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Balanced hydroxyethyl starch solution and hyperglycaemia in non diabetics — a prospective, randomized and controlled study

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Abstract

Background: There are very few studies that have examined the effect of hydroxyethyl starch (HES) solutions on blood glucose level. The study was aimed to compare the effects on blood glucose levels in patients undergoing lower limb surgeries under neuraxial block, receiving HES with those receiving 0.9% saline.

Patients and methods: 160 non-diabetic ASA I or II patients, aged between 18–65 years were selected for the trial. Patients were divided into two groups; Group C (n = 80, patients received only 0.9% saline for preloading and maintenance until six hours of the end of preloading) and Group T (n = 80, patients received Tetraspan™ 10 mL kg^{-1}, for preloading and 0.9% saline for maintenance until six hours from the end of preloading). Blood glucose was recorded prior to the start of preloading and repeated at two, four and six hours after the end of HES infusion or the preloading dose of 0.9% saline.

Results: The following blood glucose levels were comparable at all times; fasting/baseline (85.3 ± 19.2 mg dL^{-1} in group C and 95.4 ± 17.3 mg dL^{-1} in group T); increase in blood glucose concentration at 2 hours (6.44 ± 20.59 mg dL^{-1} in group C and 10.8 ± 18.1 mg dL^{-1} in group T); 4 hours (4.1 ± 12.1 mg dL^{-1} in group C and 3.5 ± 11.8 mg dL^{-1} in group T); and at 6 hours (2.9 ± 13.4 mg dL^{-1} in group C and 3.5 ± 10.6 mg dL^{-1} in group T).

Conclusion: A balanced HES solution administered intravenously did not cause an increase in blood glucose concentrations compared to those who received 0.9% saline.

Key words: colloids, balanced hydroxyethyl starch, side effects, blood glucose

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Artificial colloids such as gelatin and starch solutions have been used for years for volume support, as well as volume preloading prior to neuraxial blocks. Although hydroxyethyl starch solutions (HES) have been quite popular but they are not free of adverse effects. There had been performed many studies which evaluated their adverse effects on coagulation [1], potentially misleading effects on blood grouping [2], and kidney dysfunction [3]. However, there are very few studies which have examined their role on blood glucose concentration. One of the factors associated with both blood glucose concentration and its variations is colloid administration for volume management [4]. Moreover, 6% HES had been shown in experimental studies to cause hyperglycaemia [5]. The literature does not, however, gives any information regarding the potential of balanced HES solution to raise blood glucose. The aim of the study, therefore, was to compare the effects of 6% balanced HES solution on blood glucose levels in patients undergoing lo-

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Table 1. Demographic details and blood glucose changes in patients in control and test groups (mean ± SD)

	Control group	Test group	*P* value
Age (years)	49.6 ± 18	46.8 ± 17	0.39
Males (%)	62.5	65.0	
Body mass (kg)	61.89 ± 9.37	63.2 ± 10.74	0.48
Baseline blood glucose (mg dL^{-1})	85.33 ± 19.2	95.4 ± 17.28	0.06
Rise after 2hrs from baseline (mg dL^{-1})	6.44 ± 20.59	10.8 ± 18.1	0.56
Rise after 4hrs from baseline (mg dL^{-1})	4.06 ± 12.06	3.46 ± 11.83	0.60
Rise after 6hrs from baseline (mg dL^{-1})	2.91 ± 13.39	3.45 ± 10.64	0.23

wer limb surgeries under neuraxial block to those receiving 0.9% normal saline (NS).

METHODS

The study was conducted at Sahara Hospital, Lucknow, India after clearance from the institute's ethical committee and gaining the written informed consent from all participating patients. 160 non-diabetic ASA I or II patients (80 in each group), in the age group of 18–65 years, scheduled for lower limb surgeries under central neuraxial block (spinal/epidural/combined spinal and epidural analgesia) were selected for the trial.

