Hydroxyethyl Starch Preloading Solutions Increased Blood Glucose Level of Nondiabetic Patients Undergoing Subarachnoid Block for Lower Abdominal Surgeries

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Abstract

Key words: 6% hydroxyethyle starch 200/0.5, 6% hydroxyethyl starch 130/0.4, blood glucose, hyperglycemia, nondiabetics.

Background: Hypotension secondary to subarachnoid block is one of the main concerns of anesthesia. Hydroxyethyl starches (HES) is commonly used fluid to treat hypotension. We compared the tendency of 6% hydroxyethyl starch 200/0.5 (Haes-steril) and 6% HES 130/0.4 (Voluven) to induce perioperative hyperglycemia in nondiabetic patients undergoing subarachnoid block for lower abdominal surgery.

Methods: A prospective study was conducted from January 2014 to October 2017. Of the nondiabetic patients scheduled for elective lower abdominal surgeries under spinal anesthesia, 150 were randomly divided into three groups receiving 10 ml/kg preloading volume of normal saline 0.9% (group A), 6% HES 200/0.5 (Haes-steril) (group B), and 6% HES 130/0.4 (Voluven) (group C) 30 minutes before the subarachnoid block. Serial blood glucose measurements were obtained at regular intervals till 240 minutes after baseline reading.

Results: Blood glucose levels were significantly increased intraoperatively in groups B and C ($P < 0.001$), and in the postoperative period in group B ($P < 0.05$). Also, 6% HES 200/0.5 significantly increased perioperative blood glucose levels.

Conclusions: Preloading patients with 6% HES 200/0.5 (Haes-steril) significantly elevates the blood glucose level, more than 6% HES 130/0.4 (Voluven) in nondiabetic individuals undergoing lower abdominal surgeries.

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Introduction

Spinal anesthesia causes variable degrees of sympathetic blockade resulting in peripheral vasodilatation with subsequent hypotension. As such, anesthesiologists should pay special concern for block-induced hypotension. Many studies have been conducted to evaluate the effectiveness of various methods that either prevent or minimize subarachnoid block induced hypotension including fluid preload[1,2], timing of preload[3,4], use of vasopressors, selective position of patients, and use of lower limbs stockings.[5] Fluid preloading remains the most commonly used method.[6]

Hydroxyethyl starches (HES), nonionic starch derivatives, are made up of large glucose polymers. They are metabolized by amylase enzyme into both small glucose residues and starch polymers, which carry the potential risk of hyperglycemia under stress.[7-10]

Perioperative stress leads to catecholamine release, resulting in hyperglycemia, which might be concealed to some extent, but with concomitant metabolism of infused HES, it becomes overt.[11-13]

Hyperglycemia not only carries a detrimental ischemic risk for the myocardium, brain, spinal cord, and kidney but also causes delayed wound healing, which is exacerbated in patients with uncontrolled diabetes mellitus.[13,14]

This study was conducted to assess the effect of preloading fluids of 6% HES 200/0.5 (Haes-steril) and 6% HES 130/0.4 (Voluven), in comparison with the preloading with normal saline, on blood glucose levels of nondiabetic patients scheduled for lower abdominal surgeries under subarachnoid block.

Materials and methods

After the approval of the research and ethical committee of King Abdulaziz university Hospital (Reference no 10085/13), informed written consents were obtained from all patients. A prospective randomized double-blinded study was conducted from March 2015 to March 2017, where 150 patients aged 18 to 60 years, males and females, American Society of Anesthesiologists (ASA) class I and II, scheduled for elective lower abdominal surgeries were enrolled in the trial. Patients on steroids, adrenergic drugs, octreotides, ascorbic acid, and acetaminophen medications; obese patients; patients with a low hematocrit (<30%); patients who had a surgical procedure longer than 2 hours of duration; patients with a history of allergy to study fluids; patients with cardiac, hepatic, or renal disease; and patients that required intraoperative blood transfusion were excluded from the study.

Blood glucose levels were measured at regular intervals, using OneTouch UltraMini® Meter (LifeScan, Inc., Milpitas, CA 95035, USA). Baseline reading was obtained just before the initiation of preloading, followed by measurements of glucose at 15, 30, 45, 60, 75, 90, 105, 120, 150, 180, and 240 minutes.

Thus, a total of 12 blood glucose readings were recorded. Samples were obtained via an arterial cannula, inserted in the radial artery under local anesthesia in the preoperative holding area.

