Comparative Study of Intravenous Administration of Ringer's Lactate, Ringer's Acetate and 5% Glucose Containing These Ringer's Solutions in Human Being

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The effects of the administration of Ringer's lactate (L) and Ringer's acetate (A) solution on blood biochemistry in human subjects operated for tympanoplasty under general anesthesia were investigated. And the feasibilities of the clinical use of Ringer's lactate (LD) and Ringer's acetate (AD) solution containing 5% glucose were also assessed. In all cases the rate of infusion was 500 ml for initial 20 min, and then 5 $ml \cdot hr^{-1} \cdot kg^{-1}$ B.W. for 3 hr and 10 min.

There were significant increases in blood L- and D-lactate, pyruvate, and L-lactate/pyruvate ratio in L group. A significant increase in blood acetate but not lactate was found in A group. These metabolic changes were minimal and considered as clinically not significant. The urinary excretion of lactate, pyruvate, acetate and glucose were also negligible. In both LD and AD group, the higher blood concentrations of lactate, pyruvate, acetate and glucose were found than in L and A group. Urinary excretions of these metabolites were much higher in LD and AD group than in L and A group. So glucose containing Ringer's lactate or acetate solutions should be administered in appropriate amounts and rate not to induce clinically significant metabolic alterations. (Key words: Ringer's lactate solution, Ringer's acetate solution, glucose load, blood concentration of lactate, blood concentration of acetate)

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Both Ringer's lactate and Ringer's acetate solutions are currently accepted as intraoperative replacement solutions. Their chemical compositions are shown in table 1.

Lactate was initially introduced as an alkali[1]. Its alkalinizing effect depends on its re-utilization for glucose synthesis and its oxidative degradation to H_2O and CO_2, which converts into bicarbonate[2]. Sodium lactate used for the preparation of Ringer's lactate is a racemic compound that is composed of equal amounts of levorotatory and dextrorotatory forms[3]. In humans, lactate exists mostly in L-form, and its metabolic features are fairly well known[4], whereas those of D-lactate are not necessarily clarified.

Acetate is metabolized more efficiently in peripheral tissues[5]. Its use in intravenous solutions is becoming popular, because it

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Table 1. Chemical compositions of 4 kinds of Ringer's solutions

	Na	K	Ca	Cl	L-Lact	D-Lact	Acet	Gluc
	mEq/L							%
Ringer's lactate	130	4	3	109	14	14		
Ringer's lactate with 5% glucose	131	4	3	110	14	14		5
Ringer's acetate	130	4	3	109			28	
Ringer's acetate with 5% glucose	130	4	3	109			28	5

L-Lact: L-Lactate, D-Lact: D-Lactate, Acet: Acetate, Gluc: Glucose

Table 2. Patient's characteristics

	L group	LD group	A group	AD group
Sex (Male: Female)	4 : 6	6 : 4	4 : 7	7 : 6
Age (years)	39.0 ± 5.6*1	33.3 ± 5.1	41.3 ± 4.6	31.0 ± 3.8
Weight (kg)	57.0 ± 4.3	60.9 ± 5.7	55.2 ± 2.4	55.4 ± 2.1
Hemoglobin ($g \cdot dl^{-1}$)*2	13.5 ± 0.7	15.0 ± 0.6	13.8 ± 0.4	14.7 ± 0.4
Adrenaline (ml)*3	10.2 ± 1.1	8.4 ± 1.3	9.0 ± 0.7	11.0 ± 1.1
Blood loss (ml)	38.0 ± 11.6	59.9 ± 11.8	38.9 ± 9.7	33.5 ± 6.6

*1: expressed as mean ± SEM.
*2: preoperative values.
*3: applied to operative fields with concentrations of hundred thousandth.

is readily convertible to bicarbonate than lactate[6]. Recently 5% glucose containing Ringer's lactate and acetate solutions are commercially available in this country.

In this study, the effects of the administration of Ringer's lactate and acetate solutions on blood constituents of human subjects were investigated, and feasibilities of clinical use of Ringer's lactate and acetate solutions containing 5% glucose were assessed.

Subjects and Methods

Twenty one male and twenty three female adult patients, who were operated for tympanoplasty were selected for this study. Informed consent was obtained from each patient at the time of pre-anesthesia visit.

In the operating theater, intravenous line was obtained. Normal saline solution was administered through it at a rate of 5 $ml \cdot kg^{-1} \cdot hr^{-1}$. Anesthesia was induced with intravenous injection of droperidol and fentanyl, and maintained by NLA (droperidol-fentanyl-nitrous oxide-oxygen) with the appropriate use of pancuronium as a muscle relaxant under controlled ventilation keeping Pa_{CO_2} 35 mmHg approximately. Radial artery was cannulated to monitor the blood pressure and to obtain arterial samples.