Patients were divided into two groups by the drawing of lots - Group C patients, received 20 mL kg^{-1} normal saline for preloading, and maintenance until six hours from the end of preloading), and Group T patients, received 10 mL kg^{-1} balanced HES solution (Tetraspan™, B Braun Melsung AG, Melsung, Germany), for preloading and normal saline for maintenance until six hours from the end of preloading). Preloading with either normal saline or Tetraspan was done over 30 minutes prior to the administration of the neuraxial blockade. For maintenance, 5 mL kg^{-1} h^{-1} of NS was administered until six hours from the end of preloading in both groups.

Those with known allergies to HES and those receiving any steroid or adrenergic drugs were excluded from the study. Other exclusion criteria included renal failure, hyperkalaemia, hypokalaemia, severe hypernatremia, or severe hyperchloraemia and impaired hepatic function. The blood glucose measurement was done by a glucometer (Accu-chek Advantage, Roche). Blood glucose was measured and recorded prior to the start of preloading (baseline) and repeated at two hours, four hours and six hours after the end of HES infusion or preloading volume of normal saline. Blood glucose measurement was done by an anaesthesia technician, who was blinded to the study group. Patients who had significant blood loss or whose duration of surgery had exceeded 2 hours, were excluded from the study.

STATISTICAL ANALYSIS

Differences in patient characteristics were analyzed using Student's t-test. Blood glucose variables were analyzed between the groups, using an analysis of variance (ANOVA) for repeated measurements. Analysis was performed using SPSS version 19. A P value < 0.05 was adopted as significant.

RESULTS

One patient each in the two groups had blood loss exceeding 500 mL, and, in one patient in the control group and two patients in test group, the duration of surgery exceeded 2 hours. All these patients were excluded from the study. Therefore, we analyzed results obtained from 58 patients in the study group and 57 in the control group for comparison. Table 1 presents the demographic characteristics of the groups (no significant differences) and blood glucose measurement results. The fasting/baseline blood glucose levels, the difference in blood glucose levels at 2 hours, 4 hours and at 6 hours from baseline or fasting values were similar. The blood glucose levels at all times-baseline were also comparable.

DISCUSSION

Tetraspan® (B Braun Melsung AG, Melsung, Germany) is a colloidal plasma volume substitute containing 6% HES in a balanced electrolyte solution. The electrolyte composition includes: sodium 140 mmol L^{-1}, potassium 4.0 mmol L^{-1}, calcium 2.5 mmol L^{-1}, magnesium 1.0 mmol L^{-1}, chloride 118 mmol L^{-1}, acetate 24 mmol L^{-1}, and maleate 5.0 mmol L^{-1}. It has an osmolarity of 297 mOsmol L^{-1}. HES is a mixture of several different molecules with different molecular weights and degrees of substitution. Elimination is dependent on the molecular weight and degree of substitution. Molecules which, in terms of size are below the so--called renal threshold are excreted by glomerular filtration; larger molecules are first degraded by alpha amylase before they are excreted through the kidneys. The rate at which the molecules are degraded decreases with the increased degree of substitution of the molecules.

HES solutions are used for volume support, as well as for preloading prior to neuraxial blocks. Plasma adapted HES 130/0.42 is used widely for volume therapy. Several adverse effects had been associated with its use. Although the FDA issued warnings regarding the possibility of hyperglycaemia with the use of HES way back in 1999 [6], there are very few studies which have evaluated the effects of HES on blood glucose levels, and, for that matter, the effect of balanced HES solutions which are relatively new. We have for the first time studied the effect of infusion of a balanced HES solution on blood glucose levels in patients undergoing lower limb surgeries under central neuraxial block, compared to those receiving only normal saline.

HES has been shown in experimental studies to raise blood glucose values. It was observed that pigs that received prolonged anaesthesia and received volume support with 6% HES had higher blood glucose levels compared to those who received 4% gelatin [5].