All patients received the same preload fluid volume (10 ml kg^{-1}) 30 minutes before the performance of spinal anesthesia by infusion pump through 18 G intravenous cannula.

Patients were randomly allocated into one of the three groups based on a computer-generated ta-

ble of randomization, with 50 patients in each group. Group A received normal saline 0.9% (B. Braun Medical Inc., 1601 Wallace Drive Suite 150 Carrollton, TX 75006, USA), group B received 6% HES 200/0.5 (Haes-steril®, Fresenius Kabi Deutschland GmbH, Germany), while group C received 6% HES 130/0.4 (Voluven®, Fresenius Kabi Deutschland GmbH, Germany).

The pharmacy prepared the study fluid according to a list of study numbers in a concealed way to ensure blinding of the treating doctor. While in a sitting position, patients received spinal anesthesia with 3 ml hyperbaric bupivacaine (Marcaine® Spinal 0.5% Heavy, AstraZeneca Pharmaceuticals, Wilmington, DE 19803, USA), through 25 G pencil point spinal needle (RapID™, Smith Medical ASD, Inc., Keene, NH 03431, USA).

The level of sensory block was tested by changing in the temperature using an ice cube with the forehead as a reference point.

After the administration of preloading study fluids, the three study groups received IV normal saline as a maintenance fluid until the end of the study.The heart rate (HR), the mean arterial pressure (MAP), and blood glucose levels were reported by an observer who was blinded to the study group.

Statistical analysis

The required sample size was calculated using the G*Power software version 3.1.3 (Universität Düsseldorf, Germany).

The primary outcome measures were the maximum blood glucose level, percentage of increase in blood glucose level above baseline, time-weighted average (TWA) blood glucose, and area under the blood glucose-time curve (AUC).

It has been estimated that a sample size of 50 patients per group would achieve a power of 80% to detect a statistically significant difference among the three groups for a medium effect size equivalent to 0.25 with respect to the primary outcome measures using a two-sided F-test with a type I error of 0.5. Data were analyzed using MedCalc© version 15 (MedCalc© Software bvba, Ostend, Belgium).

Normally distributed numerical variables were presented as mean ± SD and intergroup differences were compared using one-way analysis of variance (ANOVA) with the application of the Student-Newman-Keuls post hoc test for pairwise comparison whenever the ANOVA test revealed a statistically significant difference among the groups.

Categorical variables were presented as number and percentage, and intergroup differences were compared using the chi-squared test.

P-values <0.05 were considered statistically significant.

Results

Patients' characteristics are shown in Table 1 and the operative details are shown in Table 2. The three study groups were comparable with respect to the age, body weight, height, body mass index, surgical procedures performed, and operative time. Figure 1 shows the intergroup comparison of the mean blood glucose at all 12 time points. The baseline blood glucose was comparable in all three groups.The mean blood glucose in group B at T3 through T11 was significantly higher than both group A and group C (adjusted p-values <0.05).

Table 1. Patients' characteristics in the three study groups

Variable	Group A (n = 50)	Group B (n = 50)	Group C (n = 50)	p-value
Age (years)	39.7 ± 12.6	38.5 ± 9.9	41.7 ± 10.6	0.351
Body weight (kg)	78.1 ± 14.4	72.9 ± 14.7	77.5 ± 15.4	0.165
Height (cm)	167.6 ± 7.7	167.5 ± 8.9	165.2 ± 8.3	0.254
BMI ($kg.m^{-2}$)	27.9 ± 5.8	26.2 ± 6.4	28.8 ± 7.0	0.132

Data are presented as mean ± SD.

BMI = body mass index.

Table 2. Operative data in the three study groups

Variable	Group A (n = 50)	Group B (n = 50)	Group C (n = 50)	p-value
Surgical procedure				0.787
Inguinal hernia repair	15 (30%)	14 (28%)	11 (22%)	
Knee arthroscopy	5 (10%)	6 (12%)	7 (14%)	
Abdominal hysterectomy	8 (16%)	9 (18%)	8 (16%)	
Varicocelectomy	5 (10%)	11 (22%)	9 (18%)	
Ovarian cystectomy	12 (24%)	6 (12%)	8 (16%)	
Anterior and/or posterior repair	5 (10%)	4 (8%)	7 (14%)	
Operative time (min)	98.5 ± 5.1	99.1 ± 4.3	99.5 ±4.2	0.548

Data are presented as number (%) or mean ± SD.

