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

E. Lynne Williams, FRCA, Kathy L. Hildebrand, BN, Shelley A. McCormick, MSN, and M. Jay Bedel, BSN
Anesthesiology Department, Allegheny University Hospitals, Allegheny General Hospital, Pittsburgh, Pennsylvania

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 of LR 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.

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 osmolality 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...
Table 1. Venous Blood Variables from Human Volunteers

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

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

<table>
<thead>
<tr>
<th></th>
<th>Female (n = 5)</th>
<th>Male (n = 11)</th>
<th>Male + female (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS</td>
<td>133 ± 39*</td>
<td>79 ± 37</td>
<td>106 ± 11†</td>
</tr>
<tr>
<td>LR</td>
<td>80 ± 14*</td>
<td>69 ± 40</td>
<td>75 ± 10†</td>
</tr>
</tbody>
</table>

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 < 0.01 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 arithmetic, 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 osmolality 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 osmolality (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 osmolality 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 dem-
onstrated (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 asso-
ciated 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 
urther 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 sub-
jects. However, except for one subject who had ab-
dominal 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 arithmetic 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 in-
fusion is one possible explanation of this finding. Al-
though we did not measure it, increased serum chlor-
ide 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 reten-
tion 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 admin-
istered 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 aci-
dosis, which had not changed 1 h after the infusion 
was finished.

The authors thank Dr. Michael Shaw for technical assistance, Dr. Joseph Lucke for statistical assistance, and Dr. Glenn Gravlee for helpful discussion of this manuscript.

References

1. Greger R. Units used in physiology and their definition. In: 
Greger R, Winhorst U, eds. Comprehensive human physiology 
from cellular mechanisms to integration. Berlin: Springer, 1996: 
2421–6.
neurological status with rapid infusion of lactated Ringer’s or 
5% dextrose solution following head trauma. J Neurosurg 1995: 
83:1060–6.
3. Zornow MH, Scheller MS, Shackford SR. Effect of a hypertonic 
lactated Ringer’s solution on intracranial pressure and cerebral 
water content in a model of traumatic brain injury. J Trauma 
5. Korosue K, Heros RC, Ogilvy CS, et al. Comparison of crystal-
loids and colloids for hemodilution in a model of focal cerebral 
6. Tommasino C, Moore S, Todd MM. Cerebral effects of iso-
volemic hemodilution with crystalloid or colloid solutions. Crit 
8. Walsh JC, Zhaung J, Shackford SR. A comparison of hypertonic 
to isotonic fluid in the resuscitation of brain injury and hemor-
9. Shackford SR, Zhaung J, Schmoker J. Intravenous fluid toxicitiy: 
effect on intracranial pressure, cerebral blood flow, and cerebral 
238–50.
11. Zornow MH, Todd MM, Moore SS. The acute cerebral effects of 
changes in plasma osmolality and onotic pressure. Anesthesi-
12. Kaeda R, Todd MM, Cook LN, Warner DS. Acute effects of 
changing plasma osmolality and colloid onotic pressure on the 
formation of brain edema after cryogenic injury. Neurosurgery 
13. Zornow MH, McQuitty C, Prough DS. Perioperative fluid man-
agement of the neurosurgical patient. In: Albin MS, ed. Text-
book of neuroanaesthesia with neurosurgical and neuroscience 
14. Koizumi K. The role of the hypothalamus in neuroendocrinol-
15. Zornow MH, Scheller MS. Intraoperative fluid management 
during craniotomy. In: Cottrell JE, Smith DS, eds. Anesthesia 
16. Tobias JD, Meyer DJ, Jr, Helikson MA. Monitoring of pH and 
PCO₂ in children using the Paratrend 7 in a peripheral vein. Can 