

Body mass index is a promising predictor of response to oral rehydration saline in children with vasovagal syncope

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Abstract

Background: Vasovagal syncope (VVS) greatly impairs quality of life. The therapeutic efficacy of oral rehydration saline (ORS) for unselected VVS patients is not satisfactory due to the diverse mechanisms of the disease. Body mass index (BMI) was demonstrated to reflect blood volume to a certain extent. Therefore, the present study explored the capability of BMI to predict the therapeutic response of children with VVS to ORS treatment.

Methods: Seventy-four children with VVS who visited the Syncope Unit of Pediatrics at Peking University First Hospital from November 2010 to June 2019 receiving ORS treatment were enrolled for this retrospective case-control study. A comparison of demographic, clinical, and hemodynamic characteristics was performed between responders and non-responders. The correlation between baseline BMI and response time was analyzed. To determine the value of baseline BMI in predicting the therapeutic efficacy of ORS in children with VVS, a receiver operating characteristic curve analysis was performed.

Results: Fifty-two children were identified as responders, and the remaining 22 children were identified as non-responders. The baseline BMI of the responders was much lower than that of the non-responders ($16.4 [15.5, 17.8] \text{ kg/m}^2$ vs. $20.7 \pm 3.6 \text{ kg/m}^2$, $P < 0.001$), and baseline BMI was positively correlated with response time in the head-up tilt test after adjusting for sex ($r = 0.256$, 95% confidence interval [CI]: $0.067-0.439$, $P = 0.029$). The area under the receiver operating characteristic curve of baseline BMI was 0.818 (95% CI: $0.704-0.932$, $P < 0.001$), and an optimal cut-off value of 18.9 kg/m^2 yielded a sensitivity of 83% and a specificity of 73% to predict the efficacy of ORS in VVS.

Conclusion: Prior to treatment, baseline BMI is a promising predictor of response to ORS in children with VVS.

Keywords: Vasovagal syncope; Oral rehydration saline; Body mass index; Therapeutic response

Introduction

Vasovagal syncope (VVS) is the most common type of syncope in the pediatric population.^[1-3] Medical treatment is required when recurrent syncope results in impaired quality of life and unpredictable injuries.^[4,5] Therefore, determining effective interventions for these patients is important. Oral rehydration saline (ORS) is commonly recommended for children with VVS, but its therapeutic efficacy is unsatisfactory in a significant portion of cases.^[6,7] A reasonable explanation might be that there are a variety of underlying mechanisms responsible for VVS, such as hypovolemia, abnormal autonomic nervous activity, and vasomotor dysfunction. ORS, administered to increase the body blood volume, may be beneficial for

patients with hypovolemia as the main mechanism rather than for those with other underlying mechanisms.^[8-10] Therefore, ORS treatment for unselected patients lowers its value. To improve the therapeutic efficacy of ORS for VVS in children, it is essential to seek reasonable indicators that predict the hypovolemic condition before treatment.

Body mass index (BMI), a typical and easily obtained anthropometric parameter, can reflect body blood volume to a certain extent, and people with lower BMI are more prone to undergo syncope and respond positively to a head-up tilt test (HUTT).^[11-16] Therefore, the present study explored the capability of BMI to predict the therapeutic response of children with VVS to ORS.

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Methods

Ethical approval

All procedures involving human participants in the study were in line with the 1975 *Declaration of Helsinki* and its later amendment in 2008, and the present study was authorized by the Ethics Committee of Peking University First Hospital (No. 2018112).

