Journal of Anesthesia and Advanced Research

Research Article | Volume: 1.1 | Open Access

Effect of Hydroxy Ethyl Starch on Blood Sugar Level In Comparison To Ringer Lactate -A Randomized Controlled Clinical Study

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Abstract

Background: In a randomized, double blind, prospective study, we have evaluated the blood sugar level after one load of hetastarch(450/0.7) and ringer lactate in patients posted for surgeries under spinal anaesthesia.

Aim: A comparative evaluation of Blood sugar level after administration of Hydroxy Ethyl Starch and Ringer Lactate.

Method: After approval from institutional ethical committeefifty patients of age group 20 to 70 yrs of either sex scheduled for lower abdominal and lower limb surgeries of more than 1 hr. under spinal anaesthesia were included in the studyafter informed written consent. Group I received Lactated Ringer (RL) 500 ml as preloading and Group II patients received Hydroxyethyl Starch solution 6% 500 ml as preloading.Blood sugar readings were taken at 30 min. intervals from basal reading for first 2 hours followed by one hourly reading for next 4 hours.

Results: Maximal blood glucose level in group I increased from basal value of 63.02 + 1.24 to 74.56 + 2.29 mg % at end of 2 hours which was not statistically significant. In group II at end of 3 hours blood glucose level increased from basal value of 64.12 + 1.56 to 99.4 + 2.50 mg % which was statistically significant ($p< 0.05$).

Conclusion: There was statistically significant increase in blood sugar values transiently in group II i.e. Hydroxy ethyl Starch group which was within physiological limits and not sustained to cause serious concern in healthy individuals.

Keywords: Blood sugar level; HES; Ringer lactate; Spinal Anaesthesia;

Introduction

Hyperglycemia is an undesirable but common occurrence in the perioperative period. Of the many possible adverse effects of hyperglycemia perhaps the most disturbing is the potential for hyperglycemia to worsen neurological outcome after a period of cerebral ischemia. Thus, in procedures in which intraoperative and perioperative cerebral ischemia is likely (e.g. during elective circulatory arrest for repair of complex cerebrovascular or cardiac disorders or during carotid end arterectomy, shock due to trauma or perioperative bleeding), it is desirable to treat preexisting hyperglycemia and prevent new onset of hyperglycemia.

The management of hyperglycemia may include a variety of techniques, including the use of insulin, alteration in the dose of gluconeogenesis enhancing drugs (e.g. glucocorticoids), and the reduction or deletion of exogenous sources of parenteral glucose. The introduction of artificial colloids has heralded a new alternative for volume expansion. Hydroxyethyl starch solutions are frequently used for volume expansion in preloading prior to spinal anaesthesia and also in other critically ill patients for treatment of shock caused by hemorrhage, burns, surgeries, or other trauma [1,2].

Received date: April 02, 2018; **Accepted date:** May 05, 2018; **Published date:** May 15, 2018.

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Citation: Agrawal J, Rakhi M, Arvind Kumar (2018) Effect of Hydroxy Ethyl Starch on Blood Sugar Level In Comparison To Ringer Lactate -A Randomized Controlled Clinical Study. J Anesthe Advan Res 1(1)

These Hydroxyethyl starch or glucose polymers are metabolized by serum amylase to produce smaller molecules of starch polymers and free glucose. Thus Hydroxyethyl starch solutions have potential to induce or potentiate hyperglycemia especially when given to patients who have diminished ability to metabolize exogenous glucose, e.g. patients with Diabetes Mellitus.

The incidence of Diabetes Mellitus has increased worldwide and further many patients are at risk as diagnosed by oral Glucose Tolerance Test. They have impaired glucose tolerance 3 to 4 times more in incidence in comparison to Diabetes Mellitus. The stress response due to surgery, anxiety and even Vene-puncture leads to epinephrine release which leads to adverse response like hyperglycemia, hypertension, tachycardia and increased catabolism.Hyperglycemia can be detrimental to wellbeing of the patient [3,4]. Hyperglycemia can damage many organs like brain, kidneys, heart, spinal cord and others by causing ischemia. It blights the White Blood Cells function and impairs wound healing.

