Glucose administration during volume resuscitation using dextran-40 from hemorrhagic shock ameliorates acid/base-imbalance in fasted rats under sevoflurane anesthesia

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Summary   The hyperglycemic response is an important prognostic factor for survival after hemorrhage. In this study, we investigated the effects of glucose administration during volume resuscitation from hemmorhagic shock in fasted rats under sevoflurane anesthesia on hemodynamics, acid/base-balance and glucose metabolism. Hemorrhagic shock was induced in rats by withdrawing 25 mL/kg of blood. For volume resuscitation, rats in group-Dextran[saline] and group-Dextran[glucose] underwent infusion therapy using 10% dextran-40 dissolved in physiological saline and 10% dextran-40 dissolved in 5% glucose, respectively. Arterial blood was sampled just before blood withdrawal, immediately after blood withdrawal, immediately after volume resuscitation and at 30 min after volume resuscitation for arterial gas analyses and measurement of plasma insulin levels. After volume resuscitation, group-Dextran[glucose] showed similar arterial blood pressure, significantly lower heart rate, similar arterial PO_2 and similar hematocrit in comparison with group-Dextran[saline], suggesting that there was no particular difference in oxygen demand/supply-balance between the two groups. After volume resuscitation, group-Dextran[glucose] showed significantly higher arterial pH, similar arterial PCO_2, significantly higher bicarbonate levels and significantly higher base excess in comparison with group-Dextran[saline], suggesting that metabolic acidosis is a cause of the difference in acid/base-balance between the two groups. After volume resuscitation, group-Dextran[glucose] showed significantly higher glucose levels, significantly higher insulin levels and significantly lower lactate levels in comparison with group-Dextran[saline]. At 30 min after volume resuscitation, base excess correlated significantly with lactate levels. These results suggest that glucose administration during volume resuscitation using dextran-40 from hemorrhagic shock ameliorates acid/base-imbalance associated with hyperlactatemia in fasted rats under sevoflurane anesthesia.

Keywords: Hyperlactatemia, glucose metabolism, energy demand/supply-balance, fluid therapy, plasma substitute

1. Introduction

Restoring blood volume is essential for the treatment of hemorrhagic shock; use of a plasma substitute is a practical tool for expanding blood volume. Several artificial molecules have been developed as plasma substitutes, and the efficiency of theses molecules on volume resuscitation have been evaluated (*1-5*); however, the effects of the solvent for the molecules on volume resuscitation have not been elucidated. Two kinds of molecule, dextran-40 and hydroxyethyl starch 70/0.5/4, are clinically available in Japan; dextran-40 is dissolved in either lactated-Ringer's solution or 5% glucose, and hydroxyethyl starch 70/0.5/4 is dissolved

in either physiological saline or lactated-Ringer's solution containing 1% glucose. The hyperglycemic response is known to be an important prognostic factor for survival after hemorrhage (6,7), suggesting the possible advantageous effects of glucose administration on volume resuscitation from hemorrhagic shock. In this study, infusion therapy using two kinds of 10% dextran-40 solution (dextran-40 dissolved in physiological saline and dextran-40 dissolved in 5% glucose) was given to fasted rats with hemorrhagic shock under sevoflurane anesthesia, and hemodynamics, acid/base-balance and glucose metabolism were evaluated.

2. Materials and Methods

2.1. *Subjects*

All experimental protocols were approved by the animal care committee of The University of Tokyo (protocol number: P09-125). We used 9- to 11-week-old, male, Wistar rats (Nippon Bio-Supply Center, Tokyo, Japan). Rats were housed in a regulated environment with room temperature maintained at 25°C and a 12-h light-dark cycle (7 AM and 7 PM). A standard diet (Oriental Yeast Co., Ltd., Tokyo, Japan) and water were provided *ad libitum*. Each rat was fasted for 20 h prior to the experiment; however, water was provided until the experiment started. All experiments were performed between 1 PM and 5 PM. A heat lamp and a heating pad were used to prevent hypothermia during the experiments.

