Original Article

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Effects of Preloading with Isotonically Balanced Tetra Hydroxyethyl Starch Versus Preloading with Gelufusine On Blood Glucose Level in Diabetic Patients

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Abstract

Background: The present study was conducted to study the effects of preloading with isotonically balanced tetra hydroxyethyl starch versus preloading with Gelufusine on blood glucose levels in diabetic patients. **Subjects and Methods:** 50 patients were diabetic categorized as study group (Group S) and 50 patients were nondiabetic categorized as a control group (Group C). Group C1 was non-diabetic patients who received gelofusine 10 ml/kg as preloading fluid 30 minutes prior to general anaesthesia, group C2 was non-diabetic patients who received 6% Hydroxyethyl starch 10 ml/kg as preloading fluid 30 minutes prior to general anaesthesia, group S1 was controlled diabetic patients who received gelofusine 10 ml/kg as preloading fluid 30 minutes prior to general anaesthesia and group S2 was controlled diabetic patients who received 6% Hydroxyethyl starch 10 ml/kg as preloading fluid 30 minutes prior to general anaesthesia. **Results:** There was no statistically significant difference in age, weight, height and the duration of surgery of patients between four groups ($p>0.05$). In the four groups of patients included in the study, female patients outnumbered the male patients but the difference was not statistically significant ($p>0.05$). There was no statistically significant difference in the baseline blood glucose values between all four groups. The blood glucose level in group C1 and S1 recorded a maximum decrease at 60 minutes. In group C2 and S2, there was the increase in blood glucose level at 60 minutes. **Conclusion:** Gelofusine fluid preloading produces a better outcome in diabetic patients as compared to preloading with hydroxyethyl starch fluid.

Keywords: Diabetes, Glucose, Gelofusine

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Introduction

Diabetic Mellitus is a common endocrine disorder encountered in the general population. It comprises a group of common metabolic disorders that share the phenotype of hyperglycemia. Depending upon the etiology of diabetes, a factor contributing to hyperglycemia may include decreased insulin secretion, decreased glucose usage and impaired glucose production.[1]

The administration of perioperative intravenous fluids is one of the most common and universal interventions in medicine. Crystalloid solutions are the most frequently chosen, by far, with normal saline (NS) and lactated Ringer's (LR) both being the most frequent choices. Colloids are an alternative to crystalloids, with highly variable use depending on a myriad of clinical variables.[2]

Clinically available colloids have generally exhibited similar effectiveness in maintaining colloid oncotic pressure. Thus, colloids have been viewed as a class of essentially interchangeable fluids and selection of colloids has commonly been based on cost and convenience. Differences in the physical properties, pharmacokinetics, and pharmacodynamics and safety profile exist amongst various colloids – a review of these can help us to choose the right colloid in different clinical scenarios.[3]

A colloid is defined as a high molecular weight (MW) substance that largely remains in the intravascular compartment, thereby generating an oncotic pressure. Colloids are considered to have a greater intravascular persistence when compared to crystalloids. This property is lost, however, when capillary membranes are altered in a diseased state.[4]

Colloids are of two types natural, i.e., human albumin and artificial, i.e., gelatin and dextran solutions, hydroxyethyl starches (HES). Taking into consideration the ill effects of hyperglycemia in the perioperative period and the frequent use of hydroxyethyl starches and gel of usine as volume expanders, the present study was conducted to study the effects

of preloading with isotonically balanced tetra hydroxyethyl starch on blood glucose levels.

Subjects and Methods

A prospective, randomized, observational study was conducted on 100 adult patients of physical status ASA I and II who underwent elective surgeries under general anaesthesia after approval from the institute's ethics committee and after obtaining patient's written informed consent. 50 patients were diabetic categorised as study group (Group S) and 50 patients were non-diabetic categorised as a control group (Group C).