The subjects were divided into 4 groups (table 2); the L group, consisted of 10 patients, received Ringer's lactate solution (Lactec®, Otsuka Co.), the LD group consisted of 10 patients, received Ringer's lactate solution containing 5% glucose (TDR®, Terumo Co.), the A group, consisted of 11 patients, received Ringer's acetate solution (offered by Nikken Chemical Co.), and the AD group, consisted of 13 patients, received Ringer's acetate solution containing 5% glucose (Veen-D®, Nikken Chemical Co.).

For each subject solution was infused at a rate of 500 ml for initial 20 min, then maintained at the rate of 5 $ml \cdot hr^{-1} \cdot kg^{-1}$ B.W. for subsequent 3 hr and 10 min, a total of 3.5 hr. Blood samples were obtained before starting the infusion and 30 min, 1 hr, 1.5 hr, 2.5 hr and 3.5 hr after the

Table 3. Blood levels of L-lactate, D-lactate, pyruvate, acetate, glucose, NEFA and base excess

	Pre-dosing	30 min	60 min	1.5 hr	2.5 hr	3.5 hr
L-lactate ($mg \cdot dl^{-1}$)						
(L)	8.5±1.1	11.0±1.0$^{\#\#}$	12.9±1.7$^{\#\#}$	13.5±1.9$^{\#\#}$	15.5±2.1$^{\#\#}$	15.0±2.2$^{\#\#}$
(LD)	9.6±0.9	16.1±0.8$^{\#\#**}$	20.2±1.5$^{\#\#**}$	18.2±1.4$^{\#\#}$	13.2±1.2$^{\#}$	11.9±1.5
(A)	6.7±0.5	7.6±0.7	8.4±0.8$^{\#}$	8.6±0.8$^{\#}$	10.4±0.8$^{\#\#}$	10.1±0.7$^{\#\#}$
(AD)	7.2±0.7	13.7±1.2$^{\#\#++}$	17.7±1.2$^{\#\#++}$	15.9±1.2$^{\#\#++}$	11.8±0.8$^{\#\#}$	10.1±0.9$^{\#}$
D-lactate ($mg \cdot dl^{-1}$)						
(L)	0.14±0.11	2.11±0.16$^{\#\#}$	1.27±0.11$^{\#\#}$	1.00±0.08$^{\#\#}$	1.17±0.10$^{\#\#}$	1.04±0.08$^{\#\#}$
(LD)	0.18±0.01	2.03±0.09$^{\#\#}$	1.37±0.06$^{\#\#}$	1.19±0.07$^{\#\#}$	1.16±0.13$^{\#\#}$	1.29±0.10$^{\#\#}$
(A)	0.14±0.02	0.11±0.01	0.10±0.01	0.13±0.02	0.13±0.02	0.11±0.01
(AD)	0.12±0.01	0.14±0.01	0.16±0.02	0.15±0.02	0.16±0.02	0.14±0.02
Pyruvate ($mg \cdot ml^{-1}$)						
(L)	0.77±0.01	1.00±0.11$^{\#\#}$	0.97±0.11$^{\#\#}$	1.06±0.13$^{\#\#}$	1.20±0.15$^{\#\#}$	1.10±0.11$^{\#\#}$
(LD)	0.83±0.04	1.61±0.11$^{\#\#**}$	1.88±0.18$^{\#\#**}$	1.59±0.15$^{\#\#*}$	1.17±0.11$^{\#}$	0.94±0.11
(A)	0.63±0.08	0.68±0.07	0.69±0.07	0.77±0.07	0.84±0.06$^{\#}$	0.79±0.06$^{\#}$
(AD)	0.63±0.06	1.27±0.11$^{\#\#++}$	1.62±0.12$^{\#\#++}$	1.45±0.11$^{\#\#++}$	1.03±0.07$^{\#\#}$	0.81±0.07$^{\#}$
Acetate ($mg \cdot ml^{-1}$)						
(L)	1.01±0.19	0.99±0.17	1.10±0.19	1.32±0.25$^{\#}$	1.56±0.26$^{\#}$	1.80±0.46
(LD)	1.28±0.35	2.08±0.38$^{\#*}$	3.53±0.54$^{\#\#**}$	3.46±0.54$^{\#\#**}$	4.14±0.52$^{\#\#**}$	3.07±0.35$^{\#*}$
(A)	1.31±0.24	2.86±0.33$^{\#\#}$	2.32±0.25$^{\#\#}$	1.94±0.23$^{\#\#}$	2.82±0.42$^{\#\#}$	2.32±0.29$^{\#\#}$
(AD)	1.84±0.19	3.21±0.35$^{\#\#}$	3.64±0.29$^{\#\#++}$	3.55±0.24$^{\#\#++}$	3.73±0.32$^{\#\#}$	3.37±0.16$^{\#\#+}$
Glucose ($mg \cdot ml^{-1}$)						
(L)	85±1	83±2	95±3$^{\#\#}$	94±4$^{\#}$	89±3	93±4
(LD)	92±3	252±11$^{\#\#**}$	220±9$^{\#\#**}$	201±10$^{\#\#**}$	178±9$^{\#\#**}$	178±11$^{\#\#**}$
(A)	89±3	86±4	95±6	91±5	93±5	90±04
(AD)	88±3	256±8$^{\#\#++}$	226±9$^{\#\#++}$	208±8$^{\#\#++}$	184±9$^{\#\#++}$	178±9$^{\#\#++}$
NEFA (mEq/L)						
(L)	0.62±0.06	0.77±0.15	1.02±0.14	0.76±0.03	0.56±0.11	0.70±0.12
(LD)	0.57±0.09	0.35±0.05$^{\#**}$	0.25±0.03$^{\#\#**}$	0.20±0.02$^{\#\#**}$	0.17±0.01$^{\#\#**}$	0.16±0.02$^{\#\#**}$
(A)	1.01±0.15	0.96±0.13	1.09±0.15	0.98±0.16	1.09±0.21	0.87±0.07
(AD)	0.89±0.10	0.49±0.07$^{\#\#++}$	0.31±0.06$^{\#\#++}$	0.20±0.02$^{\#\#++}$	0.13±0.01$^{\#\#++}$	0.13±0.01$^{\#\#++}$
Base excess (mEq/L)						
(L)	0.1±0.6	0.2±0.5	0.5±0.5	0.7±0.6	1.1±0.6	0.5±0.5
(LD)	0.4±0.5	−1.4±0.5$^{\#\#*}$	−0.9±0.3$^{\#*}$	−0.3±0.3	0.1±0.5	0.9±0.6
(A)	−0.2±0.5	−0.2±0.7	−0.0±0.6	0.8±0.7	0.9±0.7	0.2±0.6
(AD)	0.8±0.3	−0.7±0.4$^{\#\#}$	−0.1±0.4$^{\#}$	0.4±0.6	1.1±0.4	1.3±0.4