2.2. *Experimental protocols*

Anesthesia for surgical preparation was induced with sevoflurane (Maruishi Pharmaceutical Co., Ltd., Osaka, Japan) *via* a tightly fitting face mask. After tracheotomy and tracheal intubation, sevoflurane (2.5% in 1 L/min oxygen) was administered *via* the tracheal tube, and the lungs were mechanically ventilated; and the ventilator setting was not changed throughout the experimental period. A 19-gauge catheter was inserted into the right jugular vein. Another 19-gauge catheter was inserted into the right carotid artery.

After surgical preparation, all rats were administered 100 IU of heparin intravenously to maintain patency of the catheters. Sevoflurane administration was continued, and physiological saline was administered intravenously with a bolus dose of 4 mL/kg followed by continuous infusion at a rate of 4 mL/kg/h. The arterial catheter was connected to a low volume pressure transducer for monitoring mean arterial blood pressure (MAP) and heart rate (HR).

A 30-min stabilization period was allowed, followed by 25 mL/kg of arterial blood withdrawn at a rate of 1 mL/min to induce hemorrhagic shock. Volume resuscitation was then started. Rats in group-

Dextran[saline] (*n* = 8) underwent infusion therapy using 25 mL/kg of 10% dextran-40 dissolved in physiological saline at a rate of 1 mL/min *via* the venous catheter; dextran-40 (Sigma-Aldrich Japan, Tokyo, Japan) was sterilely dissolved in physiological saline just before administration . Rats in group-Dextran[glucose] (*n* = 8) underwent infusion therapy using 25 mL/kg of 10% dextran-40 dissolved in 5% glucose (Low Molecular Dextran D Injection; Otsuka Pharmaceutical Factory, Inc., Tokushima, Japan) at a rate of 1 mL/min *via* the venous catheter.

Arterial blood (1.5 mL) was sampled just before blood withdrawal (T-1), immediately after blood withdrawal (T-2), immediately after volume resuscitation (T-3) and at 30 min after volume resuscitation (T-4).

2.3. *Arterial blood gas analyses and measurement of plasma insulin levels*

Immediately after each blood sampling, arterial blood gas analyses were performed using an i-STAT 1 Analyzer (Fuso Pharmaceutical Industries, Ltd., Osaka, Japan). Each blood sample was spun in a pre-refrigerated centrifuge (4°C) at $1000 \times g$ for 15 min, and plasma was stored at -60°C. Plasma insulin levels were measured by enzyme-linked immunosorbent assay using AKRIN-010T (Shibayagi Co., Ltd., Gunma, Japan).

2.4. *Statistical analysis*

Data are shown as means ± S.D. Statistical analyses were performed using JMP Pro version 9.0.2. (SAS Institute, Cary, NC). For overall comparisons of serial data between the two groups, 2-way repeated-measures of analysis of variance (ANOVA), with group and time points as the factors, were used; statistical significance was set at $p < 0.05$. Homogeneity of variance was examined using a Bartlett test; statistical significance was set at $p < 0.05$. For comparisons of data with homogeneity of variance between the two groups at each time point, an unpaired *t*-test was used; statistical significance was set at $p < 0.05$. For comparisons of data without homogeneity of variance between the two groups at each time point, a Welch test was used; statistical significance was set at $p < 0.05$. Simple linear regression analysis was used to examine the correlation between base excess and lactate levels in arterial blood.

3. Results

3.1. *Hemodynamics, arterial PO_2 and hematocrit*

Rats in group-Dextran[saline] and group-Dextran[glucose] weighed 298 ± 26 g and 304 ± 34 g, respectively; and there was no significant difference between the two groups. Thus, there was no significant difference in the time required for blood withdrawal and volume

resuscitation between the two groups.

The time course of hemodynamics, arterial PO_2 and hematocrit are shown in Table 1.

There was no significant difference in the time course of MAP between the two groups ($p = 0.6193$, 2-way repeated-measures ANOVA). There was a significant difference in the time course of HR between the two groups ($p = 0.0064$, 2-way repeated-measures ANOVA); group-Dextran[glucose] showed significantly lower HR than group-Dextran[saline] at T-4 ($p= 0.0002$, unpaired t-test). There was no significant difference in the time course of arterial PO_2 between the two groups ($p = 0.0706$, 2-way repeated-measures ANOVA). There was no significant difference in the time course of hematocrit between the two groups ($p = 0.6736$, 2-way repeated-measures ANOVA).

