10±3.67 [130.2-149]	138.76±3.94 [131-149]
0 (Basal)	139.55±4.06 [131.2-146.2]	139.50±2.30 [135.3-146.3]	138.97±4.44 [130.6-148.6]	140.07±3.15 [135.1-146.6]	140.23±5.30 [131.1-152.6]
1	140.24±2.40 [136.8-146.5]	139.83±1.91 [136.8-145.6]	139.03±2.79 [132.8-145.1]	140.28±2.21 [136.1-144.7]	139.93±2.97 [130.2-145.2]
3	140.57±4.11 [132.6-149.5]	140.31±2.98 [133.2-146.1]	138.73±3.16 [132.7-145.9]	140.33±2.29 [136.1-143.7]	140.16±3.38 [131.4-149.5]
5	139.70±2.70 [133.8-146.3]	140.12±3.46 [131.3-148]	140.02±3.16 [131.2-145.7]	140.19±2.05 [135.3-143.6]	140.31±3.60 [133.6-149.4]
7	139.69±2.11 [133.4-143.9]	139.38±7.33 [103.4-146.3]	138.51±3.25 [130.4-143.8]	140.29±2.19 [135.2-145.6]	138.06±2.76 [130.6-142.5]
12	138.09±2.50 [134.2-144.6]	139.20±2.24 [132.9-143.6]	137.81±3.08 [130.7-143.7]	139.53±2.01 [135.2-142.7]	138.47±2.93 [132.4-147.6]

Mean change in serum sodium level from basal value in all the groups ranged from -2.17±6.20mEq/L to 1.05±6.27mEq/L. In all the five groups none of the patients showed significant deviation in the serum sodium level from basal value.

Table 4: Mean change in serum sodium level (± S.D.) in mEq/L from the baseline (0hrs)

Observation time (Hrs)	Group 1 (RL)		Group-2 (6%HES450/0.7)		Group-3 (6%HES200/0.5)		Group-4 (3%HES200/0.5)		Group-5 (6%HES130/0.4)	
	Mean change± S.D.(% variation)	P value (sig.)	Mean change ± S.D. (% variation)	P value (sig.)	Mean change ± S.D.(% variation)	P value (sig.)	Mean change± S.D.(% variation)	P value (sig.)	Mean change ± S.D. (% variation)	P value (sig.)
1	0.69±4.74 [0.50%]	0.4297	0.33±1.99 [0.24%]	0.3702	0.06±5.08 [0.04%]	0.9517	0.21±3.29 [0.15%]	0.733	-0.30±5.01 [-0.21%]	0.748
3	1.02±4.86 [0.73%]	0.2596	0.82±2.92 [0.59%]	0.1361	-0.24±5.41 [-0.17%]	0.8125	0.26±3.30 [0.19%]	0.665	-0.07±6.23 [-0.05%]	0.9491
5	0.15±3.97 [0.11%]	0.8412	0.62±3.80 [0.45%]	0.3758	1.05±6.27 [0.76%]	0.3653	0.12±3.46 [0.08%]	0.8549	0.08±6.76 [0.06%]	0.9488
7	0.14±3.98 [0.10%]	0.8486	-0.12±7.39 [-0.08%]	0.9317	-0.46±4.99 [-0.33%]	0.6177	0.22±3.87 [0.16%]	0.7543	-2.17±6.20 [-1.55%]	0.0649
12	-1.46±5.56 [-1.04%]	0.162	-0.30±2.74 [-0.22%]	0.5527	-1.16±5.35 [-0.83%]	0.2443	-0.54±3.98 [-0.38%]	0.4662	-1.76±5.62 [-1.25%]	0.0977

Table 5: Mean serum potassium level (± S.D.) and minimum and maximum value in mEq/L at various time intervals in patient in different groups