Central Neural Blockade before surgical incision significantly reduces or abolishes the stress response to surgery, particularly in pelvic and lower limb surgeries. So, by considering all these factors, ill effects of hyperglycemia in perioperative period and frequent use of colloids (Hydroxyethyl Starch) as plasma expander, the present study aimed at examining the effects of 6% Hetastarch 450 and Ringer Lactate on Blood Glucose Levels in non diabetic patients undergoing surgical procedures under Sub Arachnoid Block (SAB).

Preloading with Crystalloid: Crystalloid like Ringer lactate and normal saline has been used extensively for preloading.

Problems of preloading with Crystalloids:

- It has short intravascular half life. About 75-80% of this solution leaks rapidly (15-20 mins) into the interstitial space. Thus, they do not expand the volume in real sense and large volume of crystalloid is required.

- Large fluid volume may decrease O_2 carrying capacity or increase the risk of pulmonary oedema in susceptible patients.
- Large volume of infusion (20 ml/kg) may itself cause hypotension by stimulating secretion of ANH (Atrial Natriuretic Peptide Hormone) due to right atrial stretching which has direct relaxing action on vascular musculature.

Such crystalloid preloading may bring down the incidence of hypotension from 80% to 43-65%. The era of crystalloid preloading has ended due to these problems.

Preloading with Colloids: Colloids are mainly confined to the intravascular space because of their high oncotic pressure that will move fluid from the interstitial space into intravascular space resulting in augmentation of the intravascular volume by a factor that is greater than the volume of colloid infused. Such colloid solutions are called plasma expanders and need to be distinguished from plasma volume substitute that do not expand the intravascular volume.

Other advantages of colloids are-

- Maintain arterial pressure, CVP and other cardiovascular parameters for longer time (2-4 hour) due to long IV half life.
- Lower volumes of fluid are required for preloading, thus minimal risk of overloading of cardiovascular system.
- Minimizes the use of vasoconstrictor drugs.

Material and Methods

This study was carried out in the Department of Anaesthesiology, Gandhi Medical College and associated Hamidia and Sultaniazanana hospital Bhopalafterapproval from institutional ethical committee.The study comprised of 50 cases of American Society of Anesthesiologists physical status I and II were required in the study and were randomly assigned¬ into two groups of 25 each depending upon the intravenous fluid Hydroxyethyl Starch or Lactated ringer used for preloading before central neuraxial blockade.All the patients were carefully screened in the preanesthetic check-up room.

A meticulous attention was paid in excluding all the patients with systemic disorders like Diabetes Mellitus, Congestive Heart Failure & Chronic Renal Failure. Patients on drugs such as Glucocorticoids, Phenytoin, Oral Contraceptives, Furosemide, and Niacin etc. were also excluded from the study. Preloading was done 15 minutes before SAB. Heart rate (ECG), Non-invasive Blood pressure, Pulse oximetry, respiratory rate, and basal blood sugar value were recorded and monitored. Blood sugar values were taken 30, 60, 90,120, 180, 240, 300, 360 minutes after the Subarachnoid Blockby accucheck glucometer. All vital parameters were monitored carefully and the occurrence of any side effects was also looked after. The results were analyzed statistically.

After preloading with the assigned intravenous fluid the patient received only Normal Saline as subsequent intravenous fluid till the final blood sugar reading was taken at the end of six hours. Blood sugar readings were taken at 30 min. intervals from basal reading for first 2 hours followed by one hourly reading for next 4 hours (30, 60, 90,120,180,240,300,360 min. after infusion). All eight blood sugar values were recorded and the differences in values were calculated.

