Efficacy of Glucose or Amino Acid–Based Commercial Beverages in Meeting Oral Rehydration Therapy Goals After Acute Hypertonic and Isotonic Dehydration

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Abstract

Background: The efficacy of different commercial beverage compositions for meeting oral rehydration therapy (ORT) goals in the treatment of acute dehydration in healthy humans has not been systematically tested. The objective of the study was to compare fluid retention, plasma volume (PV), and interstitial fluid (ISF) volume restoration when using 1 popular glucose-based and 1 novel amino acid–based (AA) commercial ORT beverage following experimental hypertonic or isotonic dehydration.

Methods: Twenty-six healthy adults (21 males, 5 females) underwent either a controlled bout of hypertonic (n = 13) or isotonic (n = 13) dehydration (3%–4% body mass) via eccrine or renal body water and electrolyte losses induced using exercise-heat stress (EHS) or Lasix administration (LAS), respectively. Rehydration was achieved over 90 minutes by matching fluid intake to water losses (1:1) using a sports drink (SP) or AA commercial ORT beverage. Fluid retention (water and electrolytes), PV, and ISF volume changes were tracked for 180 minutes.

Results: AA produced significantly (P < 0.05) greater fluid retention (75% vs 57%), ISF volume restoration, and tended (P = 0.06) to produce greater PV restoration in trial EHS. In trial LAS, neither beverage exceeded 65% retention, but AA replaced electrolytes and preserved ISF volume better than SP (P < 0.05).

Conclusion: The results of this study demonstrate superior rehydration when using AA compared with SP for both hypertonic and isotonic dehydration. (JPEN J Parenter Enteral Nutr. 2018;42:1185–1193)

Keywords
diarrhea; diuretic; hypovolemia; sweat; volume depletion

Clinical Relevancy Statement

Controversy exists regarding the use of sports drinks and the future composition of oral rehydration solution beverages for the treatment of all-cause dehydration. We used 2 distinct models of controlled, moderate dehydration to compare oral rehydration therapy goals between sports drink and a non-glucose-containing electrolyte beverage. We demonstrate clear disadvantages of using a sports drink along with more optimal rehydration in the absence of glucose. Both of these findings should interest clinicians advising patients on commercial choices of enteral nutrition in the treatment of all-cause dehydration.

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Introduction

When mild to moderate dehydration occurs, the ingestion of electrolyte-rich fluids containing glucose (oral rehydration therapy [ORT]) is the preferred treatment regardless of dehydration etiology (all-cause) or the age of the afflicted. Treatment with an oral rehydration solution (ORS) exploits the ability of glucose to markedly stimulate intestinal sodium (and water) absorption via a unique intestinal epithelial transporter (SGLT1), thus promoting net positive intestinal water and electrolyte absorption. The goal of ORT with ORS is to replace water and electrolytes in approximate proportion to their losses while emphasizing restoration of circulating blood and interstitial fluid (ISF) volumes. Although ORS is strongly recommended to combat enteric fluid losses (e.g., isotonic dehydration from diarrhea, vomiting), similar solutions are also recommended to replace large eccrine fluid losses (e.g., hypertonic dehydration from exercise, fever). Self-treating adults and caregivers of the young frequently report the use of commercial ORT beverage formulations to recover from dehydration. Sports drinks (SPs) are often marketed for this purpose—but because they are popular, convenient, and inexpensive, SPs are designed primarily to replace exercise water loss and deliver fuel to working muscles at a physiologically optimum rate. However, their electrolyte composition is too low for optimal post-exercise rehydration and their glucose concentrations are positive stimuli for gut chloride secretion, which may exacerbate many enteric secretory disorders. Despite long-standing advice against the use of SPs, specifically with respect to the treatment of diarrheal dehydration, positive treatment outcomes have been reported. Their use is still considered satisfactory when dehydration is mild or moderate and resources are limited. The efficacy of SPs for achieving ORT goals following acute all-cause dehydration in healthy young adults has not been systematically evaluated.

