The Effect of Intravenous Lactated Ringer's Solution Versus 0.9% Sodium Chloride Solution on Serum Osmolality in Human Volunteers

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Animal studies have shown that large volumes of IV lactated Ringer's solution (LR) decrease serum osmolality, thereby increasing cerebral water. These studies have led to recommendations to limit LR to avoid cerebral edema in neurosurgical patients. Eighteen healthy human volunteers aged 20–48 yr received 50 mL/kg LR over 1 h on one occasion and 0.9% sodium chloride (NS) on another. Venous samples were taken at baseline (T1), at infusion end (T2), and 1 h after T2 (T3). Time until first urination was noted. With LR, serum osmolality decreased by 4 ± 3 mOsm/kg from T1 to T2 and increased insignificantly with NS. At T3, osmolality returned almost to baseline in the LR group. Blood pH increased from T1 to T2 with LR by 0.04 ± 0.04 and decreased with NS by 0.04 ± 0.04. These pH changes persisted at T3. Subjective mental changes occurred only with NS. Abdominal discomfort was more common with NS. Time until first urination was longer with NS (106 ± 11 min) than with LR (75 ± 10 min) ($P < 0.001$). In healthy humans, an infusion of large volumes of LR, but not NS, transiently decreased serum osmolality, whereas acidosis associated with NS persisted and urinary output was slower with NS. **Implications:** Large volumes of lactated Ringer's solution administered to healthy humans produced small transient changes in serum osmolality. Large volumes of sodium chloride did not change osmolality but resulted in lower pH.

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Lactated Ringer's solution (LR) and 0.9% sodium chloride solution (NS) are commonly used as IV fluids. The osmolarity of LR is 273 mOsm/L. In dilute physiological solutions, the values of osmolality and osmolarity are interchangeable (1). However, when measured by the depression of freezing point, the osmolality of LR is 254 mOsm/kg (2,3). This discrepancy is due to the incomplete ionization of the solutes in LR. However, the measured osmolality of NS (mOsm/kg), which is more completely ionized, is similar to the calculated osmolarity of 308 mOsm/L. Thus, the osmolality of LR is lower than, and that of NS is equal to or higher than, the osmolality of normal serum (285–295 mOsm/kg) (4). In animal studies of isovolemic hemodilution with large volumes of IV LR, the serum osmolality decreased (1,2,5–9). Because the blood-brain barrier (BBB) allows the passage of water along osmotic gradients (10), serum osmolality is a determinant of brain water content, so that low serum osmolality may contribute to cerebral edema (5–7,11,12). Based on these data, it has been recommended that IV LR be administered cautiously to neurosurgical patients (6,13).

Studies demonstrating changes in osmolality associated with the administration of large volumes of IV LR and NS have been performed only in animals (1,2,6,7). We undertook the current investigation in healthy human volunteers to determine whether large volumes of IV LR or NS would result in changes of serum osmolality.

Methods

The protocol was approved by our institutional review board. Twenty healthy human volunteers aged 20–48 yr were enrolled in the study. After giving written, informed consent, each volunteer was randomly assigned to one of two groups using sealed envelopes. The investigations were performed before noon. There was no restriction on oral intake before the IV infusions, and each subject urinated and was

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Table 1. Venous Blood Variables from Human Volunteers

	Before infusion (T1)	End of infusion (T2)	End of infusion + 1 h (T3)	(T2–T1)
Serum osmolality (mOsm/kg)				
NS	288 ± 5	289 ± 5	290 ± 5	0 ± 4*
LR	288 ± 4	285 ± 5	287 ± 4	−4 ± 3*
Serum sodium concentration (mEq/L)				
NS	140 ± 2	141 ± 2	141 ± 2	1 ± 2*
LR	140 ± 1	139 ± 2	140 ± 2	−1 ± 2*
Whole blood pH				
NS	7.42 ± 0.04	7.38 ± 0.05	7.38 ± 0.05	−0.04 ± 0.04†
LR	7.41 ± 0.05	7.44 ± 0.05	7.43 ± 0.05	0.04 ± 0.03†
Serum glucose (mg/dL)				
NS	95 ± 25	95 ± 21	99 ± 19	0 ± 15
LR	92 ± 31	84 ± 12	94 ± 15	−7 ± 26

Values are mean ± SD (n = 18 per group).
NS = 0.9% sodium chloride solution, LR = lactated Ringer's solution.
* $P < 0.05$ LR versus NS.
† $P < 0.001$ LR versus NS.

weighed immediately before the infusion. Initially, one group received LR and the other received NS. The alternate solution was infused during a second study period at least 3 days after the initial infusion. The subjects and the laboratory staff (performing the measurements) were blinded as to which solution was administered. However, the investigators administering the IV fluids, taking blood samples, and monitoring the volunteers were not blinded. After local anesthetic infiltration, a peripheral IV cannula (16 or 14 g) was inserted in the antecubital fossa. The subjects were seated or lying with head elevation, except to walk approximately 30 yards to urinate. They read, conversed, or slept as they desired. There was no oral fluid intake during the study period, and 50 mL/kg study solution was infused IV over the first hour.