3.2. Acid/base-balance

The time course of arterial pH, arterial PCO_2, bicarbonate levels and base excess are shown in Table 2.

There was a significant difference in the time course of arterial pH between the two groups ($p = 0.0098$, 2-way repeated-measures ANOVA); group-Dextran[glucose] showed significantly higher arterial pH than group-Dextran[saline] at T-4 ($p = 0.0080$, Welch test). There was no significant difference in the time course of arterial PCO_2 between the two groups ($p = 0.1592$, 2-way repeated-measures ANOVA). There was a significant difference in the time course of bicarbonate levels between the two groups ($p = 0.0014$, 2-way repeated-measures ANOVA); group-Dextran[glucose] showed significantly higher bicarbonate levels than group-Dextran[saline] at T-3 and T-4 ($p = 0.0052$ and $p = 0.0007$, respectively, unpaired t-test). There was a significant difference in the time course of base excess between the two groups ($p = 0.0008$, 2-way repeated-measures ANOVA); group-Dextran[glucose] showed significantly higher base excess than group-Dextran[saline] at T-3 ($p = 0.0202$, unpaired t-test) and T-4 ($p = 0.0004$, Welch test).

Table 1. The time course of hemodynamics, arterial PO_2 and hematocrit during the experiments

Groups	Time point			
	T-1	T-2	T-3	T-4
Mean arterial blood pressure (mmHg)				
Dextran[saline]	93 ± 22	22 ± 2	78 ± 13	37 ± 11
Dextran[glucose]	84 ± 15	22 ± 2	78 ± 13	38 ± 13
Heart rate (beats/min)				
Dextran[saline]	402 ± 38	334 ± 58	448 ± 25	441 ± 26
Dextran[glucose]	367 ± 53	361 ± 53	423 ± 38	354 ± 44*
Arterial PO_2 (mmHg)				
Dextran[saline]	511 ± 12	420 ± 78	451 ± 39	477 ± 38
Dextran[glucose]	483 ± 23	412 ± 53	489 ± 48	387 ± 138
Hematocrit (%)				
Dextran[saline]	44 ± 3	35 ± 2	12 ± 1	15 ± 3
Dextran[glucose]	42 ± 2	33 ± 1	11 ± 1	15 ± 3

Data are shown as means ± S.D. There are no significant differences in the time course of mean arterial blood pressure, arterial PO_2 and hematocrit between the two groups ($p > 0.05$ in all comparisons, 2-way repeated-measures ANOVA); however, there is a significant difference in the time course of heart rate between the two groups ($p < 0.05$ in all comparisons, 2-way repeated-measures ANOVA). *$p < 0.05$ *versus* group-Dextran[saline] at each time point, unpaired t-test.

Table 2. The time course of acid/base-balance during the experiments

Groups	Time point			
	T-1	T-2	T-3	T-4
Arterial pH				
Dextran[saline]	7.505 ± 0.038	7.614 ± 0.032	7.332 ± 0.087	7.334 ± 0.035
Dextran[glucose]	7.505 ± 0.020	7.617 ± 0.050	7.381 ± 0.039	7.437 ± 0.080†
Arterial PCO_2 (mmHg)				
Dextran[saline]	33.8 ± 0.9	13.4 ± 2.1	33.5 ± 4.4	25.9 ± 5.9
Dextran[glucose]	31.4 ± 2.3	14.7 ± 1.1	35.3 ± 2.5	31.4 ± 9.7
Bicarbonate levels (mmol/L)				
Dextran[saline]	26.7 ± 2.2	13.6 ± 2.0	17.7 ± 2.1	13.9 ± 3.7
Dextran[glucose]	24.8 ± 1.4	15.0 ± 1.6	20.9 ± 1.8*	20.5 ± 2.3*
Base excess (mmol/L)				
Dextran[saline]	4 ± 3	-8 ± 2	-8 ± 3	-12 ± 4
Dextran[glucose]	2 ± 1	-6 ± 3	-4 ± 2*	-4 ± 2†

Data are shown as means ± S.D. There are significant differences in the time course of arterial pH, bicarbonate levels and base excess between the two groups ($p < 0.05$ in all comparisons, 2-way repeated-measures ANOVA); however, there is no significant difference in the time course of arterial PCO_2 between the two groups ($p > 0.05$, 2-way repeated-measures ANOVA). *$p < 0.05$ *versus* group-Dextran[saline] at each time point, unpaired t-test. †$p < 0.05$ *versus* group-Dextran[saline] at each time point, Welch test.