The recent observation that even small amounts of glucose stimulate gut chloride secretion may help explain why ORS has never been demonstrated to reduce stool volume or duration of diarrheal illness. A novel glucose-free commercial blend of amino acids (AA) and electrolytes (enterade®, Entrinsic Health Solutions, LLC, Norwood, MA) was recently developed to leverage the ability of AA to stimulate epithelial sodium (and water) absorption by carrier-mediated transport without stimulating gut chloride secretion. Therefore, the degree to which glucose is required in an ORS formulation may be questioned. The beverage also appears to increase the potential for non-nutrient-dependent sodium absorption and may confer gut health benefits to include tightening of the mucosal barrier. It was also recently demonstrated to have a beverage hydration index (BHI) quantitatively better than water (P <0.05) and qualitatively similar to other more energy-dense drinks. Like SPs, the efficacy of enterade® for achieving ORT goals following all-cause dehydration has not yet been tested.

The popular choice of commercially available, non-ORS beverage solutions for the treatment of moderate dehydration in adults merits systematic study of how well they achieve ORT goals for promoting net positive rehydration and restoring circulating blood and ISF volumes. In this study, we compared ORT goal outcomes using enterade® and a SP (Gatorade®, PepsiCo, New York, NY).

Methods

Volunteers

Twenty-six physically active soldier and civilian volunteers took part in this study (21 males, 5 females; mean ± SD age, 23 ± 8 years; body mass (BM), 79.56 ± 18.48 kg; height, 178 ± 9 cm; total body water [TBW], 43.76 ± 9.32 L). All volunteers had passed the Army Physical Fitness Test (or equivalent fitness) within the previous 6 months and received a general medical clearance prior to participation; thus, all volunteers were considered physically fit and healthy. Use of alcohol, dietary supplements, and any medication other than an oral contraceptive was prohibited. No female volunteer was or became pregnant during the course of the study. Menstrual cycle phase could not be standardized, but small potential fluid handling differences due to sex were accepted as a part of the between-subject variation inherent to the research design. Volunteers were provided informational briefings and gave voluntary, informed written consent to participate. Investigators adhered to AR 70-25 and U.S. Army Medical Research and Materiel Command Regulation 70-25 on the use of volunteers in research. The U.S. Army Research Institute of Environmental Medicine Human Use Review Committee approved this study.

Study Design

The study consisted of 3 consecutive days of experimental testing. Twenty-four hours before test day 1, volunteers were given 3 L of fluid to consume in addition to ad libitum beverage consumption coupled to habitual dietary practices. It was estimated that food intake would provide an additional 0.6 L of fluid each day, bringing daily fluid intake totals to ≥3.6 L. Physical exercise was permitted, but it was restricted to a short list of allowable activities and work durations. No food or drink was permitted after 2200 hours; thus, all subsequent morning measurements were made in a >8-hour fasted state. This process was repeated 2 more times to produce stable body weight and urine and blood parameters consistent with euhydration on the morning of day 3 (euhydration), from which baseline
TBW and plasma volume (PV) could be estimated indirectly. Immediately following euhydration measurements on day 2, TBW was determined by measurement of lean body mass (LBM) using dual energy x-ray absorptiometry (DEXA) (Lunar iDXA, General Electric, Madison, WI), multiplied by the universal hydration constant.\(^{24}\) PV was calculated using LBM and the equation of Sawka et al.\(^{25}\) On the third morning of testing, following first morning urine, nude weight, and blood measurements (euhydration, described below), volunteers were fed a small, standardized breakfast (450 kcal; 57% carbohydrate, 30% fat, 13% protein, 450 mg Na\(^+\)) and were provided 250 mL of water. Volunteers then rested quietly for \(~1\) hour before being randomly assigned to 1 of 2 dehydration protocols. The 26 volunteers were evenly but randomly assigned to either the hypertonic dehydration trial or the isotonic dehydration trial (\(n = 13\) in each group).

**Dehydration Protocols**

Hypertonic dehydration (\(n = 13\)) was achieved using exercise-heat stress (trial EHS), which consisted of intermittent (50 minutes exercise, 10 minutes rest) treadmill (3.5 mph, 7% grade) or cycle ergometer exercise (120 W) inside an environmental chamber set to 40°C, 20% relative humidity as previously described.\(^{26}\) Sweat was sampled twice during the exposure (hour 1 and hour 2) using the arm-bag method (Continental Plastic Corp., Delavan, WI) and a previously described cleaning procedure.\(^{27}\) Whole-body sweat losses were measured gravimetrically and corrected\(^{28}\) before multiplying by the average arm-bag sweat electrolyte concentration to determine total sweat solute content. Exposure continued until 3 hours elapsed or until 3%–4% dehydration was achieved, after which volunteers showered and were provided with a small protein bar (190 kcal, 13% carbohydrate, 44% protein, 43% fat, 210 mg Na\(^+\)) and 250 mL water before resting quietly up to 3 hours before rehydration.