Observation time(hrs)	Group 1 (RL)	Group-2 (6%HES450/0.7)	Group-3 (6%HES200/0.5)	Group-4 (3%HES200/0.5)	Group-5 (6%HES130/0.4)
	Mean± S.D.	Mean± S.D.	Mean± S.D.	Mean± S.D.	Mean± S.D.
Pre op	4.15±0.47 [3.45-5.2]	3.94±0.53 [3.11-5.69]	4.02±0.51 [3.18-5.1]	4.01±0.30 [3.31-4.6]	4.11±0.53 [3.21-5.3]
0 (Basal)	4.87±0.58 [3.61-6.09]	4.53±0.57 [3.33-5.97]	4.69±0.90 [2.94-6.48]	4.92±0.66 [3.5-6.13]	4.76±0.78 [3.14-5.99]
1	4.63±0.56 [3.16-5.49]	4.33±0.62 [2.87-5.56]	4.18±0.86 [2.97-5.83]	4.64±0.64 [3.22-5.85]	4.22±0.62 [3.08-5.46]
3	4.29±0.69 [2.47-5.27]	4.13±0.63 [2.37-5.4]	4.35±0.88 [2.67-5.79]	4.79±0.56 [3.56-6.1]	4.25±0.54 [3.42-5.59]
5	4.05±0.57 [2.95-5.17]	3.93±0.51 [2.4-4.61]	4.04±0.76 [2.75-5.62]	4.59±0.45 [3.74-5.9]	4.01±0.57 [3.19-5.86]
7	3.88±0.45 [2.94-4.8]	3.83±0.54 [2.36-4.88]	3.83±0.81 [2.68-5.84]	4.32±0.50 [3.42-5.5]	3.67±0.73 [2.84-5.67]
12	3.81±0.57 [2.91-5.18]	3.70±0.48 [2.33-4.77]	3.68±0.71 [2.41-5.38]	4.12±0.51 [3.27-5.32]	3.50±0.49 [2.66-4.64]

In all the groups there was a continuous and statistically significant decline in mean serum potassium level compared to basal value and serum potassium level remained below the basal value throughout the study period. Group 3 (6% Pentastarch 200) and group 5 (6% Tetrastarch 130) exhibited the maximum fall in serum potassium level from 7th hour onwards. Out of all five groups, group 4 (3% Pentastarch) exhibited the least deviation in serum potassium level and this was the reason, when the group 4 was compared with other groups the comparison was highly significant.

Table 6: Mean change in serum potassium level (± S.D.) in mEq/L from the baseline (0hrs)

Observation time (Hrs)	Group 1 (RL)		Group-2 (6%HES450/0.7)		Group-3 (6%HES200/0.5)		Group-4 (3%HES200/0.5)		Group-5 (6%HES130/0.4)	
	Mean change± S.D.(% variation)	P value (sig.)	Mean change ± S.D. (% variation)	P value (sig.)	Mean change ± S.D.(% variation)	P value (sig.)	Mean change± S.D.(% variation)	P value (sig.)	Mean change ± S.D. (% variation)	P value (sig.)
1	-0.24±0.61 [-4.83%]	0.0419	-0.21±0.37 [-4.54%]	0.0052	-0.51±0.69 [-10.83%]	0.0003	-0.28±0.55 [-5.78%]	0.008	-0.53±0.69 [-11.20%]	0.0002
3	-0.58±0.59 [-11.81%]	<0.001	-0.40±0.46 [-8.82%]	<0.001	-0.33±0.84 [-7.10%]	0.0379	-0.13±0.71 [-2.55%]	0.3376	-0.51±0.83 [-10.67%]	0.0024
5	-0.82±0.72 [-16.90%]	<0.001	-0.60±0.40 [-13.30%]	<0.001	-0.65±0.71 [-13.78%]	<0.001	-0.33±0.72 [-6.62%]	0.0195	-0.74±0.79 [-15.63%]	<0.001
7	-0.99±0.70 [-20.30%]	<0.001	-0.70±0.32 [-15.46%]	<0.001	-0.86±0.77 [-18.32%]	<0.001	-0.60±0.64 [-12.20%]	<0.001	-1.09±0.94 [-22.87%]	<0.001
12	-1.06±0.79 [-21.73%]	<0.001	-0.83±0.35 [-18.37%]	<0.001	-1.01±0.87 [-21.54%]	<0.001	-0.80±0.74 [-16.32%]	<0.001	-1.26±0.81 [-26.43%]	<0.001

Table 7: Mean serum chloride level (± S.D.) and minimum and maximum value in mEq/L at various time intervals in patient in different group