In the study group (Group S), we included all patients who were on diet control for blood sugar level, on oral hypoglycemic medications or insulin treatment. Patients who were on oral hypoglycemic agents, were switched over to insulin 3 days prior to surgery. Doses of insulin were titrated on the basis of body weight as 0.7 – 0.8 IU/kg BW. Total doses were divided into $2/3^{rd}$ (given in the morning before breakfast) and$1/3^{rd}$ (given in the evening before dinner). $2/3^{rd}$ of morning dose was NPH and $1/3^{rd}$ of morning dose was regular insulin. $2/3^{rd}$ of the evening dose was NPH and $1/3^{rd}$ was regular insulin. So that we had controlled diabetic patients as preoperative blood sugar level less than 130 mg/dl in the morning of the day of surgery.

Once patients were selected and categorised under group S or group C, they were randomised by a closed envelope lottery system whether they receive hydroxyethyl starch (130/0.42, 6% tetra starch, B BRAUN) or gelofusine (modified fluid gelatin, MW 30 kDa, B BRAUN) as preloading fluid during surgery. During randomisation, the closed envelope was opened by a person not involved in this study.

Both group C and group S were divided into two sub groups:-

Group C1 – Non-diabetic patients who received gelofusine 10 ml/kg as preloading fluid 30 minutes prior to general anaesthesia.

Group C2 - Non-diabetic patients who received 6% Hydroxyethyl starch 10 ml/kg as preloading fluid 30 minutes prior to general anaesthesia.

Group S1 - Controlled diabetic patients who received gelofusine 10 ml/kg as preloading fluid 30 minutes prior to general anaesthesia.

Group S2 - Controlled diabetic patients who received 6% Hydroxyethyl starch 10 ml/kg as preloading fluid 30 minutes prior to general anaesthesia.

Patients were thoroughly examined in pre anesthetic clinics for pre-anaesthetic evaluation. History of presenting illness, history of diabetes mellitus, duration of the disease, whether patients were on insulin and how much doses were given, presence of any other co-existing diseases, history of previous surgery were noted. A thorough physical and systemic examination was done. Height and weight of the patient was noted. An examination of vital signs and airway assessment was done. Then Routine investigations were done in all patients.

The patients were kept nil per orally from 10 pm on the previous night and were premedicated with tab alprazolam 0.25 mg and tab Ranitidine per orally 150 mg previous night at 10 pm and next morning at 6 am.

On the day of surgery, patients were randomly allocated into different groups as mentioned above. Then patient was taken inside the operation theatre and then shifted onto the operation table. After that Pulse oximeter, ECG and NIBP monitor were connected. Then basal pulse rate and blood pressure were recorded. Intravenous access was established with an 18G or 16G (BD Insyte -W^{TM} / BD Venflon^{TM} Pro) intravenous cannula. Once the vein was cannulated, a sample of blood was taken for testing the blood glucose level using an ACCUTREND glucometer. This reading was taken as the baseline value. Then Radial artery cannulation was done with 20-22G (BD Insyte-W^{TM} / BD Venflon^{TM} Pro) cannula for performing repeated arterial blood gas analysis. The pressure transducer was connected to this arterial line for invasive blood pressure monitoring in some cases wherever indicated. Through this arterial line, blood sample was taken at regular time intervals for arterial blood gas analysis and measuring serum lactate level. Patients were catheterised with Foley's catheter wherever indicated.

As per the allocated group, the intravenous fluid infusion was started and preloading was done with the calculated dose of 10 ml/kg over a period of 30 minutes. After preloading, induction was done with general anaesthesia. Once preloading has been done with allocated intravenous fluid, patients were given 0.9 % normal saline as maintenance intravenous fluid. During the intraoperative period occurrence of hypotensive episodes was managed with rapid infusion of maintenance fluid. A small dose of vasopressors like mephenterine, phenylephrine was given if hypotension was not managed with fluid.

Different readings of blood sugar levels were recorded at regular intervals of 30 minutes from 0 minutes to 360 minutes. Serum lactate levels were also recorded at every 2 hours interval with baseline value recorded at 0 hour. Results thus obtained were statistically analysed. A P-value of less than 0.05 was considered significant.