Besides, the mean blood glucose levels in group C at T6 through T9 were significantly higher than group A. The previously observed differences among the three groups disappeared at T12 as the blood glucose levels returned to their baseline values. Table 3 shows the results of serial measurements analysis for blood glucose levels in the three study groups. All three groups were comparable with respect to the baseline blood glucose levels. The maximum blood glucose level was significantly higher in group B than in both group A and group C (adjusted p-values <0.05). Also, the maximum blood glucose level in group C was significantly higher than in group A. The maximum increase above baseline blood glucose level was the highest in group B, followed by group C and then group A. The differences between group B and both group A and group C were statistically significant. The difference between group C and group A was statistically significant. The percentage of maximum increase above baseline blood glucose level was significantly higher in group B than in group A and group C. The difference between group C and group A was also statistically significant.

The time-weighted average (TWA) blood glucose was 90.2 ± 1.8 mg dl^{-1}, 103.5 ± 4.4 mg dl^{-1}, and 93.6 ± 2.4 mg dl^{-1} for group A, group B, and group C, respectively. The differences between group B and both group A and group C were statistically significant. Moreover, the difference between group C and group A was statistically significant.

ANOVA test showed that there were no statistically significant differences between the study groups regarding the average level of changes in HR and MAP.

Linear regression analysis showed that neither age nor BMI is a significant independent predictor for the changes in the blood glucose level (P >0.05).

Table 3. Serial measurement analysis for the blood glucose levels in the three study groups

Variable	Group A (n = 50)	Group B (n = 50)	Group C (n = 50)	p-value
Blood glucose level				
Baseline (mg.dl^{-1})	85.1 ± 6.2	85.1 ± 6.6	85.9 ± 6.4	0.742
Maximum (mg.dl^{-1})	96.5 ± 2.3	123.6 ± 15.0†‡	105.4 ± 8.9†	<0.001
Maximum increase above baseline (mg.dl^{-1})	10.1 ± 8.9	38.2 ± 16.3†‡	17.7 ± 13.6†	<0.001
Percentage of maximum difference above baseline (%)	12.6 ± 11.1	45.6 ± 20.1†‡	21.4 ± 16.9†	<0.001
Time-weighted average (TWA) (mg.dl^{-1})	90.2 ± 1.8	103.5 ± 4.4†‡	93.6 ± 2.4†	<0.001
Area under the curve blood glucose-time curve (AUC)	56.9 ± 56.2	201.9 ± 69.0†‡	84.3 ± 61.8†	<0.001

Data are presented as mean ± SD.

†p-value <0.05 versus Group A.

‡p-value <0.05 versus Group C.

Discussion

Most of the studies conducted on starch solutions have evaluated their volume expansion properties and their impact on blood coagulation.[15-17] Few studies have examined the possibility of starches producing hyperglycemia despite their pharmacodynamic potential to cause hyperglycemia.[8,18]

This study evaluated the effect of 6% HES 200/0.5 (Haes-steril) and 6% HES 130/0.4 (Voluven) preloading on the blood glucose levels of nondiabetic patients undergoing lower abdominal surgery under subarachnoid block. There was a significant increase in blood glucose in 6% HES 200/0.5 (Haes-steril) compared to 6% HES 130/0.4 (Voluven) or normal saline. Jung et al. showed an increase in the serum glucose level after preloading patients with 6% HES 130/0.4 (Voluven) and Ringer's lactate in patients undergoing lower limb surgery under spinal anesthesia. There was no statistical difference between the two groups, and the increased glucose levels were within the physiologic range.[18]

Murty et al. studied the effect of Hestar 6%-450, Pentastarch 200, and Ringer's lactate as preloading fluids in spinal anesthesia on blood glucose levels. They concluded that both starches significantly elevated the blood glucose levels, with peak levels at the end of 2 hours in Hestar 6%-450 group and at the end of 3 hours in pentastarch 6% group that persisted for 6 hours in both groups.[8] In the current study, the blood glucose levels returned to baseline values at 240 minutes.