All values are expressed as mean ± SEM. () shows experimental group.
$^{\#}$ $P < 0.05$ significant difference from Pre-dosing value in the identical Group.
$^{\#\#}$ $P < 0.01$ significant difference from Pre-dosing value in the identical Group.
* $P < 0.05$ significant difference between L group and LD group.
** $P < 0.01$ significant difference between L group and LD group.
$^{+}$ $P < 0.05$ significant difference between A group and AD group.
$^{++}$ $P < 0.01$ significant difference between A group and AD group.

initiation of infusion. Foley's catheter was inserted after induction of anesthesia, urine volume measurement and urinary sampling were done at the same time as shown for blood sampling.

Blood L-lactate, D-lactate and pyruvate were measured enzymatically with a simultaneous assay method for L-lactate, D-lactate and pyruvate developed by Kuze et al[3,7]. Blood was deproteinized immediately after

Table 4. Urinary outputs during anesthesia of 3.5 hr

	Urinary volumes (ml)	L-Lactate (mg)	Pyruvate (mg)	Acetate (mg)	Glucose (mg)
(L)	628 ± 131	3.21 ± 0.40	1.08 ± 0.16	5.38 ± 1.37	3 ± 3
(LD)	833 ± 132	14.38 ± 4.04*	3.16 ± 0.66*	16.62 ± 6.37	2029 ± 416**
(A)	674 ± 157	2.26 ± 0.67	0.69 ± 0.17	9.01 ± 1.42	4 ± 2
(AD)	647 ± 98	9.75 ± 2.84^{+}	2.13 ± 0.31^{++}	14.88 ± 2.90	2717 ± 646^{++}

All values are expressed as mean ± SEM. () shows experimental group.
* $P < 0.05$ significant difference between L group and LD group.
** $P < 0.01$ significant difference between L group and LD group.
$^{+}$ $P < 0.05$ significant difference between A group and AD group.
$^{++}$ $P < 0.01$ significant difference between A group and AD group.

sampling with perchloric acid, then centrifuged. Supernatant was used for the determination. Serum acetate was measured by gas chromatography (GC-7A, Shimazu Co.) with the Chromosorb WAW column containing silicone filler SP-1200 (10%) and H_3PO_4 (1%).