Results

[Table 1] shows that there was no statistically significant difference in age, weight, height and the duration of surgery of patients between four groups ($p>0.05$). In the four groups of

Table 1: Demographic data of patients

	Group C 1	Group C 2	Group S 1	Group S 2
Age in yrs (mean±SD)	46.12±16.41	49.04±17.17	51.96±13.22	53.20±13.56
Weight in kg (mean±SD)	52.36±8.63	54.56±9.90	58.40±7.40	61.68±7.49
Height in cm (mean±SD)	160.57±7.82	159.20±8.50	161.32±7.82	160.57±7.54
Duration of surgery in hours (mean±SD)	3.40±0.82	3.16±0.66	4.00±1.05	3.82±0.81
Sex distribution (male: female)	12:13	11:14	11:14	12:13

patients included in the study, female patients outnumbered the male patients but the difference was not statistically significant ($p>0.05$).

[Table 2] shows a comparison of the average rise of blood glucose levels at different period of time. There was no statistically significant difference in the baseline blood glucose values between all four groups. The blood glucose level in group C1 and S1 recorded a maximum decrease at 60 minutes. In group C2 and S2, there was an increase in blood glucose levels at 60 minutes.

[Table 3] shows blood sugar levels 0 minute and subsequent time periods.

[Table 4] shows p value between all groups at different period of time.

[Table 5] shows that no single p-value is significant i.e. (p-value < 0.05) as shown in the above table. There were no significant changes in serum lactate levels at different time intervals in all four groups of patients involved in this study.

[Table 6] shows that when a comparison was made in the blood glucose levels between group C1 and group C2, it was found that initially, the blood glucose level in group C1 was lower than group C2 but as time period increases, the blood glucose level in group C1 is higher as compare to group C2. There were no statistically significant changes in blood glucose level at any given time intervals. When the blood glucose levels were compared between group S1 and group S2, it was noted that blood glucose levels were higher in group S2 than group S1 at all-time intervals. The change in blood glucose levels was statistically significant up to 120 minutes, thereafter in the next 120 minutes, no statistically significant changes in blood glucose levels were found.

Discussion

Diabetes is a chronic illness that requires continuing medical care and patient self-management education to prevent acute complications and to reduce the risk of long-term complications. Diabetic care is complex and requires many issues, beyond glycemic control, that to be addressed. A large body of evidence exists that supports a range of interventions to improve diabetes outcomes.[5]

After intravenous infusion gelatin is rapidly distributed in the intravascular compartment. Acute hypervolemia before the administration of a gelatin-based plasma volume substitute does not seem to influence hyperglycemia. In a non-diabetic group of patients who received gelofusine, blood glucose level has decreased during an initial one hour after preloading with gelofusine before the start of surgery. This decrease was not statistically significant. After one hour, the blood glucose level has increased over the next two hours, which was also statistically not significant. Then the blood glucose level gradually decreased over the next one and a half hours, which was also not statistically significant.[6]

In a non-diabetic group of patients who received hydroxyethyl starch fluid, the blood glucose level has increased during an initial one hour after preloading with hydroxyethyl starch before the start of surgery. This increase in blood sugar level was considered to be statistically significant. After the initial one hour, the blood glucose level gradually decreased over the next two and a half hours, which was not statistically significant. A similar observation was recorded in the study by Murthy et al,[7] in 2004 who also recorded a statistically significant increase in blood glucose levels in non-diabetic patients who received 6% Hydroxyethyl starch as preloading fluid.

In diabetic patients who received gelofusine fluid, blood glucose level has decreased over the initial one hour after preloading with gelofusine before the start of surgery, which was statistically significant. During the next two hours, there was a significant increase in blood sugar levels. After that in the next hour, the blood sugar level has slightly decreased, which was found to be statistically significant.

In diabetic patients who received hydroxyethyl starch fluid, blood glucose levels have increased during the initial period of one hour after preloading with hydroxyethyl starch fluid before the start of surgery. This increase was statistically significant. Then the blood glucose level has decreased over the next four hours, which was not statistically significant.