Patki and Shelgaonkar compared 6% HES-450 with Dextran 40 as preloading fluids for their potential to raise perioperative blood glucose levels. The study used Ringer's lactate as control. All the three preloading fluids, including Ringer's lactate, were found to increase the capillary blood glucose levels intraoperatively, but the rise with Dextran 40 was seen to be sustained and highly significant.[19] Ringer's lactate used as a control in this study has been shown to cause hyperglycemia, which was attributed to the conversion of lactate to glucose via the Cori cycle.[20]

In a study involving 160 non-diabetic ASA I-II patients, Nath et al studied the effect of preloading with normal saline 0.9% to Tetraspan (a colloidal plasma volume substitute containing 6% HES in a balanced electrolyte solution) on the blood glucose level. They concluded that a bal-

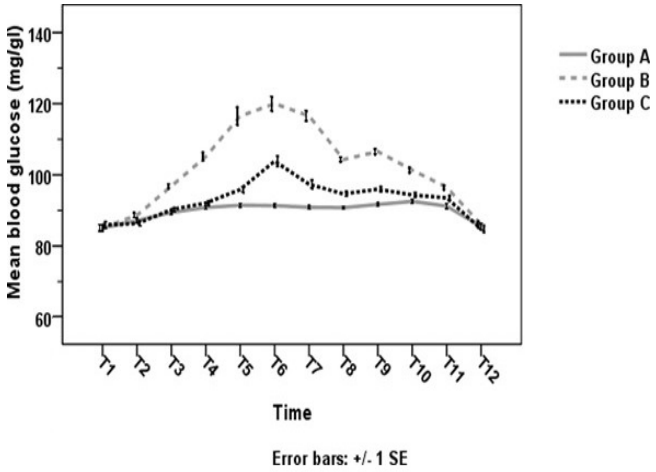

Figure 1. Mean blood glucose level at all 12 time points of the three study groups.
(T1 = baseline, T2 = 15 minutes after baseline, T3 = 30 minutes after baseline, T4 = 45 minutes after baseline, T5 = 60 minutes after baseline, T6 = 75 minutes after baseline, T7 = 90 minutes after baseline, T8 = 105 minutes after baseline, T9 = 120 minutes after baseline, T10 = 150 minutes after baseline, T11 = 180 minutes after baseline, T12 = 240 minutes after baseline)

anced HES solution did not cause an increase in blood glucose concentrations compared to 0.9% saline.[21] Their use of normal saline 0.9% as a maintenance fluid might have contributed to the limited changes in blood glucose level. On the other hand, the current study results came in concordance with a trial carried out by FDA-USA on animals that showed an increase in blood glucose levels after HES infusion for a long time.[22] Catecholamine release induced by surgical stress leads to hyperglycemia.[23] Stress related to surgical intervention and anesthesia can lead to a rise in the blood glucose level.[12] Regional anesthesia was chosen in this trial as it abolishes the adrenocortical response without subsequent increase in the glucose level by both the denervation of suprarenal medulla and blockade of the afferent sensory neurons, so this confounding variable of stress response was excluded, midazolam was administered as a premedication to prevent any anxiety-induced catecholamine release, and general anesthesia was excluded to prevent endotracheal tube-associated stress response.

In the present study, there was a statistically significant difference in blood glucose levels, compared to the baseline with the infusion of 6% HES 200/0.5 (Haes-steril) and 6% HES 130/0.4 (Voluven). The pharmacokinetic profile of HES is complex and largely dependent on its molar substitution as well as its molecular weight. When administered intravenously, molecules smaller than the renal threshold (60,000–70,000 daltons) are readily and rapidly excreted in the urine, while molecules with higher molecular weights are metabolized by plasma α-amylase before excretion via the renal route.[22] The mean molecular weight of Voluven in plasma is 70,000–80,000 daltons immediately following infusion so a considerable amount will readily and rapidly be excreted in the urine without being metabolized to form glucose or hydroxyl glucose residues.

Limitations of the study

First, the measurement of serum blood glucose was continued as long as arterial cannula was kept in place, and this limited the follow-up period to the maximum allowable time for patient to stay in the post-anesthesia care unit.

Second, this trial conducted on ASA I-II patients and the behavior of starches in diabetics, renal patients and other medically compromised patient needs to be assessed in further studies as those patients are more vulnerable for starch infusion.

Conclusion

Preloading patients with 6% HES 200/0.5 (Haes-steril) significantly elevates the blood glucose level, more than 6% HES 130/0.4 (Voluven) in nondiabetic individuals. Both fluids significantly elevate the blood glucose level, more than normal saline. Further larger clinical studies are needed to evaluate that effect among diabetic patients and those with high risk of intra and post-operative hyperglycemia.

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Conflicts of interest: None.

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