Isotonic dehydration (\(n = 13\)) was produced by oral administration of a loop diuretic (80 mg, Lasix, Sanofi Aventis US LLC, Cambridge, MA) (trial LAS)\(^{29}\) in order to stimulate increased urinary water and electrolyte losses while resting in a temperate environment.\(^{26}\) Total urine losses were determined gravimetrically and multiplied by electrolyte concentrations to determine total urine solute content. At least 6 hours elapsed before providing the same snack described above, followed by an additional 1–2 hours of rest. Prior to rehydration, urine, weight, and blood measurements were made in the hypertonic or isotonic dehydrated condition (\(~90\) minutes).

**Blood, Urine, and Fluid Spaces**

All urine was collected into preweighed sample urine cups or 24-hour urine containers (Fisherbrand 24-hour urine container, Tucson, AZ). Nude BM was measured on a platform scale (Model WSI-600, Mettler Toledo, Toledo, OH) verified daily for performance (\(\pm 0.05\) kg). Phlebotomy was performed by venipuncture after volunteers sat quietly for 20 minutes. Plasma, urinary, and beverage electrolytes were determined in triplicate for sodium, chloride, and potassium by direct ion-selective electrode. Plasma glucose was analyzed by enzymatic determination. Whole blood was assayed for hemoglobin by multi-wavelength reflectance with conductivity correction. All of these analyses were performed using a Stat Profile Critical Care Xpress (Nova Biomedical, Waltham, MA). Plasma (Posm), urinary (Uosm), and beverage (Bosm) osmolalities were measured in triplicate by freezing-point depression (Model 210, Fiske Micro-osmometer, Norwood, MA). Hematocrit was performed manually in triplicate using the micro-hematocrit technique (Damon/IEC Micro-Capillary Reader, Needham Heights, MA). Relative changes in PV were calculated from hemoglobin and hematocrit according to Dill and Costill\(^{30}\) using day 3 euhydration measurements as baseline. Absolute changes in PV were taken as the product of PV\(^{25}\) and its relative change. Compartmental fluid losses and shifts were estimated indirectly using osmometric formulae\(^{31}\) that allow partitioning of TBW into extracellular fluid (ECF) and intracellular fluid (ICF) compartments. The ECF is further divided into PV and ISF volume using ECF – PV = ISF. Equation usage conforms to well-established physiologic principles of body water and electrolyte behavior, distribution, and clinical treatment.\(^{32,35}\) Although precise quantitative accuracy of the equations has not been demonstrated, the general responses of body fluid compartments to dehydration and rehydration compare favorably between indirect\(^{31,36}\) and direct assessment methods.\(^{37}\) Dehydration as a percentage of body mass was calculated conventionally as: (\(\Delta\)BM/BM)*100.

**Rehydration Protocol**

After dehydrated urine, weight, and blood measures (\(~90\) minutes), a venous catheter was placed into an antecubital vein for serial blood sampling. Both groups of volunteers (\(n = 13\) each group) were randomly assigned to rehydrate with enterade\(^{®}\) (AA: \(n = 7\) in EHS, \(n = 6\) in LAS) or Gatorade\(^{®}\) (SP: \(n = 6\) in EHS, \(n = 7\) in LAS). The TBW volume lost was given back as enterade\(^{®}\) (67 mmol/L Na\(^+\), 60 mmol/L Cl\(^-\), 4.2 mmol/L K\(^+\), 8 AA blend (lysine, aspartic acid, glycine, isoleucine, threonine, tyrosine, valine, serine); Bosm = 197 mmol/kg) or Gatorade\(^{®}\) (21 mmol/L Na\(^+\), 26 mmol/L Cl\(^-\), 3.9 mmol/L K\(^+\), 322 mmol/L glucose; Bosm = 330 mmol/kg) in 3 equal boluses spaced 30 minutes apart (i.e., total of 90 minutes). The rate of oral rehydration was similar to often used i.v. infusion rates for mild-to-moderate dehydration.\(^{38}\) Beverage compositions
listed are the study means. Although composition varied little, beverage composition was measured before each test and the precise values were used for analysis. A blood sample was drawn at the end of 90 minutes (minute 0) and again at 30, 60, 90, and 180 minutes into recovery. A 20-minute seated posture was imposed before each blood draw to control for postural effects on PV. \( ^{223}c \) thus allowing 10 minutes of every 30 minutes for volunteers to urinate as needed. The total volume of urine was collected for biochemical analysis. Body water and cation balances were calculated as the differences between losses (sweat, urine) and gains (beverages) during dehydration and rehydration, respectively.