Observation time(hrs)	Group 1 (RL)	Group-2 (6%HES450/0.7)	Group-3 (6%HES200/0.5)	Group-4 (3% HES200/0.5)	Group-5 (6%HES130/0.4)
	Mean± S.D.	Mean± S.D.	Mean± S.D.	Mean± S.D.	Mean± S.D.
Pre op	103.80±2.92 [98.3-110.5]	104.76±3.38 [101.1-114.4]	104.63±3.38 [98.2-111.2]	103.81±2.67 [99.5-112.5]	105.29±2.79 [100.8-113]
0 (Basal)	101.64±2.69 [96.4-108.7]	103.72±2.18 [100.6-111]	101.95±4.56 [95.2-115.5]	101.54±2.05 [98.2-105.2]	102.60±2.96 [97.4-108.6]
1	101.29±2.52 [95.4-105.8]	103.99±3.64 [98.2-113.2]	101.33±4.17 [95.3-114.9]	102.05±2.46 [96.1-105.7]	101.72±2.89 [96.6-108.8]
3	100.6±2.79 [94.3-107.8]	104.65±4.25 [98.6-115.5]	101.72±3.38 [95.8-112]	101.65±2.22 [96.1-106.7]	100.67±2.79 [95.6-109.5]
5	101.46±2.02 [95.6-105.3]	103.73±3.97 [97.4-113.1]	101.53±3.75 [96.2-112.7]	100.86±2.14 [96.5-104.3]	100.56±2.23 [95.3-105.4]
7	100.77±2.39 [96.8-106.7]	103.55±2.69 [98.2-110.7]	101.36±3.40 [95.4-110.1]	100.75±2.16 [96.4-105.4]	101.35±2.49 [95.4-106.4]
12	100.34±2.17 [95.8-105.4]	102.72±2.54 [96.7-108.1]	100.61±3.51 [95.2-111.2]	101.06±1.55 [98.6-104.6]	100.51±2.29 [96.1-104.8]

In group 1, 3 and 4 there was statistically no significant change in Mean serum chloride level from baseline value throughout the study period. In group 2 there was statistically significant (P value <0.05) decrease (0.96%) in Mean serum chloride level at 12 hours from baseline value. Mean serum chloride level varied in the range of -2.10 to-0.93 mEq/L from baseline value. This difference was clinically and statistically not significant most of the time.

Table 8: Mean change in serum chloride level (± S.D.) in mEq/L from the baseline (0hrs)

Observation time (Hrs)	Group 1 (RL)		Group-2 (6%HES450/0.7)		Group-3 (6%HES200/0.5)		Group-4 (3%HES200/0.5)		Group-5 (6%HES130/0.4)	
	Mean change± S.D.(% variation)	P value (sig.)	Mean change ± S.D. (% variation)	P value (sig.)	Mean change ± S.D.(% variation)	P value (sig.)	Mean change± S.D.(% variation)	P value (sig.)	Mean change ± S.D. (% variation)	P value (sig.)
1	-0.35±3.64 [-0.34%]	0.6026	0.28±2.58 [0.27%]	0.5622	-0.62±3.69 [-0.60%]	0.3673	0.5±13.05 [0.50%]	0.3706	-0.89±3.83 [-0.87%]	0.2147
3	-1.04±3.92 [-1.02%]	0.1583	0.93±3.61 [0.90%]	0.1679	-0.23±5.20 [-0.23%]	0.8102	0.11±3.38 [0.11%]	0.864	-1.93±4.15 [-1.88%]	0.0164
5	-0.18±3.47 [-0.18%]	0.7785	0.01±3.21 [0.01%]	0.9865	-0.41±4.74 [-0.41%]	0.6362	-0.68±3.33 [-0.67%]	0.2755	-2.04±3.84 [-1.99%]	0.0068
7	-0.87±3.64 [-0.86%]	0.2012	-0.16±2.46 [-0.16%]	0.7192	-0.58±4.09 [-0.57%]	0.4405	-0.79±2.58 [-0.78%]	0.1035	-1.25±3.33 [-1.22%]	0.049
12	-1.30±4.01 [-1.28%]	0.0874	-1.00±1.95 [-0.96%]	0.0089	-1.34±4.95 [-1.31%]	0.1492	-0.48±2.90 [-0.47%]	0.3723	-2.10±3.48 [-2.04%]	0.0026