Maximal blood glucose level in group I increased from basal value of 63.02 + 1.24 to 74.56 + 2.29 mg % at end of 2 hours which was not statistically significant. After this the blood sugar level gradually declines. Similarly in group II at end of 3 hours blood glucose level increased from basal value of 64.12 + 1.56 to 99.4 + 2.50 mg % which was statistically significant ($p< 0.05$). After this the blood sugar level gradually declines.

Observation

The present study was carried out in 50 patients of ASA grade I and II scheduled for lower abdominal and lower limb surgery under central neuraxial blockade in the department of anaesthesiology at Gandhi medical college and associated Hamidia and SultaniaZanana hospital Bhopal.The following observations were recorded- [Tables: 1,2]

The above table records variations in pulse rate after neuraxial blockade and crystalloid or colloid administration. There was no statistically significant change in pulse rate. [Table: 3]

There were no significant changes in systolic blood pressure after Subarachnoid Block and crystalloid or colloid administration.[Table: 4]

It can be seen that there was no significant change in mean respiratory rate.

Table 1: Effects on Blood Sugar Levels

Time (in min.)	Avg. Rise in Blood sugar level in group I (RL) (in mg %)	Avg. Rise in blood sugar level in group II (HES) (in mg %)
Preop	63.02±1.24	64.12+1.56*
0	62.01 ± 1.77	63.52+1.864*
30	59.36 ± 1.42	76.04+1.68*
60	66.49 ± 1.56	79.08 ± 1.82*
90	66.49 ± 1.56	88.24 ± 1.64*
120	74.568 ± 2.29	96.45 ± 2.26*
180	70.34 ± 1.81	99.40 ± 2.50*
240	68.85 ± 1.56	92.54 ± 2.12*
300	67.56 ± 1.62	90.36 ± 1.92*
360	67.32 ± 1.58	89.80 ± 1.96*

P<0.05

Table 2: Effect on pulse rate

S.No.	Time of observations	Group I (RL)			Group II (HES)			Significance
		Mean	SD	P value	Mean	SD	P value	
1	0	86.45	8.72	--	89.12	4.40	--	--
2	15 min.	87.45	9.45	0.6228	90.32	3.73	>0.05	Insignificant
3	30 min.	86.85	9.37	0.8433	89.56	5.08	>0.05	Insignificant
4	45 min.	85.57	8.27	0.6432	89.36	7.64	>0.05	Insignificant
5	60 min.	86.55	9.39	0.8433	89.20	4.04	>0.05	Insignificant
6	2 hour	83.80	7.13	0.1367	89.84	4.69	>0.05	Insignificant
7	3 hour	84.30	6.16	0.2027	90.38	3.81	>0.05	Insignificant

Table 3: Effect on Systolic Blood Pressure

S.No.	Time of observations	Group I (RL)			Group II (HES)			Significance
		Mean	SD	P value	Mean	SD	P value	
1	0	127.44	6.47	--	129.52	7.92	--	
2	15 min.	118.16	9.93	>0.05	131.44	7.99	>0.05	Insignificant
3	30 min.	126.56	3.19	>0.05	128.80	6.76	>0.05	Insignificant
4	45 min.	122.48	4.45	>0.05	127.04	6.74	>0.05	Insignificant
5	60 min.	129.92	5.82	>0.05	128.48	6.59	>0.05	Insignificant
6	2 hour	124.40	6.94	>0.05	129.68	5.94	>0.05	Insignificant
7	3 hour	125.53	4.74	>0.05	130.24	6.01	>0.05	Insignificant

Table 4: Effect on Respiratory Rate

S.No.	Time of observations	Mean Resp. rate		SD		P value		Significance
		I	II	I	II	I	II	
1	0	20.67	20.25	2.28	2.30	>0.05	>0.05	Insignificant
2	1 hour	20.25	19.57	2.30	2.38	>0.05	>0.05	Insignificant
3	2 hour	19.70	19.37	2.13	2.29	>0.05	>0.05	Insignificant

Result

Maximal blood glucose level in group I increased from basal value of 63.02 + 1.24 to 74.56 + 2.29 mg % at end of 2 hours which was not statistically significant. In group II at end of 3 hours blood glucose level increased from basal value of 64.12 + 1.56 to 99.4 + 2.50 mg % which was statistically significant ($p< 0.05$).