Table 3. The time course of glucose metabolism during the experiments

Groups	Time point			
	T-1	T-2	T-3	T-4
Blood glucose levels (mg/dL)				
Dextran[saline]	129 ± 21	193 ± 89	139 ± 61	55 ± 16
Dextran[glucose]	130 ± 21	177 ± 70	$625 \pm 62^*$	$252 \pm 61^\dagger$
Plasma insulin levels (ng/mL)				
Dextran[saline]	0.8 ± 0.2	3.0 ± 2.5	1.7 ± 1.0	0.6 ± 0.2
Dextran[glucose]	0.9 ± 0.4	2.2 ± 1.3	$6.8 \pm 5.3^\dagger$	$5.9 \pm 4.9^\dagger$
Blood lactate levels (mmol/L)				
Dextran[saline]	0.83 ± 0.11	4.53 ± 1.10	4.71 ± 1.56	8.38 ± 3.65
Dextran[glucose]	0.75 ± 0.09	4.09 ± 1.32	$3.14 \pm 0.82^*$	$3.76 \pm 1.07^\dagger$

Data are shown as means ± S.D. There are significant differences in the time course of blood glucose levels, plasma insulin levels and blood lactate levels between the two groups ($p < 0.05$ in all comparisons, 2-way repeated-measures ANOVA). $^*p < 0.05$ *versus* group-Dextran[saline] at each time point, unpaired *t*-test. $^\dagger p < 0.05$ *versus* group-Dextran[saline] at each time point, Welch test.

3.3. *Glucose metabolism*

The time course of blood glucose levels, plasma insulin levels and blood lactate levels are shown in Table 3.

There was a significant difference in the time course of glucose levels between the two groups ($p < 0.0001$, 2-way repeated-measures ANOVA); group-Dextran[glucose] showed significantly higher glucose levels than group-Dextran[saline] at T-3 ($p < 0.0001$, unpaired *t*-test) and T-4 ($p < 0.0001$, Welch test). There was a significant difference in the time course of insulin levels between the two groups ($p = 0.0002$, 2-way repeated-measures ANOVA); group-Dextran[glucose] showed significantly higher insulin levels than group-Dextran[saline] at T-3 and T-4 ($p = 0.0432$ and $p < 0.0001$, respectively, Welch test). There was a significant difference in the time course of lactate levels between the two groups ($p < 0.0001$, 2-way repeated-measures ANOVA); group-Dextran[glucose] showed significantly lower lactate levels than group-Dextran[saline] at T-3 ($p = 0.0243$, unpaired *t*-test) and T-4 ($p = 0.0086$, Welch test).

3.4. *Correlation between base excess and blood lactate levels*

Base excess at T-4 significantly correlated with lactate levels at T-4 ($p < 0.0001$, $R^2 = 0.8644$, simple linear regression analysis; Figure 1).