Table 9: Mean serum calcium level (± S.D.) and minimum and maximum value in mg% at various time intervals in patient in different groups

Observation time(hrs)	Group 1 (RL)	Group-2 (6%HES450/0.7)	Group-3 (6%HES200/0.5)	Group-4 (3%HES200/0.5)	Group-5 (6%HES130/0.4)
	Mean± S.D.	Mean± S.D.	Mean± S.D.	Mean± S.D.	Mean± S.D.
Pre op	9.50±0.58 [8.26-10.83]	9.26±0.62 [7.8-10.3]	9.10±0.77 [7.32-10.2]	9.58±0.49 [8.2-10.3]	9.12±0.76 [7.3-10.39]
0 (basal)	9.67±0.75 [8.04-10.97]	9.19±0.68 [7.0-10.26]	9.15±1.00 [6.86-10.85]	9.71±0.52 [8.6-10.52]	9.27±0.76 [7.91-10.67]
1	9.24±0.86 [6.39-10.82]	9.15±0.71 [7.4-10.6]	8.39±1.11 [6.01-10.07]	9.41±0.76 [7.47-10.39]	8.70±0.91 [6.78-10.37]
3	9.09±0.82 [6.86-10.25]	8.86±0.77 [6.86-10.8]	8.34±1.33 [6.11-10.93]	9.36±0.56 [8.21-10.16]	8.77±1.26 [6.13-11.5]
5	8.92±1.01 [5.74-10.45]	8.59±0.58 [7.48-9.81]	8.32±1.42 [5.76-10.42]	9.21±0.51 [8.27-10.02]	8.64±1.32 [5.71-10.99]
7	8.84±1.06 [5.16-10.85]	8.43±0.51 [6.78-9.24]	8.4±1.32 [4.99-10.36]	9.23±0.56 [8.02-10.61]	8.72±1.18 [6.36-10.57]
12	9.12±0.91 [6.26-10.46]	8.47±0.37 [7.71-9.3]	8.72±1.27 [6.26-10.88]	9.15±0.42 [8.49-10.16]	8.94±1.15 [6.14-10.6]

In all the groups there was continuous decline in Mean serum calcium level from basal value throughout the study period. The comparison of group 4 with groups 2, 3 and 5 was statistically highly significant since the deviation in the concentration of serum calcium was least in group 4 throughout study period i.e. at 1,3 5,7,12 hrs but the maximum decrease was found in Hetastarch group (6% HES-450) to the extent of 7.85% and least in tetrastarch group (6% HES-130) i.e. 3.62% at 12 hrs.

Table 10: Mean change in serum calcium level (± S.D.) in mg% from the baseline (0hrs)

Observation time (Hrs)	Group 1 (RL)		Group-2 (6%HES450/0.7)		Group-3 (6%HES200/0.5)		Group-4 (3%HES200/0.5)		Group-5 (6%HES130/0.4)	
	Mean change± S.D.(% variation)	P value (sig.)	Mean change ± S.D. (% variation)	P value (sig.)	Mean change ± S.D.(% variation)	P value (sig.)	Mean change± S.D.(% variation)	P value (sig.)	Mean change ± S.D. (% variation)	P value (sig.)
1	-0.43±0.68 [-4.47%]	0.0015	-0.04±0.44 [-0.41%]	0.6446	-0.76±0.76 [-8.32%]	<0.001	-0.29±0.52 [-3.04%]	0.0041	-0.57±0.70 [-6.13%]	0.0001
3	-0.58±0.81 [-6.04%]	0.0004	-0.33±0.76 [-3.58%]	0.0249	-0.81±1.02 [-8.88%]	0.0001	-0.35±0.51 [-3.62%]	0.0007	-0.50±1.03 [-5.40%]	0.0123
5	-0.75±0.82 [-7.79%]	<0.001	-0.60±0.57 [-6.50%]	<0.001	-0.84±1.11 [-9.12%]	0.0003	-0.50±0.46 [-5.11%]	<0.001	-0.64±1.01 [-6.85%]	0.0017
7	-0.83±0.90 [-8.58%]	<0.001	-0.76±0.53 [-8.24%]	<0.001	-0.75±1.11 [-8.21%]	0.0009	-0.48±0.67 [-4.92%]	0.0006	-0.55±1.01 [-5.97%]	0.0056
12	-0.56±0.88 [-5.76%]	0.0017	-0.72±0.60 [-7.85%]	<0.001	-0.43±1.20 [-4.72%]	0.0579	-0.55±0.72 [-5.71%]	0.0002	-0.34±1.16 [-3.62%]	0.1243