Statistical Analysis

All the continuous variables were presented as the mean + SD. And nonparametric data were reported as percentage. 95% confidence interval (CI) was mentioned in different analysis. We performed chi square test, which is used for testing hypothesis about nominal data. Survival analysis was done by using Kalpan-meri curve. Statistical analysis was conducted with IBM SPSS 17.0 for windows and Medcalc version 11.5.0.0. All the comparisons were performed with 2-tailed P values. The results were considered significant at P value < 0.05.

Discussion

The exacerbation of hyperglycemia in known diabetics and the new onset of hyperglycemia in previously non diabetics are well appreciated occurrences in perioperative surgical patients. The increases in blood glucose concentrations may be related to a variety of conditions, including stress, corticosteroid use, anaesthetic agents, i.v. infusions of glucose, and i.v. hyper alimentation other than glucose.

In hyperglycemic patients, increases in blood glucose concentrations, per se, are credited with the initiation of a number of conditions that may adversely affect patients. The increased osmotic load introduced by glucose may result in an osmotic diuresis, making it difficult to assess intravascular volume status by measuring hourly urine output. Hyperglycemia may inhibit wound healing and, because of an inhibition of white blood cell activity, may inhibit the ability to fight infections.Although a variety of techniques may be used to acutely decrease blood glucose values in the perioperative period, one option is to delete hyperglycemia-inducing drugs and solutions from the patient's therapy, particularly during periods in which the patient is at greatest risk for an adverse effect from hyperglycemia.

The present study entitled "Blood sugar level after the administration of Hydroxyethyl Starch – comparison of one volume load of Hetastarch and Ringer Lactate "was carried out in the Department of Anaesthesiology, Gandhi Medical College and associated Hamidia & Sultania Zanana Hospital Bhopal after approval from institutional ethical committee.

As stress and pain causes release of catecholamines which lead to rise in blood sugar level as occur due to fluctuation in depth of anaesthesia. Our study has been carried out in 50 patients of ASA grade I and II who were scheduled for lower limb or lower abdominal surgery under central neuraxial blockade as SAB or Epidural causes little or no stress response in these surgeries.Subarachnoid block or epidural causes sympathetic blockade resulting in hypotension. We have used ringer lactate and

Hydroxyethyl starch as preloading fluid before the block was given.

McClain CD, McManus ML et al studied that fluid and electrolyte disturbances are common among children and fluid management is critical to the successful care of a wide range of pediatric conditions. The chapter outlined the basic anatomy and physiology of fluid compartments, their developmental maturation, and a general approach to fluid administration. Clinical assessment of hydration states, perioperative fluid management, and the care of common pathophysiologic states are discussed in detail. Specific attention is given to acid–base balance and to disorders of sodium, potassium, and water homeostasis [5].

YACOBI A, STOLL RG et al. on the other hand told about pharmacokinetics of hydroxyethyl starch in normal subjects. Ten volunteers were given 500 ml 6% HES solution by intravenous infusion, and serial blood and urine samples were collected for nonglucose total carbohydrate determination. As expected, the infusion of HES resulted in plasma volume expansion over a 48-hour period during which time levels of nonglucose carbohydrates were above 3.5 mg/ml. HES is metabolized by α-amylase in the body. During the first 48 hours after infusion of HES, plasma α-amylase activity was significantly increased over control. Concomitantly, α-amylase activity in urine was also elevated but not significantly so [6].