3.5. *Relationship between glucose levels and lactate levels*

The mean levels of glucose and lactate in all rats at T-4 were 111 mg/dL and 6.07 mmol/L, respectively. The relationship between glucose levels at T-4 and lactate levels at T-4 was assessed using these parameters: lower glucose levels with lower lactate levels (category-I), higher glucose levels with lower lactate levels (category-II), higher glucose levels with higher lactate levels (category-III) and lower glucose levels with higher lactate levels (category-IV). All data in group-Dextran[saline] were within category-I and category-IV, while all data in group-Dextran[glucose] were within category-II (Figure 2).
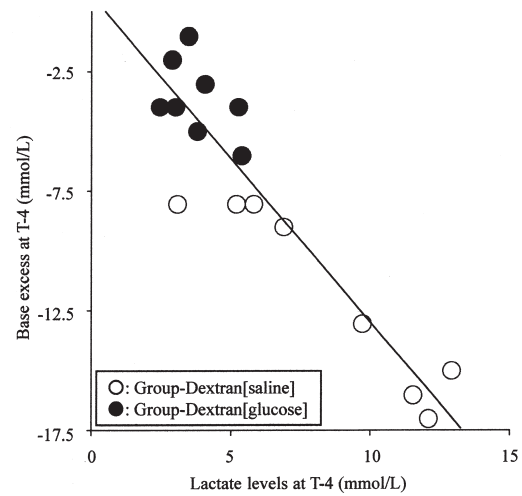

Figure 1. Correlation between base excess at T-4 and lactate levels at T-4. Simple linear regression analysis shows a significant correlation between base excess at T-4 and lactate levels at T-4 ($p < 0.0001$, $R^2 = 0.8644$).
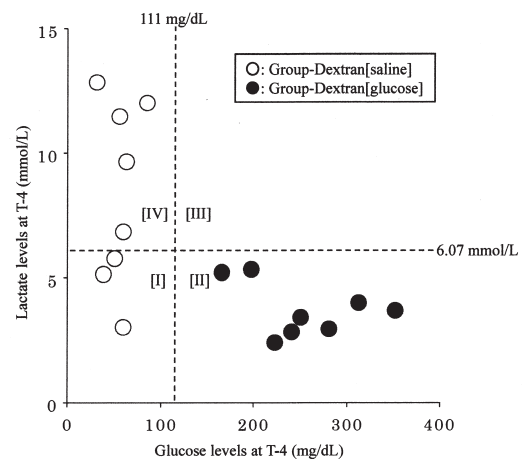

Figure 2. Relationship between glucose levels at T-4 and lactate levels at T-4. The mean glucose level at T-4 in all rats is 111 mg/dL, and the mean lactate level at T-4 in all rats is 6.07 mmol/L. The relationship between glucose levels at T-4 and lactate levels at T-4 was assessed using these parameters: lower glucose levels with lower lactate levels (category-I), higher glucose levels with lower lactate levels (category-II), higher glucose levels with higher lactate levels (category-III) and lower glucose levels with higher lactate levels (category-IV).

4. Discussion

Acid/base-imbalance after volume resuscitation from hemorrhagic shock in group-Dextran[glucose] was significantly less than that in group-Dextran[saline]. It is conceivable that metabolic acidosis is a cause of the difference in acid/base-balance between group-Dextran[saline] and group-Dextran[glucose], because there were no significant differencein arterial PCO_2 throughout the experimental period between the two groups. Lactate levels after volume resuscitation from hemorrhagic shock in group-Dextran[glucose] were significantly lower than those in group-Dextran[saline]. The significant correlation between base excess at T-4 and lactate levels at T-4 reflects the contribution of hyperlactatemia to acid/base-imbalance in group-Dextran[saline], although the blood concentration of other anions (*i.e.*, citrate and acetate), which have been reported to be responsible, to some extent, for metabolic acidosis after hemorrhagic shock, were not examined (*8*). Volume resuscitation, using a plasma substitute alone, from hemorrhagic shock is not practical in clinical settings; however, results in this study using fasted rats suggest the possible advantageous effect of glucose administration during volume resuscitation from hemorrhagic shock.

Increased lactate production *via* anaerobic glucose metabolism due to oxygen demand/supply-imbalance (*9,10*), increased lactate production *via* enhanced aerobic glycolysis coupled with Na^+, K^+-ATPase activities in skeletal muscle (*11*) and impaired lactate clearance in the liver can be considered as mechanisms underlying elevated lactate levels after volume resuscitation from hemorrhagic shock.