**Statistics**

Descriptive statistics are presented using mean ± SD. Values are sometimes expressed normalized for BM to reduce between-subject variation. Group × time variables (water and cation balance, PV) were analyzed using a mixed-model, 2-way ANOVA with Newman Keuls post hoc procedure. Single-variable group differences (e.g., fluid retention, fluid spaces) were analyzed using independent samples t-tests. Ordinary least squares regression was also employed to estimate sodium ingestion required for zero sodium deficit. The principal outcome measure in this study was beverage retention 3 hours post-consumption (i.e., ORT rehydration efficacy). We estimated that 6 to 8 volunteers per group would be ample to detect a significant (\( P < 0.05 \)) and important (effect size > 1.5) difference in fluid retention between groups. \(^{41}\) All data were analyzed with GraphPad Prism 5.0 (GraphPad Software, Inc., La Jolla, CA).

**Results**

**Dehydration**

Prior to rehydration, Trial LAS TBW losses from urine were \( 2.37 ± 0.49 \) L and \( 3.11 ± 0.4% \) of BM. Urine solute concentrations were \( 117 ± 8 \) mmol/L (Na\(^+\)), \( 139 ± 10 \) mmol/L (Cl\(^-\)), and \( 18 ± 3 \) mmol/L (K\(^+\)), respectively. Both volumes and concentrations were consistent with most types of 24-hour diarrheal losses. For the EHS trial, TBW losses from sweat and urine were \( 3.19 ± 0.67 \) L and \( 3.9 ± 0.5% \) of BM. Body fluid solute concentrations were \( 62 ± 18 \) mmol/L (Na\(^+\)), \( 63 ± 3 \) mmol/L (Cl\(^-\)), and \( 11 ± 3 \) mmol/L (K\(^+\)), respectively. Both volumes and concentrations were consistent with ordinary sweat loss ranges reported by others, although both K\(^+\) and Cl\(^-\) were higher due to small volumes of highly concentrated urine, whereas urinary sodium was low due to volume losses. \(^{34,44}\)

**Rehydration**

Figures 1A and 1B plot the relationship between TBW losses (\( x, \) mL/kg) and cation losses (\( y, \) mEq/kg). The dotted line represents isotonicity whereby water and solute are lost in equal proportion to plasma. \(^{45}\) Values above and below the dotted line are relatively hypertonic or hypotonic, respectively. In the LAS trial (Fig 1A), dehydration was isotonic to begin (–90 minutes). After 90 minutes of rehydration, TBW recovered back to 0 minutes baseline (by design), but cation balance remained negative and body fluids were hypotonic. Although negative, cation balance was superior (\( P < 0.05 \)) in AA compared with SP from 0–180 minutes. TBW recovery in AA was numerically higher than SP, consistent with
greater absolute drink retention (64.9 ± 4.8% vs 53.0 ± 6.2%), but neither was statistically significant (P = 0.15). In AA, urinary sodium concentration from 0–180 minutes was 22 ± 15 mmol/L, while in SP it was 13 ± 2 mmol/L, both of which suggest moderate to strong renal sodium retention.44

For trial EHS (Figure 1B), dehydration was hypertonic to begin (−90 minutes). In AA, both TBW and cation balance returned to baseline following 90 minutes of rehydration (by design). Throughout recovery, body fluids remained isotonic. Beverage retention was greater in AA than SP (75.4 ± 2.5% vs 56.9 ± 5.4%, P < 0.05). Body fluids were hypotonic during recovery in SP as TBW and cation balance were both significantly lower than AA (P < 0.05). The urinary sodium concentration from 0–180 minutes was 79 ± 29 mmol/L in AA and 24 ± 6 mmol/L in SP, suggesting weak to moderate renal sodium retention, respectively.44