In another similar study, Jungheinrich C, Neff TA et al found that hydroxyethyl starch has recently become the subject of renewed interest because of the introduction of a new specification, hydroxyethyl starch 130/0.4, as well as the clinical availability of a solution using a previous hydroxyethyl starch type (hydroxyethyl starch 670/0.75) with a carrier other than 0.9% saline.Various types of hydroxyethyl starch show different pharmacokinetic behaviour. Since hydroxyethyl starch is a polydisperse solution acting as a colloid, pharmacodynamic action depends on the number of oncotically active molecules, not on the plasma concentration alone; the pharmacodynamics with respect to the volume effect does not directly mirror pharmacokinetics in the case of hydroxyethyl starch solutions. Equivalent volume efficacy has been proven for hydroxyethyl starch 130/0.4 compared with 200/0.5. Prolonged persistence of hydroxyethyl starch in plasma and tissues can be avoided by using rapidly metabolisablehydroxyethyl starch types with molar substitution <0.5. Influence on coagulation is minimal with hydroxyethyl starch 130/0.4, and no adverse effects on kidney function have been observed even with large repetitive doses when used according to the product information [7].

Klotz U, Kroemer H. et al studied clinical pharmacokinetic considerations in the use of plasma expanders. This review deals with the pharmacokinetics of dextrans and hydroxyethylstarch, the most commonly used plasma expanders. The complex composition of these colloidal agents (broad range of molecular weight distribution in vitro and in vivo,) confounds their specific assay and meaningful pharmacokinetic analysis. Extrarenal excretion and metabolism of dextrans by dextranases account for only 2 to 10% of the overall drug loss from the body. Dextran species with a molecular weight below 15,000 daltons are filtered unrestricted, and consequently the elimination half-life of dextran 1 is relatively short (2 hours) and that of dextran 40 (10 hours) or dextran 60 (42 hours) much longer. In conclusion, the disposition and pharmacological effects of plasma expanders are related to time-dependent changes in the molecular weight distribution of the plasma concentration decline. Unfortunately, the analytical assays applied in most studies were not able to differentiate the complex mixture of the infused colloids [8].

Murty SS, Kammath S et al did a randomized double blind study on the effects of hydroxyethyl starches on blood sugar levels. Hofer RE, Lanier WL et al in a similar study saw effect of hydroxyethyl starch solutions on blood glucose concentrations in diabetic and nondiabetic rats. The effects of i.v. infusions of 6% hetastarch or 10% pentastarch on blood glucose concentrations were tested. Neither hetastarch nor pentastarch infusions significantly altered blood glucose values over the 3-hr study period, regardless of whether the rats were diabetic or nondiabetic. Assuming these data are transferable to humans, the authors conclude that hydroxyethyl starch solutions do not produce or exacerbate hyperglycemia, and furthermore, that their use is not contraindicated in subjects having hyperglycemia from diabetes mellitus or iatrogenic causes [9,10].

Cullingford DW etal studied the blood sugar response to anaesthesia and surgery in southern Indians During the course of anaesthesia and surgery in South India, it was noticed that Indian and European patients responded differently. In an attempt to evaluate these differences, blood sugar values were used as a guide to the sympathetic nervous response. Under general anaesthesia values rose and stayed higher in Indian patients than in Europeans in India or England. General anaesthesia by itself provoked no elevation until the commencement of surgical trauma. Under subarachnoid or epidural analgesia, no major change in blood sugar occurred during surgery. During the study involving 141 patients, three collapsed unexpectedly and resuscitative measures invalidated the blood sugar results. Although nutrition might play some part, the differences are considered to be racial and not climatic [3].