The following measurements were also performed; arterial blood gases analysis with ABL-2 (Radiometer Co.), serum protein and specific gravity of urine with clinical refractometer, hemoglobin with azide methemoglobin method (RaBA II, Chugai Co.), and hematocrit with microhematocrit tube method. Serum adrenaline and noradrenaline levels were measured with high performance liquid chromatography (HPLC, trihydroxyindol method; column I, Develosil ODS 7 u; column II, TSK IEX 510 SP; column III; Chemcosorb ODS-H 7u, and Hitachi 650-10s fluorometer detector). Blood electrolytes, Na^+, K^+, Ca^{2+} and Cl^-, were measured with ion-selective electrodes (type 1 and 2 from Nova Biomedical Co.). Blood glucose and urine glucose were measured enzymatically with Glucose Analyzer (YSI Co.). Serum non-esterified fatty acids (NEFA) were measured enzymatically (ACOD from ACS Co.). The ketone bodies in serum and urine were determined by test paper (Multisticks 3, Miles Co.).

Osmotic pressures of serum and urine were measured with micro-osmometer (Precision System Co.). The osmolar clearance (C_{osm}) and free water clearance (C_{H_2O}) were calculated from urine volume and osmotic pressure of serum and urine.

During study, pulse rate and blood pressure were monitored.

The significance of the difference in the observed mean value between the pre-infusion state and every time point during infusion in identical group was tested by the paired t-test, and that between two groups of L and LD, and again between two groups of A and AD at the identical time point was examined by the non-paired t-test. The statistical significance was defined as $P < 0.05$.

Results

No significant differences were seen in relation to sex, age, body weight, height and the time of starting anesthesia, doses of adrenaline applied to the operative field, the volume of blood loss between L and A group, L and LD group, and A and AD group, respectively (table 2.).

1. Comparison between L group and A group (table 3. and 4.)

Blood sugar was slightly increased in L group, whereas no significant change was found in A group. L-lactate in blood was elevated significantly in both groups, and the elevations in L group were somewhat higher than in A group. D-lactate in blood showed no significant change in A group, and about five times higher than normal level was seen in L group. Pyruvate in blood increased significantly in L group, and only slight increase was seen in A group.

Thus, L-lactate:pyruvate ratio was elevated significantly in L group, and no significant change was seen in A group.

Serum acetate remained unchanged in L group, whereas significantly greater increase was seen in A group than L group. The increase in serum NEFA was not significant and comparable in L group and A group. The changes in serum electrolytes and serum osmolality were negligible in both groups. Urinary excretion of L-lactate, pyruvate, acetate and glucose in 3 hr and half of study were very low in both groups.

2. *Comparison between L group and LD group*

Significantly greater elevations were seen in blood sugar, blood L-lactate, blood pyruvate and serum acetate in LD group than in L group. Thus, increased amounts of glucose, L-lactate and pyruvate excreted in urine in LD group. Serum NEFA was strikingly decreased in LD group. Serum osmolality and osmolar clearance were higher and base excess in arterial gas analysis was lower in LD group than in L group.

3. *Comparison between A group and AD group*

Significantly higher elevations in blood glucose, blood L-lactate, blood pyruvate, serum acetate and serum osmolality were seen in AD group compared with those of A group. Urinary excretions of glucose, L-lactate, and pyruvate were significantly greater in AD group. The decrease in serum NEFA and base excess was significant in AD group.

4. *Comparison between LD group and AD group*

The elevations in blood sugar, blood L-lactate, blood pyruvate and serum acetate were almost comparable in both groups. Urinary excretions of L-lactate, pyruvate, acetate and glucose were also comparable in two groups.

Concerning with other data which were measured in this study, such as hemoglobin, hematocrit, electrolytes and catecholamines (both adrenaline and noradrenaline), their concentrations in one group were not significantly different to other groups, respectively. No ketone bodies in serum and urine were observed in all cases. And no difference was noted between groups as to urinary output, specific gravity and osmolality of urine, free water clearance, somatic blood pressure, pulse rate, partial pressure of oxygen and oxygen saturation in arterial blood measured upon collection of blood.