**Compartmental Fluids: Dehydration and Rehydration**

The restoration of blood volume was indexed using PV changes in response to dehydration and rehydration. In trials LAS and EHS, PV was reduced by −12% ± 5% (−0.380 ± 0.180 L) and −9% ± 5% (−0.277 ± 0.147 L), respectively. Figure 2A shows that in trial LAS, PV recovered from dehydration (−90 minutes) from minutes 30 through 90 post-rehydration, then fell again and was not different from dehydration by 180 minutes. Table 1 shows the corresponding plasma concentrations of electrolytes at 4 distinct time points, all of which were consistent with mild (AA) to more severe (SP) hypotonic dilution. In trial EHS (Figure 2B), PV recovered similarly when compared with trial LAS. However, it remained significantly different from dehydration (−90 minutes) from 30–180 minutes. Plasma electrolytes in Table 2 are consistent with hypertonicity followed by isotonic (AA) or hypotonic (SP) recovery.

Figures 3A and 3B show fluid shifts among body compartments in trials LAS (A) and EHS (B). TBW losses in LAS derived from plasma and ISF spaces only, consistent with observations related to TBW losses in diarrhea.7,46 In fact, a small portion of ECF losses occurred not through absolute losses (urine), but through a relative loss (shift) to within the ICF compartment. In response to rehydration, PV behavior was similar between beverages, but both the absolute (urine) and relative (migration to ICF space) loss of ISF was greater in SP than AA (P < 0.05).

In trial EHS, the loss of TBW was shared among all 3 body water compartments as has been reported previously for hypertonic dehydration.31,36,37 The PV response was similar between beverages (Figure 2B), but the slight expansion of PV in AA remained above that of SP (P = 0.06). As with trial LAS, both absolute and relative ISF space losses were significantly larger in SP than AA (P < 0.05).

**Discussion**

This study compared the potential for 1 popular and 1 novel non-ORS commercial ORT beverage to rehydrate adults following experimental isotonic and hypertonic dehydration. Efficacy was gauged using the goals of ORT, namely, net positive rehydration and restoration of circulating blood and ISF volumes.2,7 Our findings were that AA performed better than SP on all 3 goals following hypertonic dehydration. In response to isotonic dehydration, AA generally performed better than SP on 2 goals and equivalently on 1 goal category.

The superior rehydration achieved using AA during hypertonic dehydration was anticipated given that enterade®
Table 1. Plasma Measurement Responses to Dehydration and Rehydration in Trial LAS.

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Euhydration</th>
<th>Dehydration (minute −90)</th>
<th>Rehydration (minute 0)</th>
<th>Rehydration (minute 180)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AA</td>
<td>SP</td>
<td>AA</td>
<td>SP</td>
</tr>
<tr>
<td>Sodium</td>
<td>138.2 ± 0.7</td>
<td>138.2 ± 0.9</td>
<td>140.5 ± 1.4</td>
<td>136.4 ± 0.9</td>
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<tr>
<td>Potassium</td>
<td>3.8 ± 0.2</td>
<td>4.1 ± 0.3</td>
<td>3.8 ± 0.2</td>
<td>3.7 ± 0.4</td>
</tr>
<tr>
<td>Chloride</td>
<td>106.6 ± 1.1</td>
<td>105.7 ± 1.3</td>
<td>102.4 ± 0.6</td>
<td>102.0 ± 0.6</td>
</tr>
<tr>
<td>Glucose</td>
<td>5.5 ± 0.1</td>
<td>5.3 ± 0.3</td>
<td>5.2 ± 0.3</td>
<td>4.5 ± 0.3</td>
</tr>
</tbody>
</table>

*Indicates $P < 0.05$ between AA and SP.
All units in mmol/L; †indicates $P < 0.05$ vs euhydration.
AA, amino acid–based commercial oral rehydration therapy beverage; LAS, Lasix; SP, sports drink.

Table 2. Plasma Measurement Responses to Dehydration and Rehydration in Trial EHS.