Venous samples were taken through the same cannula in the antecubital fossa without a tourniquet. The first sample (T1) was taken before the IV infusion tubing was attached. The second sample was taken at the end of the infusion (T2): the IV infusion was disconnected, the first 5 mL of blood was discarded, and a sample taken and used for measurements. The cannula was then flushed with 5 mL of the study fluid, and over the next hour, 25 mL was infused to keep the cannula patent. One hour after the end of the infusion (T3), the third sample was taken in a manner identical to the second sample, and the IV cannula was removed.

If requested by the subject, IV furosemide 5–10 mg was administered via the cannula and flushed in with 5 mL of study solution after the third sample was taken and before removal of the cannula. The objective of furosemide administration was to promote a diuresis, which would decrease the duration of sensations associated with hypervolemia, such as the feeling of distension of the head and neck, ankles, and abdomen.

Throughout the study period, blood pressure, heart rate, peripheral oxygen saturation, and respiratory rate were recorded at 10-min intervals. The volunteers were also closely observed for symptoms of discomfort or abnormal physical signs, and the subjects' comments were noted by the observers who administered the infusions.

Serum sodium, glucose, osmolality, and pH were measured from each venous blood sample. Serum sodium concentration was measured using an ion-selective electrode. Serum glucose was determined using the oxygen rate method with an oxygen electrode. Serum osmolality was measured by determination of freezing point depression, and whole blood pH was measured with a pH-sensitive glass electrode.

We also recorded the length of time from the start of the infusions until the subjects first urinated.

The data for venous serum osmolality, pH, glucose, and sodium concentrations were each analyzed with a two-solution (LR vs NS) by three-episode (T1, T2, T3) mixed-model repeated-measures analysis of variance. Time to urination was analyzed as a two-solution paired t-test. Forward stepwise logistical regression was used to assess whether the incidence of mental changes or abdominal discomfort was associated with any of the solution variables.

Results

Two subjects withdrew from the study after the first infusion. The first subject experienced abdominal discomfort after the first infusion (NS). The other subject withdrew because of causes unrelated to the study. The results of the remaining 18 subjects (6 women and 12 men) were used for analysis. The measured venous blood variables are displayed in Table 1.

Table 2. Time to First Urine Output

	Female (n = 5)	Male (n = 11)	Male + female (n = 16)
NS	133 ± 39*	79 ± 37	106 ± 11†
LR	80 ± 14*	69 ± 40	75 ± 10†

Values are mean ± SD expressed in minutes.
NS = 0.9% sodium chloride solution, LR = lactated Ringer's solution.
* $P < 0.05$ LR versus NS.
† $P < 0.001$ LR versus NS.

When LR was infused, serum osmolality (Table 1) decreased by 4 ± 3 mOsm/kg from T1 to T2, whereas it showed an insignificant increase with the NS infusion. This difference between the infusions was statistically significant ($P < 0.05$). At T3, serum osmolality returned to baseline after LR and remained unchanged after NS. When NS was infused, serum sodium concentration (Table 1) increased 1 ± 2 mEq/L between T1 and T2 and decreased insignificantly when LR was infused, but these differences were statistically significantly different from each other ($P < 0.05$). Whole blood venous pH (Table 1) increased from T1 to T2 by 0.04 ± 0.04 after the LR infusion and decreased by 0.04 ± 0.04 after NS. This difference was significant ($P < 0.001$). The pH at T3 after the administration of NS remained the same as T2. After LR infusion, the pH at T3 insignificantly trended toward baseline. Serum glucose concentration (Table 1) showed no significant difference between the two infusions and did not change over time.

The time from T1 until first urination (Table 2) was significantly different between the two infusions ($P < 0.001$): NS 106 ± 11 min compared with LR 75 ± 10 min. Women demonstrated a 53-min difference in time to urination with NS (133 ± 39 min) compared with LR (80 ± 14 min). This differed significantly from the 10-min difference (69 ± 40 min with LR and 79 ± 11 min with NS) in men ($P < 0.05$). Furosemide was administered to 10 subjects 1 h after each infusion.

Blood pressure, heart rate, and peripheral oxygen saturation were stable throughout the study in all subjects. With both solutions, all subjects reported mild discomfort associated with swelling of the head and neck, abdominal girth, and extremities. However, lassitude and a perceived difficulty in abstract thinking (such as mental arithmatic, reading medical journals, or replying to anesthesiology board questions) were noted by 13 subjects with NS and none with LR. These subjective mental changes did not correlate with any other measured variable. Ten subjects experienced abdominal discomfort with NS, one subject experienced it after both LR and NS, and seven did not experience it after either LR or NS. Logistical regression revealed no correlation between abdominal discomfort and any measured variable, except that pH at T2 was associated with abdominal discomfort in the NS group ($P < 0.01$).