Table 2: Comparison of an average rise of blood glucose level

Study period	Group C 1mean± SD (mg/dl)	Group C 2mean± SD (mg/dl)	Group S 1mean± SD (mg/dl)	Group S 2mean± SD (mg/dl)
0 min	115.16±24.57	104.04±25.72	149.96±32.28	140.36±25.68
30 min	114.80±23.08	117.36±26.46	143.28±30.66	159.52±24.98
60 min	113.56±22.06	123.64±25.42	139.88±29.83	164.72±21.42
90 min	116.67±19.83	119.60±23.79	140.28±24.97	159.76±21.63
120 min	117.50±17.68	119.15±23.52	141.32±29.78	154.10±29.49
150 min	121.95±17.92	116.88±19.39	142.00±36.07	152.91±28.62
180 min	123.17±20.61	116.44±20.19	144.84±26.10	152.32±22.45
210 min	120.33±16.26	115.89±12.62	141.40±38.60	150.15±15.12
240 min	117.38±17.22	118.17±26.33	140.82±21.71	148.38±15.83
270 min	115.67±21.02	115.00± 23.61	139.20±24.87	139.00±15.13
300 min	117.00± 19.19	114.62±21.69	132.78±25.10	132.50±14.95

Table 3: Comparison of the average difference in the blood glucose level

Time (minutes)	Group C1mean± SD (mg/dl)	Group C2mean± SD (mg/dl)	Group S1mean± SD (mg/dl)	Group S2mean± SD (mg/dl)
30 mins	-0.36±11.54	13.32±9.62	-6.68±10.96	19.16±15.34
60 mins	-1.60±13.57	19.60±16.28	-10.08±10.15	24.36±10.39
90 mins	1.51±19.43	15.56±20.89	-9.68±21.26	19.40±12.26
120 mins	2.34±21.52	15.11±25.27	-8.64±28.60	13.74±21.04
150 mins	6.79±24.05	12.84±27.53	-7.96±20.32	12.55±24.10
180 mins	8.01±27.01	12.40±24.42	-5.12±16.06	11.96±14.00
210 mins	5.17±21.50	11.85±32.99	-8.56±24.11	8.02±28.11
240 mins	2.18±24.41	14.13±27.68	-9.14±20.02	9.79±24.06
270 mins	0.51±31.43	12.16±19.27	-10.76±19.06	10.36±16.64
300 mins	1.94±24.61	11.82±18.66	-17.18±25.72	7.86±18.38

Table 4: Determination of p value by ANOVA and Post hoc with Bonferroni's correction between blood glucose levels of four study groups

Study periods	Gp C1-C2	Gp C1-S1	Gp C1-S2	Gp C2-S1	Gp C2-S2	Gp S1-S2
0 min	0.150	0.001"	0.001"	0.001"	0.001"	0.021'
30 mins	0.730	0.001"	0.001"	0.001"	0.001"	0.030'
60 mins	0.250	0.001"	0.001"	0.023'	0.001"	0.001"
90 mins	0.970	0.001"	0.001"	0.001"	0.001"	0.018'
120 mins	0.590	0.011'	0.001"	0.002"	0.001"	0.007"
150 mins	0.710	0.014'	0.001"	0.017'	0.001"	0.060
180 mins	0.890	0.003"	0.001"	0.003"	0.001"	0.101
210 mins	0.850	0.001"	0.001"	0.001"	0.001"	0.230
240 mins	0.830	0.014'	0.001"	0.052	0.005"	0.190

Table 5: Determination of p-value by ANOVA and Post hoc with Bonferroni's correction between serum lactate levels

Study period	Gp C1-C2	Gp C1-S1	Gp C1-S2	Gp C2-S1	Gp C2-S2	Gp S1-S2
0 hour	0.740	0.330	0.460	0.520	0.670	0.820
2 hours	0.740	0.290	0.040	0.460	0.090	0.320
4 hours	0.460	0.030	0.006	0.200	0.060	0.490

Table 6: Comparison between two consecutive time periods and determination of p-value in all four groups by Post hoc Bonferroni's test

Blood sugar (BS) at two consecutive time period (in minutes)	Group C1	Group C2	Group S1	Group S2
BS 30 vs BS 60	0.84	0.39	0.69	0.43
BS 60 vs BS 90	0.61	0.29	0.62	0.42
BS 90 vs BS 120	0.27	0.66	0.96	0.24
BS 120 vs BS 150	0.83	0.94	0.32	0.93
BS 150 vs BS 180	0.42	0.71	0.31	0.89
BS 180 vs BS 210	0.98	0.94	0.95	0.48
BS 210 vs BS 240	0.83	0.82	0.84	0.76
BS 240 vs BS 270	0.74	0.37	0.82	0.27
BS 270 vs BS 300	0.65	0.49	0.98	0.61