Hydroxyethyl Starch (HES), a commonly used resuscitation fluid, has the property to induce hyperglycemia as it contains large ethyl starch, which can be metabolized to produce glucose. Jung KT, Shim SB et al studied effect of hydroxyethyl starch on blood glucose levels.in non-diabetic patients undergoing elective lower limb surgery under spinal anesthesia.Fifty-eight patients were divided into two groups according to the type of the main intravascular fluid used before spinal anesthesia (Group LR: lactated Ringer's solution, n = 30 vs. Group HES: 6% hydroxyethyl starch 130/0.4, n = 28). Blood glucose levels were measured at the following time points: 0 (baseline), 20 min (T1), 1 h (T2), 2 h (T3), 4 h (T4), and 6 h (T5). Mean blood glucose levels at T5 in the LR group and at T4, T5 in the HES group, increased significantly compared to baseline. There were no significant changes in the serial differences of mean blood glucose levels from baseline between the two groups. Administration of 6% HES-130 increased blood glucose levels within the physiologic limits, but the degree of glucose increase was not greater than that caused by administration of lactated Ringer's solution. In conclusion, the authors did not find evidence that 6% HES-130 induces hyperglycemia in non-diabetic patients [11].

In another similar study, which also corelates well with our study, Patki A, Shelgaonkar VC et al. studied effect of 6% hydroxyethyl starch-450 and low molecular weight dextran on blood sugar levels during surgery under subarachnoid block.The following study was designed to compare 6% hydroxyethyl starch-450 with Dextran 40, both used as preloading fluids, for their potential to raise peri-operative blood glucose levels. All the three preloading fluids, were seen to significantly increase the capillary blood glucose levels intra-operatively ($P < 0.05$), but the rise with Dextran-40 was seen to be sustained and highly significant ($P < 0.001$). We thus conclude that, Dextran40 causes a sustained and significant rise in peri-operative blood glucose levels [12].

Li Y, He R, Ying X, Hahn RG. Ringer's lactate, but not hydroxyethyl starch, prolongs the food intolerance time after major abdominal surgery. The infusion of large amounts of Ringer's lactate prolongs the functional gastrointestinal recovery time and increases the number of complications after open abdominal surgery. The order of the infusions had no impact on the outcome. Both the administration of ≥ 2 L of Ringer's lactate and the development of a surgical complication were associated with a longer time period of paralytic ileus and food intolerance (two-way ANOVA, $P < 0.02$), but only surgical complications prolonged the length of hospital stay ($P < 0.001$). The independent effect of Ringer's lactate and complications of food intolerance time amounted to 2 days each. The infusion of ≥ 1 L of hydroxyethyl starch did not adversely affect gastrointestinal recovery. To conclude, Ringer's lactate, but not hydroxyethyl starch, prolonged the gastrointestinal recovery time in patients undergoing laparoscopic cancer surgery [13].

Wilkes NJ, Woolf R et al. studied the effects of balanced versus saline-based hetastarch and crystalloid solutions on acid-base and electrolyte status and gastric mucosal perfusion in elderly surgicalpatients. Forty-seven elderly patients undergoing major surgery were randomly allocated to one of two study groups. Patients in the Balanced Fluid group received an intraoperative fluid regimen that consisted of Hartmann's solution and 6% hetastarch in balanced electrolyte and glucose injection (Hextend). Patients in the Saline group were given 0.9% sodium chloride solution and 6% hetastarch in 0.9% sodium chloride solution (Hespan®). Biochemical indices and acid-base balance were determined. Gastric tonometry was used as a reflection of splanchnic perfusion. Postoperative chloride levels demonstrated a larger increase in the Saline group than the Balanced Fluid group. In this study, the use of balanced crystalloid and colloid solutions in elderly surgical patients prevented the development of hyperchloremic metabolic acidosis and resulted in improved gastric mucosal perfusion when compared with saline-based solutions [14].

Conclusion

The consequences of hyperglycemia are disastrous for patients like bad neurological outcome, damage to kidney, heart, and other organs by causing ischemia, also impairs white blood cells function and wound healing.Thus there was statistically significant increase in blood sugar values transiently in group II which was within physiological limits and not sustained to cause serious concern in healthy individuals.

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