DISCUSSION

The artificial colloid Hydroxyethylstarch (HES) is available in different types according to their concentration, molecular weight, degree of substitution,C2/C6 ratio, source of starch (waxy maize derived or potato starch derived) and their carrier solution (normal saline or balanced salt solution). The older HES products were associated with adverse effects like pruritus, coagulopathy, platelet dysfunction, elevated serum amylase level, hemodilution, renal dysfunction, hyperbilirubinemia, hearing loss, tissue accumulation etc. So they evolved over time retaining their volume efficacy with improved safety and pharmacological profile. Reduction in molecular weight and degree of substitution led us to newer third generation HES with shorter half life, improved pharmacokinetic and pharmacodynamics properties and lesser side effect[1,2]. Hydroxyethyl starch was introduced in 1957 and the first generation Hetastarch was introduced into clinical practice during the 1970s. Older HES were semisynthetic colloid produced by hydroxyethyl substitution of amylopectin, a D-glucose polymer obtained from sorghum or maize. So this conformationally different polysaccharide is difficult to be metabolized by serum amylases. This leads to increase in half life of the HES and is more prominent when the hydroxyethyl residue is bound to C2 or C6 position of glucose. But they were associated with many adverse effects[1,2]. Various molecular modifications during the 1980s and 1990s leave us with the second generation Pentastarches and subsequently third generation low molecular weight tetra starches in common use today. They differ in their mean molecular weight (MW), molar substitution (MS) and C2/C6 ratio, source of starch, and carrier solution. These above modifications were mainly done to increase in half life along with to decrease incidences of adverse effects[1,2]. HES are identified by three numbers, for eg. 6% HES 450/0.7, 3% HES 200/0.5 etc. the first number denotes the concentration of the solution, the second represents the mean molecular weight in kiloDalton (kDa) and the third one is Molar substitution. These three indicators are highly relavant to the pharmacokinetic of the HES[1,2].

Concentration: it mainly reflects initial volume effect ie 6% HES solutions are isooncotic with blood, means one litre HES replaces one litre of blood loss.10% HES are hyperoncotic having volume effect more than the volume infused(about 145%)

Molecular weight: may be high (>400kD), medium (200-400 kD), and low (<200 kD) molecular weight solution.

Molar substitution: defined as mole hydroxyethyl residue per mole glucose subunit. They may be highly (0.62-0.75;hetastarch), medium (0.5; pentastarch), low substituted solution (0.4; tetrastarch)

C2/C6 ratio: solution with high (>8) and low (<8) C2/C6 ratio. After an IV infusion smaller HES molecules (less than renal threshold ie 45-60 kDa) are excreted and bigger molecules are enzymatically metabolized into smaller molecules until the renal threshold for excretion is reached. HES with low Molecular Substitution are broken down more rapidly to produce greater concentration of oncotically active particles. Part of HES diffuses into interstitial space, redistributed and ultimately eliminated and other is taken up by the reticuloendothelial system and broken down slowly. Thus, the degree of plasma and tissue accumulation is highly dependent on structure, the specific HES type, and its physicochemical properties. HES with high molecular weight, C2/C6 ratio and degree of substitution are associated with more side effects[1,2]. There are various studies evaluating HES and their volume expansion, pharmacodynamics and pharmacokinetic properties, effect on coagulation, acid base status, blood sugar level, platelet function etc. There

is no such study comparing all saline based three generation HES and their effect on blood sugar level and serum electrolytes. So this study was planned with the aim to evaluate effect of different generation of saline based HES and balanced salt solution ringer lactateon blood sugar and serum electrolytes. We have taken 150 patients, 30 patients in each group.