However, Mishler JM,[8] who studied the pharmacokinetics of 6% Hydroxyethyl starch found that blood glucose levels rose the following dosing, but it remained elevated for 24 hours following infusion. In a similar study by Beyer et al,[9] they also found the usage of 6% Hydroxyethyl starch was associated with an increase in blood glucose levels which reached a maximum at 6 – 12 hours after surgery.However, studies by Usha rani P, Singh, Lee WH, concluded that transfusion of 6% Hydroxyethyl starch was not associated with a significant increase in blood glucose levels.[10–12]

When a comparison was made in the blood glucose levels between the non-diabetic (gelofusine) group and non-diabetic (hydroxyethyl starch) group, it was found that blood glucose level in the non-diabetic (gelofusine) group decreased within the first hour of infusion of drug whereas in non-diabetic (hydroxyethyl starch) group, blood glucose level increased within the first hour of infusion of the drug, but in both cases, changes in blood sugar level were not significant. After a one-hour blood glucose level in non-diabetic (gelofusine) group has raised and in non-diabetic (hydroxyethyl starch) group has declined during intraoperative period.

When the blood glucose levels were compared between the diabetic (gelofusine) group and diabetic (hydroxyethyl starch) group, it was noted that the blood glucose levels were higher in the diabetic group of patients who received hydroxyethyl starch.[13] In the diabetic (gelofusine) group, blood glucose level has initially decreased and in the diabetic (hydroxyethyl starch) group, blood glucose level has initially increased within the first hour of infusion of preloading fluids. In both groups, changes in blood glucose levels were statistically significant. After the initial one hour, blood glucose levels started rising in the diabetic (gelofusine) group and decline in the diabetic (hydroxyethyl starch) group during the intraoperative period. Changes in blood glucose levels were not significant during this time interval.

Infusion of 6% hydroxyethyl starch for preloading prior to general anaesthesia resulted in a statistically significant increase in blood glucose levels in both controlled diabetic and non-diabetic patients.[14] However, the increase in blood glucose levels in diabetic patients who received 6% Hydroxyethyl starch was higher than that observed in non- diabetic patients. This increase was immediate and present even before any surgical stimulus was given. On the other hand, a decrease in blood glucose level was noted in those patients who received gelofusine as preloading fluid in both non-diabetic as well as diabetic patients. This decrease in blood glucose levels was not significant.

Apart from blood glucose level, we have also measured serum lactate level in all four groups of patients at two hours intervals, which has increased subsequently in the intraoperative period but no value was considered to be statistically significant. It was found that there was no correlation between blood glucose level and serum lactate level at any time period during surgery. Hence the rise in the blood glucose levels in the groups of patients who received 6% Hydroxyethyl starch could be attributed to the use of hydroxyethyl starch solution, which

is metabolized in the body to produce glucose. Though there was a statistically significant increase in blood glucose in those diabetic patients who received 6% Hydroxyethyl starch as preloading fluid, the maximum value reached was well within the normal physiological limits. On the other hand, a decrease in blood glucose levels in groups of patients who received gelofusine as preloading fluid, the value reached was well within the normal physiological limits.

Conclusion

It was concluded that blood glucose level increased during the initial time period after preloading with 6% hydroxyethyl starch fluid, so it should be used cautiously in controlled diabetic and partially controlled diabetic patients in whom increase in blood glucose level can be due to either stress response or hydroxyethyl starch fluid preloading. So, it probably may require another study having a bigger sample size for determining any conclusion regarding the increase in blood glucose levels in these patients. On the other hand, blood glucose levels decreased during the initial time period after preloading with gelofusine fluid. So, our study may suggest that gelofusine fluid preloading produces a better outcome in diabetic patients as compared to preloading with hydroxyethyl starch fluid.

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