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Euhydration</th>
<th>Dehydration (minute −90)</th>
<th>Rehydration (minute 0)</th>
<th>Rehydration (minute 180)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AA</td>
<td>SP</td>
<td>AA</td>
<td>SP</td>
</tr>
<tr>
<td>Sodium</td>
<td>139.1 ± 0.9</td>
<td>138.1 ± 0.8</td>
<td>142.2 ± 0.7</td>
<td>140.2 ± 2.5</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.1 ± 0.3</td>
<td>4.1 ± 0.1</td>
<td>4.3 ± 0.3</td>
<td>4.3 ± 0.2</td>
</tr>
<tr>
<td>Chloride</td>
<td>107.0 ± 2.4</td>
<td>105.4 ± 0.9</td>
<td>108.0 ± 1.5</td>
<td>107.1 ± 2.0</td>
</tr>
<tr>
<td>Glucose</td>
<td>5.5 ± 0.7</td>
<td>5.5 ± 0.6</td>
<td>5.2 ± 0.7</td>
<td>5.1 ± 0.4</td>
</tr>
</tbody>
</table>

*Indicates $P < 0.05$ between AA and SP.
All units in mmol/L; †indicates $P < 0.05$ vs euhydration.
AA, amino acid–based commercial oral rehydration therapy beverage; EHS, exercise-heat stress; SP, sports drink.

Figure 3. Fluid shifts among body compartments in response to isotonic, LAS (A) or hypertonic, EHS (B) dehydration ([Deh] −90 minutes) and recovery. RehSP and RehAA, rehydration with sports drink or enterade® (180 minutes). Deh, $n = 13$; Reh, $n = 6$ or 7 (see Methods). Deh is for characterization. *Significant difference between only Reh trials for PV, ISF, or ICF, respectively ($P < 0.05$). EHS, exercise-heat stress; ICF, intracellular fluid; ISF, interstitial fluid; LAS, Lasix; PV, plasma volume.

contains more than 3.0 times the sodium of SP, while glucose present in SP played no additive recovery role. The beverage retention levels achieved after 180 minutes with SP (56.9%) and AA (75.4%) are difficult to compare directly with other literature given differences in the absolute volume of fluids lost and replaced, elapsed time, and precise beverage compositions. However, AA was closer in composition to sweat losses and, therefore, produced a smaller TBW and cation deficit with an isotonic (AA) rather than hypotonic (SP) extracellular composition (Figure 1B). Neither beverage reflected the composition of isotonic TBW losses achieved with diuretic, and both resulted in TBW and cation deficits with a hypotonic extracellular composition (Figure 1A). If we hold the fractional replacement (%) constant with increasing sodium concentrations between 50 and 100 mmol/L, we estimate a zero sodium deficit would have required the equivalent of ~0.45% saline in EHS (~77 mmol/L) or ~0.9% saline in LAS (~154 mmol/L) to fully restore losses (data not shown). In practical terms, larger volumes of the same beverage concentrations might also have worked, but it is unlikely that ~4.5 L of fluid could have been comfortably ingested and emptied from
the stomach in 90 minutes in EHS, while larger ingested volumes in LAS could have increased hyponatremia risk.\textsuperscript{35} Therefore, it is intuitive that the optimal ORT formulation depends on the composition of fluids requiring replacement.

PV restoration kinetics were similar between test beverages in both trials, although there was a trend for PV to be more expanded (EHS only) with AA in conjunction with better fluid retention and extracellular isotonicity (Figure 2B, Figure 3B). Similar to retention, it is difficult to make direct comparisons to the literature, but in general the results are consistent with similar studies.\textsuperscript{41} In the case of trial LAS, neither PV nor retention were different, and extracellular hypotonicity differed only by degree (Figure 1A). At a minimum, the PV results suggest that the sum of gastric emptying, intestinal absorption, and peripheral distribution of beverages were similar, despite dissimilar beverage compositions. Importantly, the quantitative differences in retention between AA and SP were best matched by the sum of absolute (urine) and relative (ICF migration) ISF losses, both of which were significantly greater in SP by the sum of absolute (urine) and relative (ICF migration) ISF losses, whereby extracellular hypotonicity differed only by degree (Figure 3A and 3B).