Blood Sugar Level: There was a steady rise in the blood sugar level in all the groups and it did not return to basal value in any group even up to 12 hours. The highest increase (42.72%) in blood sugar level was in 6% HES-450 group. However this finding is valid only statistically since the basal value in this group was much lower in comparison to other groups. The values of mean blood sugar level were otherwise comparable to other groups throughout the study period. It was a surprising finding that in group 1 eleven patients had blood sugar level more than 131 mg/dl at 3hours. As far blood sugar level is concerned group 2 exhibited a fair compliance. Thus it is evident that the breaking of the HES molecule to glucose is delayed in hetastarch. Even control group had a statistically significant rise in blood sugar level. The increase in glucose level although statistically significant was thought not to be clinically relevant in all these patients. Ringer's lactate has the potential to cause hyperglycemia due to conversion of lactate to glucose via the Cori's cycle. In the diabetic patients, peripheral disposal of lactate may be impaired because of inactivation of pyruvate dehydrogenase, while gluconeogenesis will be enhanced simultaneously. Thus in diabetic patients, lactate will be converted to glucose causing marked hyperglycemia although this does not hold true in non-diabetics to the same extent. In the non diabetics also, an increase in blood sugar level was found. Murty et.al[13](2004) studied effects of 6% Hetastarch, 6% Pentastarch 200 and Ringers lactate as preloading fluids in spinal anaesthesia on blood sugar levels and concluded starches significantly increased blood sugar levels ($p<0.05$), with peak at the end of two hours with hetastarch and at the end of 3hours with Pentastarch, RL however did not increase blood sugar levels. While in our study rise in BSL was also in RL group. Abhiruchi Patki and VC Shelgaonkar[8] (2010) concluded that Ringer's lactate and Hydroxyethyl starch 6%-450 significantly raise the blood sugar level, albeit within physiological limits. So our study is in correlation with this study. A study done by D.J.B. Thomas and K.G.M.M. Alberti[14] (1978) who used hartmann solution in diabetic and nondiabetic patients. The rise in blood sugar was more in diabetics as compared to nondiabetics. R. Beyer *et al*[6] (1997) also found similar rise in BSL with the use of 6%HES 200. Ki Tae Jung *et al*[10] (2016) and R. Raghu *et al*[11] (2015) also observed increase in BSL both in RL and 6% HES group but more in high molecular weight HES. In a study by Norbert H. Vogt *et al*[5](1996) there was gradual decline in mean BSL at 1,3, 6 hrs postoperatively different from our study. It might be due to different type and duration of surgery (>2 hrs) with substantial blood loss and simultaneous replacement of the losses with PRBC, FFPs and platelets along with HES intraoperatively. Study by S.S.Nath *et al*[9] (2015) with balanced 6% HES 130 shows no increase in BSL compared to Normal saline group. Results are different from our study, because they used 10 ml/kg tetrastarch as preloading which is less than our study. So from above studies it is concluded that higher molecular weight HES raises BSL significantly more as compared to low molecular weight HES. Ringer Lactate is associated with increased BSL than Normal Saline but to a lesser degree than HES.

Serum Sodium Level: There was no significant Mean change in serum sodium level from basal value in any group throughout the study period. The variation ranges from -2.17 to +1.05 mEq /L from basal value. A study done by Norbert H. Vogt *et al*[5] (1996), R. Beyer *et al*[6] (1997), G. B. Lehmann *et al*[4] (2007) showed there were no change in the serum electrolytes (Na^+, K^+andCl^-) even after using 3000,2400,500 ml for 5 days respectively in the time course of study period. Our study results for serum sodium are similar to these studies. Nicholas J Wilkies *et al*[15] (2001) and Subir K Brahma *et al*[16] (2017) in their study with use of balanced versus saline based HES and crystalloid solution perioperatively found no significant changes in serum sodium level in both the group. So these result further supported our study. In our study we used saline based HES as preloading fluid and balanced salt solution RL as subsequent fluid for the entire study period. So it might be the cause for no significant changes in serum sodium level.