Discussion

L-lactate is a by-product of intracellular glucose oxidation[8]. Pyruvate is the only precursor and lactate situates a metabolic dead end[8]. Therefore, both production and utilization of lactate have to occur via pyruvate in the following reaction catalyzed by lactate dehydrogenase (LDH)[4,8],

$$\text{Pyruvate} + \text{NADH} + \text{H}^+ \overset{(LDH)}{\rightleftharpoons} \text{Lactate} + \text{NAD}^+ \quad (1)$$

Lactate can be utilized either for energy production in mitochondrial oxidation processes or as a precursor for gluconeogenesis[2]. On the other hand, acetate is normally available in human tissues in relatively small quantities[5]. The activation of acetate requires ATP and Coenzyme A as follows[9];

$$\text{ATP} + \text{Acetate} + \text{CoA} \rightleftharpoons \text{AMP} + \text{PPi} + \text{Acetyl CoA}$$

Acetyl CoA is utilized in a variety of biological processes, such as biosynthesis of fatty acids, sterols, acetoacetate and acetylcholine[5,9]. The major fate of this molecule is condensation with oxaloacetate to form citrate, the initial step in oxidation via the citric acid cycle. Acetate itself is assumed not to proceed to the production of pyruvate, L-lactate and glucose[10]. Probably that is why A group showed only slight elevations in L-lactate, pyruvate and glucose in blood.

It has been reported that the rate of metabolic degradation of D-lactate is about one fourth that of L-lactate[11]. Thus, the concentrations of D-lactate was elevated in L-group.

The total calories required for human activity, about 60% of it is delivered from

carbohydrates[12]. Carbohydrates are mainly transported in the body in the form of glucose. The liver acts as a buffer organ and releases glucose to maintain a constant concentrations of glucose in blood, when there is an interference in absorption by intestinal tracts. Thus, blood glucose levels are maintained by a balance between hepatic output and peripheral uptake. The rate-limiting factor during intravenous delivery of glucose is determined by the rate in cellular membrane transport.If glucose is not transported from the blood into cells for its utilization, then blood glucose concentrations will exceed the tubular threshold of the kidney, resulting in an osmotic diuresis. The maximal speed of administration of glucose without exceeding metabolic capacities and producing glucosuria is approximately 0.5 gram·kg^{-1}·hr^{-1} for adults[12].

In this study, glucose was administered at a rate of 25 gram/20min initially, and at a rate of 0.25 gram·kg^{-1}·hr^{-1} for 190 min thereafter. As a result blood concentrations of glucose exceeded the tubular threshold and glucosuria occurred.

The glucose loaded groups, i.e. LD and AD groups, showed significant elevations in blood L-lactate. In the 1940s an elevated lactate level, and especially an increased lactate:pyruvate ratio, were assumed to signal lack of oxygen in the tissues and anaerobic metabolism[8]. As shown in equation (1) lactate formation occurs when hydrogen is transferred to pyruvate from NADH. The reduction of pyruvate results in the reoxidation of NADH to NAD$^+$. The lactate-pyruvate reaction favors lactate formation, so that under normal conditions the pyruvate level is only about one tenth to one twentieth of the lactate level[13]. NAD$^+$ is necessary for the glycolytic process in the cells[14]. At the triose phosphate level of glycolysis, 4 atoms of hydrogen are released from each triose phosphate molecule[14]. These hydrogen atoms combine immediately with NAD$^+$, which serves as hydrogen acceptor and NADH is formed. The main route of reoxidation of NADH in the cell is by transfer of H$^+$ through the respiratory chain to oxygen. This process is possible under aerobic conditions. When oxygen is lacking the mitochondria ceases to generate NAD$^+$. In anaerobic situations the reoxidation of the NADH formed during glycolysis thus coupled mainly to the reduction of pyruvate to lactate according to equation (1). NAD$^+$ is utilized at the triose phosphate level so that glycolysis can proceed[8]. This means that the formation of lactate is not only regulated by the pyruvate concentration but also by the NADH:NAD$^+$ concentration ratio (i.e. the redox state of the cytosol) and the hydrogen ion concentrations[8].

In this study, the elevated blood L-lactate levels found in LD and AD groups, which were mainly resulted from the higher pyruvate concentrations due to enhanced metabolic flow through glycolytic pathway following glucose administration. During administration of lactated Ringer's and acetated Ringer's solution, slight metabolic changes were observed, but clinically not significant. Glucose containing Ringer's solution seems to affect the metabolism, especially given in large amounts, so should be used in appropriate amounts and rate to avoid metabolic alterations.

The increased concentration of blood lactate accompanied by certain base deficit, which was found in the human subjects receiving glucose infusion as shown in this study, is easily taken as a sign indicating the presence of circulatory insufficiency. So we should be very careful to evaluate the clinical significance of such laboratory data.

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