Hemocytometric Measures Predict the Efficacy of Oral Rehydration for Children with Postural Tachycardia Syndrome

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Objective To explore whether hemocytometric measures could be qualified predictors for the effect of oral rehydration salts (ORS) in children with postural tachycardia syndrome (POTS).

Study design Thirty-five children with POTS and 29 healthy children were enrolled. General information, hemodynamic status, and baseline hemocytometric variables were collected. Children with POTS received ORS therapy and were followed up for 3 months. The independent risk factors of developing POTS were explored. A receiver-operating characteristic curve was used to evaluate predictive value of hemocytometric variables for therapeutic effectiveness of ORS therapy.

Results Children with POTS had larger mean corpuscular volume (MCV) and lower mean corpuscular hemoglobin concentration (MCHC) values than controls ($P < .05$). The baseline MCV values positively correlated with heart rate elevation from supine to upright ($r = 0.294$, $P < .05$). Both larger MCV and lower MCHC values were independent risk factors of developing POTS (for MCV, $P < .05$, OR 1.222; for MCHC, $P < .05$, OR 0.936). In children with POTS, responders to ORS had baseline lower MCV and higher MCHC than nonresponders ($P < .05$). The receiver-operating characteristic curve for the predictive value of MCHC showed that area under the curve was 0.73.

Conclusions MCHC values could be used to predict the effectiveness of ORS for treating POTS in children. *(J Pediatr 2017;187:220-4).*

Postural tachycardia syndrome (POTS) is a multifactorial disorder characterized by exaggerated postural tachycardia that results in symptoms of orthostatic intolerance (OI), thus impacting the daily life of the patients.[1] Oral rehydration salts (ORS) have been used widely for treatment and to ameliorate the symptoms for some patients with POTS.[2-5] However, efficacy has been reported to be inconsistent among individuals.[6-9] Thus, finding predictors of the therapeutic effectiveness of ORS for children with POTS could be very useful. Previous studies showed that the baseline 24-hour urinary sodium excretion could be used as a predictor of the therapeutic efficacy of ORS for treating POTS.[10,11] Lin et al[12] suggested that an increase in heart rate (HR) during the head-up test (HUT) and the maximum upright HR within 10 minutes of the test could be a predictor of ORS efficacy. Li et al[13] suggested that lower body mass index might imply better response to ORS. Although these indexes are noninvasive, economic, and convenient, they have limitations in their predictive ability.

Hypovolemia is one of the most important underlying causes of POTS.[14-16] ORS can be used to replenish the blood volume (BV). Previous studies have shown that both low red blood cell volume[17] and low iron storage,[18,19] which could be measured by hemocytometric variables, play important roles in POTS. Therefore, we suspected that the hemocytometric variables could reflect the status of hypovolemia in children with POTS and thus predict the effectiveness of ORS therapy. This study was designed to explore whether the hemocytometric variables could be useful predictors of therapeutic effectiveness of ORS for POTS in children.

Methods

Thirty-five children with POTS (median age 11.4 years, ranging from 5 to 16 years) and 29 healthy children (median age 10.8 years, ranging from 5 to 16 years) were enrolled in this study. The children with POTS were diagnosed at the Department of Pediatrics, Peking University First Hospital, Beijing, China, from April 2012 to November 2014 via the following diagnostic criteria[20-24]: (1) 2 or more symptoms of OI (including dizziness, headache, chest discomfort, palpitation, nausea, tremor in hands, profuse

AUC	Area under the curve	MCV	Mean corpuscular volume
BP	Blood pressure	NO	Nitric oxide
BV	Blood volume	OI	Orthostatic intolerance
EV	Erythrocyte volume	ORS	Oral rehydration salts
HR	Heart rate	POTS	Postural tachycardia syndrome
HUT	Head-up test	PV	Plasma volume
MCHC	Mean corpuscular hemoglobin concentration	ROC	Receiver-operating characteristic

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perspiration, pale face, blurred vision, lightheadedness, concentration difficulties, or syncope) when upright; (2) normal supine HR and no evidence of any cardiovascular disease; (3) symptoms relieved or diminished by lying in the recumbent position and that recurred for at least 1 month; (4) a POTS diagnostic response (the HR increases ≥40 beats/min or the maximum HR is >120 beats/min, with a decrease of blood pressure [BP] <20/10 mm Hg) during HUT; and (5) exclusion of cardiovascular, neurologic, and endocrine diseases after history-taking, physical examination, electrocardiogram, electroencephalography, magnetic resonance imaging, or other clinical examinations and tests. The healthy children were volunteers who had neither history of OI symptoms mentioned previously nor were diagnosed with cardiovascular diseases, neurologic diseases, hematologic diseases, renal diseases, or endocrine diseases and had a negative result during the HUT. All the participants had no history of fever, nor were they taking any cardiovascular/autonomic agents in the 2 weeks before the HUT. No patients had received pharmacotherapies or nonpharmacotherapies for POTS previously. The study protocol was authorized by the Ethics Committee of Peking University First Hospital, and the study was conducted according to the principles expressed in the Declaration of Helsinki. Informed consent was obtained from all the participants and their parents.