Urinary sodium concentrations (0–180 minutes) further support a relative water overload (too little solute)\textsuperscript{44} proportional to the migration of ISF into the ICF compartment. For example, the largest and smallest (none) intracellular water shifts (Figures 3A and 3B; trials LAS+SP and trial EHS+AA) occurred with the smallest (13 ± 2 mmol/L) and largest (79 ± 29 mmol/L) urinary sodium concentrations, respectively. Large water and solute losses, when replaced by large water and small solute beverages, result in a sodium retentive state whereby renal loss of water (poor retention), renal sodium conservation (<20 mmol/L),\textsuperscript{44} and water movement toward more osmotically concentrated compartments (Figures 3A and 3B) act to defend or preserve plasma sodium concentrations (Tables 1 and 2).

In our study we classify the dehydration achieved (3%-4% body weight) as moderate. The World Health Organization\textsuperscript{47} and others consider dehydration <5% as mild or undetectable. However, the method used to calculate dehydration in response to illness often exaggerates the true level of water loss,\textsuperscript{26} which was experimentally induced and precisely measured in the present work. Hirschhorn\textsuperscript{6} suggested a label of mild dehydration when TBW losses were <2.4 L/d (30 mL/kg × 80 kg), while Sperotto \textsuperscript{38} suggested anything >3–4 L/d was severe. According to Cheek et al.,\textsuperscript{46} severe dehydration is defined only by ECF losses, whereby >4.8 L (60 mL/kg × 80 kg) is enough to compromise circulation and renal perfusion. Our volunteers lost a mean of 2.37 L (LAS) and 3.19 L (EHS) of TBW during 6 hours. Their ECF losses were 2.37 L in LAS, while in EHS it was ~70% of 3.19 L or ~2.2 L. In our laboratory and with others performing similar work, 2%-4% dehydration is common, while ≥6% is a typical Institutional Review Board threshold for safety. Therefore, we believe that the results of this study should be justifiable for application to cases of mild to moderate hypertonic and isotonic dehydration originating from exercise or diarrhea, respectively.

The meaningful application of our findings rests with certain defensible assumptions. The hypertonic model of dehydration via sweat loss (exercise or fever) and fluid restriction is very commonly employed with high ecologic validity. The use of diuretics to model isotonic dehydration similar to that seen in diarrheal disease is much less common, but it has been employed previously to mimic clinical dehydration testing in humans\textsuperscript{26} and to diarrheal dehydration in animals.\textsuperscript{48} Importantly, the volume of TBW and content of electrolyte losses measured herein are entirely consistent with many types of secretory diarrhea,\textsuperscript{42} as was the character of fluid compartment losses.\textsuperscript{7,46} Ours was a “healthy” gut model of diarrheal-type dehydration. Although active intestinal sodium transport remains intact with most types of gastroenteritis,\textsuperscript{13} the absence of microvilli damage, hypersecretory function, etc., common with genuine illness, could alter study outcomes. As with Walker et al.,\textsuperscript{48} water and electrolyte losses in the present study were entirely renal (LAS) or principally eccrine (EHS), rather than enteric. While this is a limitation for a model of diarrheal illness, our experimental results offer informative and useful information for treating all-cause dehydration and the efficacy of ORT.

Conclusions

A variety of commercial non-ORS beverages are used in the daily treatment of all-cause dehydration.\textsuperscript{9,10} The novel commercial AA beverage used in this study replaced electrolytes and preserved ISF volumes better than the more popular SP after isotonic dehydration. AA also performed better than SP on fluid retention (water and electrolytes) and restoration of ISF volumes in response to hypertonic dehydration. Given the different magnitudes and profiles of water and electrolyte losses in health and disease, the results of this study support the need for uniquely formulated commercial beverages when rehydration effectiveness is important.\textsuperscript{1,10} While this study demonstrates superior rehydration using AA vs SP for both hypertonic and isotonic dehydration, more work is needed\textsuperscript{8,17} to demonstrate equivalence or superiority with conventional ORS-type beverages.

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Statement of Authorship

S.N. Cheuvront, R.W. Kenefick, and S. Vidyasagar equally contributed to the conception and design of the research; S.N. Cheuvront, R.W. Kenefick, N. Cahrkoudian, K.M. Mitchell, A.J. Luippold, and K.E. Bradbury contributed to acquisition, analysis, and interpretation of the data; all authors drafted and critically revised the manuscript, agree to be fully accountable for all aspects of work ensuring integrity and accuracy, and read and approved the final manuscript.

References