There was no significant difference in MAP between group-Dextran[saline] and group-Dextran[glucose] throughout the experimental period. There were no significant difference in HR between group-Dextran[saline] and group-Dextran[glucose] at T-1, T-2 and T-3; however, a significant difference was detected only at T-4 between the two groups. There were no significant difference in arterial PO_2 throughout the experimental period between group-Dextran[saline] and group-Dextran[glucose]. Dilutional anemia was observed after volume resuscitation from hemorrhagic shock in both group-Dextran[saline] and group-Dextran[glucose]; and there was no significant difference in hematocrit throughout the experimental period between the two groups. Taken together, we believe that oxygen demand/supply-balance after volume resuscitation from hemorrhagic shock in group-Dextran[glucose] was not considerably different from that in group-Dextran[saline].

Rats were fasted for 20 h prior to the experiments; it is, therefore, assumable that glycogen storage in the body was markedly reduced (*12*). Group-Dextran[saline] showed hypoglycemia (55 ± 16 mg/dL) without increases in insulin levels (0.6 ± 0.2 ng/mL) at T-4, suggesting shortness of energy substrates after volume resuscitation from hemorrhagic shock. Hyperlactatemia was associated with hypoglycemia at T-4 in group-Dextran[saline]; therefore, we suppose that the enhanced aerobic glycolysis coupled with Na^+, K^+-ATPase activities in skeletal muscle was not the cause of hyperlactatemia after volume resuscitation from hemorrhagic shock in group-Dextran[saline].

Assurance of energy demand/supply-balance is definitely important for preventing organ failure in critical situations. In group-Dextran[glucose], glucose administration during volume resuscitation from hemorrhagic shock significantly increased glucose levels, but rapid decreases in glucose levels were observed at 30 min after volume resuscitation. The rapid decreases in glucose levels with significantly higher insulin levels reflect a sufficient energy supply after volume resuscitation from hemorrhagic shock in group-Dextran[glucose]. In contrast, hypoglycemia that was not accompanied by increases in insulin levels was observed at T-4 in group-Dextran[saline], suggesting that energy supply *via* stress-induced endogenous glucose production was insufficient after volume resuscitation from hemorrhagic shock.

Among the several types of glucose transporters (GLUTs), the target molecule for insulin is GLUT-4. Glucose use in the liver is dependent on both GLUT-2 and glucokinase enzyme activities; plasma insulin levels affect hepatic glucokinase enzyme activities, although glucose uptake *via* GLUT-2 is independent of insulin (*13*). It was reported that co-administration of glucose with insulin during resuscitation from hemorrhagic shock increases hepatic ATP (*14*). Lactate is metabolized by lactate dehydrogenase in the liver, and the metabolite (*i.e.*, pyruvate) is used as an energy substrate. We, therefore, suppose that glucose administration (*i.e.*, the exogenous energy supply) during volume resuscitation from hemorrhagic shock ameliorated energy insufficiency and maintained lactate clearance in the liver, resulting in the prevention of an acid/base-imbalance related to hyperlactatemia.

The importance of maintenance of energy demand/supply-balance is generally accepted. In addition, recent studies (*15-19*) reported that hyperglycemia increases morbidity and mortality and hypoglycemia associated with intensive insulin therapy increases mortality, suggesting that control of blood glucose levels is important in critically ill patients. Although results in this study using fasted rats suggest possible advantageous effects of glucose administration during volume resuscitation from hemorrhagic shock, we cannot simply extrapolate the finding in this animal study to clinical practicefor several reasons. First, the significance of intraoperative glucose administration under general anesthesia has been controversial. Second, glucose administration during volume resuscitation from hemorrhagic shock is not considered as a clinically

standard procedure at this moment. Third, rats in group-Dextran[glucose] showed drastic hyperglycemia (625 ± 62 mg/dL) immediately after volume resuscitation from hemorrhagic shock in this study, and adverse effects associated with hyperglycemia are well known in clinical settings. We, thus, consider that further clinical investigation is required to elucidate the efficiency of glucose administration during volume resuscitation from hemorrhagic shock; furthermore, the appropriate dose of glucose administration should be determined.

In conclusion, glucose administration during volume resuscitation using dextran-40 from hemorrhagic shock ameliorates acid/base-imbalance related to hyperlactatemia in fasted rats under sevoflurane anesthesia, suggesting the importance of maintaining energy demand/supply-balance by the exogenous energy supply in critical situations.

Acknowledgements

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