In a study on 150 ASA I, non-diabetic patients undergoing elective surgery, patients received either 20 mL kg^{-1} of Ringer's lactate, 10 mL kg^{-1} of 6% HES 450/0.7 or 10 mL kg^{-1} of 6% HES 200/0.5 for preloading prior to spinal anaesthesia over a period of 1 hour. No significant changes in blood sugar concentrations until 360 min after the end of the infusion were seen in the Ringer's lactate group, whereas blood sugar concentration significantly increased in the HES 450/0.7 (maximum increase 37.9 ± 2.85 mg dL^{-1}) and HES 200/0.5 group (maximum increase 31.48 ± 3.47 mg dL^{-1}) [7]. In this study, the authors infused Ringer's lactate in the control groups [7]. Ringer's lactate solution itself can raise blood glucose as almost half of the lactate contained in it is converted to glucose by Cori's cycle [8]. This is why those who received Ringer's lactate cannot be considered ideal controls. We have used "true" controls, as our control group patients were administered only normal saline throughout the study period. Normal saline had not been reported to have any influence on blood glucose levels.

The US FDA has also reported that blood glucose levels rose after an infusion of HES solution [6]. The reason behind this rise in blood glucose could also be the presence of lactate (sodium lactate 317 mg per 100 mL) in this preparation (Hextend) whereas the preparation used by us contained no lactate, instead containing acetate. Lactate may be converted to pyruvate and can enter the gluconeogenic pathway to be converted to glucose [9]. Acetate, on the other hand, is quickly converted to acetyl-CoA by the enzyme acetyl--CoA synthetase [10]. It was shown that intravenous sodium acetate (NaAc) administration had a large suppressive effect upon both fat and carbohydrate utilization (decreases of 81% and 22%, respectively, when compared with pre-infusion values). Moreover, infusion of acetate decreases plasma glucose concentration [9].

Stress related to surgery and anaesthesia can raise blood glucose levels [11] by releasing catecholamines which are known to cause hyperglycaemia and hyperketonaemia. Blood glucose concentration is known to increase during surgery because of cortisol and catecholamine-induced increased hepatic glycogenolysis and gluconeogenesis and decreased peripheral utilization of glucose [12]. An increase in blood glucose levels is related to the intensity of the surgical injury and closely follows the increases in levels of catecholamine. In cardiac surgery, blood glucose concentration can increase up to 10–12 mmol L^{-1} and remains elevated for 12 hours after surgery [11]. Moreover, surgery also causes a reduction in insulin sensitivity proportional to the length and technique of the procedure. It has been demonstrated that laparoscopically-performed cholecystectomy resulted in a significantly less reduction in insulin sensitivity compared to the conventional open surgical technique [13].

Surgeries conducted under neuraxial blocks produce minimal stress response. In our study all the patients had their surgeries conducted under neuraxial block, had minimal blood loss and the duration of surgery was 2 hours or less. Thus, most of the confounding factors that could have influenced blood glucose levels were excluded.

It is known that exclusive use of normal saline (30 mL kg^{-1} h^{-1}) produces a hyperchloraemic acidosis, with this acidosis being derived from the chloride load [14]. Although it is recognized that there appears to be some side-effects associated with saline use, to date these have not translated into clinically important outcomes, though this may be through a lack of data. There is little evidence that in the 50 years of normal saline usage, there has been significant morbidity from the use of this fluid. A mild exogenous acidosis may even be protective before or during an insult, setting the scene for immediate enhanced oxygen delivery [14]. The nature and longevity of an acidosis had been described by Bruegger et al. who showed an acidosis developing intraoperatively which then cleared spontaneously within 24 h [15].

In this study we used an Accu-Chek Advantage glucometer, manufactured by Roche Diagnostics to measure capillary blood glucose. This glucometer utilized glucose dehydrogenase and the coenzyme pyrroloquinoline quinine [16].

The present study shows that there is no significant rise in blood glucose levels due to an intra-operative infusion of balanced HES solution. We believe that although clinically relevant changes in blood sugar levels due to an infusion of balanced HES appears to be unlikely, large clinical trials including patients with established diabetes mellitus and using new HES preparations would be helpful to revalidate the findings.

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