Discussion

These results indicate that, in healthy humans, the infusion of large volumes of LR but not NS tends to decrease serum osmolality. This is in agreement with previous animal studies (6,11), although those studies examined the infusion of large volumes of crystalloid to replace blood loss, whereas our study did not remove large volumes of blood. However, our study also shows that, within an hour of ending the infusion of LR, serum osmolality returns toward baseline. This is to be expected, because changes in serum osmolarity are sensed in the hypothalamus by neurons that terminate in the posterior pituitary (14). Decreased osmolality inhibits the release of antidiuretic hormone from these neurons, and the resulting diuresis of hypotonic urine causes the serum osmolality to return to normal.

In the experimental literature, decreased serum osmolality after infusion of LR is associated with increased cerebral water content. When LR was used to resuscitate a porcine model of head injury, Walsh et al. (8) and Shackford et al. (9) demonstrated a decrease in osmolarity (from 290 ± 4 to 277 ± 10 mOsm/L and from 291 ± 3 to 286 ± 5 mOsm/L) with a worsening of cerebral water content and intracranial pressure (ICP) in both. In a rabbit model of hemodilution with LR, Tommasino et al. (6) showed that there was a transient decrease in osmolality (from 279 ± 9 to 275 ± 2 mOsm/kg) accompanied by a transient increase in ICP and cerebral water content. An increase in cerebral water content and ICP was also demonstrated in a rabbit model of head injury by Zornow et al. (3) when the infusion of LR resulted in a decrease of osmolality of 5 ± 3 mOsm/kg.

Theoretically, a difference of 1 mOsm across a semipermeable membrane, such as the BBB, exerts a pressure of >19 mm Hg in osmotic pressure (15), so that even small changes in osmolality can be expected to have a marked effect on water transfer. Evidence to support this is provided by Hyodo et al. (7), who reported increased cerebral water content in dogs hemodiluted with LR after middle cerebral artery occlusion. The osmolarity of these animals was 295 ± 1 mOsm/L, compared with 296 ± 1 mOsm/L in the control animals. However, when Feldman et al. (2) administered LR to a rat model of head injury, there was no increase in cerebral water content, despite a decrease of serum osmolality from 293 ± 11 to 287 ± 6 mOsm/kg.

In our study, the difference in osmolality after LR infusion was small (4 ± 3 mOsm/kg), and the human volunteers showed no clinical signs or symptoms of increased ICP or cerebral edema after LR. This may indicate the presence of compensatory mechanisms that protect the brain. Unfortunately, these mechanisms may not be intact in the clinical situation in

which large volumes of IV crystalloid infusion are required for patients with intracranial pathology. Therefore, care should still be taken to ensure iso- or hyperosmolarity in the presence of possible brain injury.

NS did not change serum osmolality but resulted in a decrease in venous blood pH. Although the pH in venous blood is lower than arterial pH, consistent correlation between the two has previously been demonstrated (16) when the samples are taken from the same site, with subjects in the resting state as they were throughout the study. The decrease in pH associated with NS infusion has been observed before and is attributed to hyperchloremic metabolic acidosis (17,18). We presume that this was the cause, but we did not measure serum chloride. It was interesting that the pH changes did not return to baseline 1 h after the infusion. Furosemide has been recommended to treat hyperchloremic acidosis (19). However, although it was administered to a number of the volunteers, no further blood samples were taken in our study to evaluate the efficacy of this treatment.

The symptoms of abdominal discomfort and mental changes were unexpected observations. There was no systematic quantification of these observations, and they were simply recorded as comments by the subjects. However, except for one subject who had abdominal pain with both NS and LR, this was only noted after the NS infusion. Drowsiness or decreased mental capacity for performing tasks such as reading and mental arithmatic was observed in 13 subjects only after NS. Although the possibility of bias cannot be excluded from these findings because the observers were not blinded, it is an interesting speculation that early recovery from anesthesia might be modulated by the type of IV fluid if large quantities have been administered. However, further investigation with a double-blinded protocol and a structured mental state examination would be required to verify these observations.

The longer time before urination after NS versus LR implies that NS may be associated with more fluid retention than LR. Inhibition of ADH secretion caused by the lowered osmolality (14) observed after LR infusion is one possible explanation of this finding. Although we did not measure it, increased serum chloride concentration, which could have resulted from the infusion of NS, decreases renal blood flow and glomerular filtration rate (20), thereby causing urinary retention. We observed more prolonged urinary retention in women than in men with both types of fluid. These observations may have clinical implications in that the type of IV fluid, as well as the volume, may influence urinary output, especially in women. The administration of furosemide had little effect on the time at which the subjects first urinated. It was administered 120 min after the start of the infusion, by which time all subjects—except four after NS and one after LR administration—had already urinated.

In summary, LR 50 mL/kg administered IV over 1 h to healthy human volunteers resulted in a transient small decrease in serum osmolality. An equal volume of IV NS administered over 1 h did not affect the serum osmolality but was associated with a mild acidosis, which had not changed 1 h after the infusion was finished.

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