Serum Potassium Level: In all the study groups, serum potassium level remained below basal value throughout the study period. In fact no possible valid / justifiable explanation can be produced for the decline in potassium level in our study. Surprisingly even in control group there was a significant decrease in serum potassium level from baseline value at 1st hour and the decrease became highly significant from 3rd hour onward. Out of all five groups, group 4 exhibited the least deviation in serum potassium level and this was the reason, when the group 4 was compared with other groups the comparison was highly significant. It seems that 3% Pentastarch produces the least displacement of serum potassium; the comparison of this group with other groups made the statistical significance prominant. The mean values of serum potassium were within the physiologic range throughout the study period and the clinical progress

throughout the surgical course remained uneventful. Bogumila Woloszczuk-Gebicka (2006)[17]supported our study while studies by Norbert H. Vogt *et al*[5] (1996) R. Beyer *et al*[6] (1997), G. B. Lehmann *et al*[4] (2007), Nicholas J Wilkies[15] (2001) *et al* and Subir K Brahma *et al*[16](2017) have different results. It might be due to difference in volume of HES used, duration of the study period and use of arterial blood for sampling.

Serum Chloride Level: Mean serum chloride level varied in the range of -2.10 to-0.93 mEq/L from baseline value. In group 5 there was a statistically significant (P value <0.05) change in Mean serum chloride level from 3rd hour onwards but the mean values were well within the physiological limits. Sodium chloride is often administered because it is isotonic with plasma and is initially distributed in the extracellular compartment. Non physiologic levels of chloride however have been linked to the development of metabolic acidosis and the possible impairment of splanchnic perfusion as judged by the abdominal discomfort and reduced urine output. Norbert H. Vogt *et al*[5] (1996), and G. B. Lehmann *et al*[4] (2007), supported our study while studies by Bogumila Woloszczuk-Gebicka[17] (2006) and Nicholas J. Wilkes[15] (2001) showed hyperchloridemia in their studies. Nicholas J Wilkies *et al*[15] (2001)and Subir K Brahma *et al*[16] (2017) in their study with use of balanced versus saline based HES and crystalloid solution perioperatively found significant changes in serum chloride level ie hyperchloridemia in saline based solution group. Use of balanced salt solution RL throughout study period after initial preloading with saline based HES might explain minimal variation in serum chloride level. Nicholas J Wilkies *et al*[15] and Subir K Brahma[16] also found significant variation in saline based groups rather than in balanced group. The comparison of group 2 with other groups was found statistically significant though the values in other groups were also well within the physiologic range.

Serum Calcium Level: In all the groups there was continuous and statistically significant (p value <0.05)decline in Mean serum calcium level from basal value throughout the study period. Group 2 and 3 exhibited the fall in a large number of patients. Once again, the tendency to cause a fall in serum calcium did not even spare the control group. R. Beyer *et al*[6] (1997) compared HES and Gelatin in 48 patients of orthopedic surgery. serum calcium Values in the HES group remained significantly low for up to 12 hours (7.8±0.7mg%) after operation. At 24 hours postoperatively it was 8.1±0.4mg%. Our results also correlate very well with this study. Nicholas J Wilkies *et al*[15] in their study with use of balanced versus saline based HES and crystalloid solution perioperatively found highly significant (p value 0.0001) decrease in serum calcium level in both the group. The decrease in total serum calcium in all the groups can be explained by the known "rule of thumb" whereby a decrease in albumin concentration of 1g/dl is accompanied by a decrease in total serum calcium of 0.8mg%. However, Studies by Vogt, Schönberger and Kilian[18] have confirmed that HES does not specifically affect ionized calcium even at higher doses. The comparison of group 4 with groups 2, 3 and 5 was statistically highly significant since the deviation in the concentration of serum calcium was least in group 4. The effect of 3% HES 200/0.5 on plasma oncotic pressure, total plasma proteins and serum albumin requires further study to provide a further clue as to the fact that why it produces least deflection in serum calcium.

CONCLUSION

In our study, increase in blood sugar level was seen in both Ringer Lactate and Hydroxy Ethyl Starch group. Hydroxyl ethyl starch produces a rise in blood sugar level to a variable degree according to the concentration, molecular weight and extent of substitution. There is no appreciable effect on serum sodium and chloride level while there is a marked drop in serum calcium and potassium in balanced salt solution Ringer Lactate as well as in all Saline based different generation Hydroxyl ethyl starch groups which was evident even up to 12 hours. 3% pentastarch 200 produces the least disturbances in serum calcium and serum potassium level.

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