General information (age, sex, height, and weight) was collected by history-taking and physical examination. The baseline hemodynamics including supine BP, HR, and their upright change were collected from the HUT (Dash 2000 Patient Monitor; GE Healthcare, Madison, Wisconsin).

Hemocytometric variables including red blood cell count, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration (MCHC), and red cell distribution width were collected by routine tests (XE-5000; SYSMEX Corporation, Kobe, Japan). Serum sodium concentrations (serum Na^+) of the children with POTS were collected from the blood biochemistry test (RxL Max; Siemens, Muenchen, Germany). Blood samples for testing (2 mL for a routine test and 2 mL for biochemical analysis) were collected between 7:30 and 8:30 a.m., after the patients had fasted for more than 4 hours and were supine for 5 minutes. Specific gravity of urine was collected from a routine urine test (AX-4030; ARKRAY, Inc, Kyoto, Japan). The urine samples were collected between 7:30 and 8:30 a.m.

The pre- and post-treatment occurrence of symptoms for the children with POTS were collected and recorded by the use of symptom scores, which were designed to evaluate the severity of POTS symptoms[25] by grading the symptoms (dizziness, headache, shortness of breath, gastrointestinal symptoms, fatigue, pallor, blurred vision, palpitations, sweating, and tremulousness) from 0 to 4 according to their frequency of onset during follow-up. Score 0 indicated no occurrence; score 1, 1 episode per month; score 2, 2-4 episodes per month; score 3, 2-7 episodes per week; and score 4, frequent symptom occurrence daily.

The HUT was performed between 8:00 and 10:30 a.m. in a quiet and dark room under comfortable conditions (22°C temperature, 50%-55% humidity). Children rested for 10 minutes or longer, until their HR and BP were stable, before being asked to stand independently for 10 minutes. The supine and tilt HR and BP were monitored simultaneously during the test (Dash 2000 Patient Monitor; GE Healthcare). The participants could lie down as soon as the POTS-positive response occurred.

All children with POTS received ORS therapy as the only initial pharmacotherapy. The protocol was as follows. Patients were prescribed ORS III (Amjan Pharma Company, Xi'an, China) of 5.125 g (containing sodium chloride 0.650 g, sodium citrate 0.725 g, potassium chloride 0.375 g, and glucosum anhydricum 3.375 g) daily, dissolved in 500 mL of water before being administered. In addition, patients were educated about how to care for their condition, including increasing water intake, ensuring sufficient sleep, and performing emergent management when suffering symptoms of OI.

Follow-up by telephone was conducted 3 months after treatment. The children and their parents were asked to record the symptom and frequency of onset during the treatment and report their execution of ORS treatment and the OI symptoms. Information on symptoms was evaluated by the symptom score system. The patients were defined as responders if their symptom scores decreased more than 2 scores after ORS therapy without any other pharmacotherapy[26,27]; otherwise, they would be categorized as nonresponders.

Statistical analysis was performed with SPSS 19.0 (IBM Corp, Armonk, New York). The distribution of continuous variables was evaluated. Independent samples with a normal distribution were compared with the Student *t* test because of the relative small sample; otherwise, they were compared with the Mann-Whitney *U* test. Paired samples with normal distributions were compared with a paired-samples *t* test and ANOVA. Categorical variables were compared with the χ^2 test. A binary regression was performed to evaluate the independent risk factors for developing POTS in children. We included variables showing significant differences between children with POTS and healthy children or variables having important clinical implications in the analysis. The correlation between the hemocytometric variables and HR elevation when upright was analyzed with the Pearson correlation test. A P value < .05 was considered to be statistically significant. A receiver-operating characteristic (ROC) curve analysis was used to evaluate the predictive value of potential hemocytometric variables in predicting the therapeutic effect of ORS therapy. The area under the curve (AUC) implies the predictive value, with the AUC of 0.5-0.7 indicating low predictive value, 0.7-0.9 indicating a moderate predictive value, and >0.9 indicating high predictive value.[28,29]

Results

The median age of the 35 patients with POTS was 11.4 ± 2.7 years, ranging from 5 to 16 years, with a female predominance (male/female: 14:21). Median age of the healthy children was 10.8 ± 3.0 years, ranging from 5 to 16 years. There was no significant statistical difference in the age between children with POTS and healthy children. There was no loss to