Patients

This was a retrospective case-control study. Seventy-eight patients with VVS who visited the Syncope Unit of Pediatrics at our hospital from November 2010 to June 2019 and underwent ORS treatment were included in the study; they had a median age of 10.0 (8.0, 13.0) years. Detailed histories and physical examinations were obtained routinely, and medical tests, such as blood tests, electrocardiography, Holter electrocardiography, echocardiography, electroencephalography, and intracranial computed tomography (CT) or magnetic resonance imaging (MRI), were performed to exclude cardiogenic or neurologic diseases. VVS was finally diagnosed with the help of the HUTT according to the guidelines provided by the Chinese Pediatric Cardiology Society.^[10,17,18] The exact diagnostic criteria which have not changed since 2009 were as follows: 1) syncopal episodes; 2) syncope commonly induced by predisposing factors, such as rapid postural changes, prolonged upright positions and hot and stuffy environments; 3) a positive hemodynamic response in the HUTT; and 4) the exclusion of other causes of syncope-like events. Patients with a history of heart failure, hypertension or renal disease, and those without complete clinical information were excluded. Patients who refused to undergo ORS treatment were also excluded.

Protocol for the HUTT

The protocol for the HUTT and the positive response criteria were in accordance with those previously described.^[19,20] Three types of positive hemodynamic responses were identified according to the changes in heart rate and blood pressure: 1) a cardioinhibitory response, with an obvious reduction in heart rate and no marked decrease in blood pressure; 2) a vaso-inhibitory response, with a marked decrease in blood pressure and no obvious reduction in heart rate; and 3) a mixed inhibitory response, with both an obvious blood pressure decrease and a significant heart rate reduction.

Measurement of BMI

BMI (kg/m^2) was calculated as body weight (kg) divided by the square of height (m). For the measurement of body weight, subjects were required to wear only one layer of clothes and gently step onto a digital weighing scale. The reading was recorded when it became stable. To measure height with the use of a stadiometer, subjects were asked to take off their hats and shoes and remain in an upright position with their backs, buttocks and heels against a pole and their eyes looking forward. An operator adjusted the slide plate to drop down slowly and gently until there was

contact between the cranial vertex and the bottom of the slide plate. All operators were trained in advance. BMI prior to treatment was regarded as the baseline BMI.

Treatment and follow-up

All included VVS patients received 5.125 g of ORS III (Anjian Pharma Company, Xi'an, China) daily. It contained 3.375 g of anhydrous glucose, 0.725 g of sodium citrate, 0.650 g of sodium chloride and 0.375 g of potassium chloride which were dissolved in 250 mL of water. ORS III has been produced since 2009 in China. Three months after starting therapy, the patients were followed up to assess their response to the intervention by telephone or during clinic visits. Questionnaires were used to evaluate therapeutic efficacy and adverse effects. Symptom scoring was used to reflect the severity of VVS, and the scores were calculated on the basis of the occurrence and frequency of syncopal and presyncopal events: 0, no syncope or presyncope; 1, once per month; 2, 2–4 events per month; 3, 2–7 events per week; 4, > once per day. The scoring system was used to assess each patient both before treatment and 3 months after follow-up. The therapeutic efficacy was determined to be effective when the symptom score decreased by at least 1 point, and correspondingly, these patients were considered “responders”; otherwise, they were considered “non-responders” [Figure 1].^[20,21] All follow-up tasks were completed by the same professionally trained researcher.

Statistical analysis

SPSS 22.0 (IBM Corp, Armonk, NY, USA) was used for data analysis. Continuous variables were examined for normality using the Shapiro-Wilk test, and they are presented as the means and standard deviations or the medians (25th, 75th percentiles) as appropriate. Differences between two groups were analyzed using Student's *t* test or the Mann-Whitney *U* test. Categorical variables are shown as frequencies and were compared with the chi-squared test. Predictors of response to ORS treatment were examined by forward stepwise logistic regression analysis. Correlations between nonnormally distributed parameters were evaluated with partial Spearman correlation coefficients to avoid potential confounders. A receiver operating characteristic (ROC) curve was drawn to evaluate the predictive ability of BMI for ORS treatment in children with VVS. The predictive value was represented by the area under the curve (AUC), with a low predictive value when the area was greater than 0.5 and less than or equal to 0.7, a moderate predictive value when the area was greater than 0.7 and less than or equal to 0.9 and a high predictive value when the area was >0.9. The maximum Youden index, which was calculated as sensitivity plus specificity minus 1, was used to determine the cut-off value. It was considered significant with a *P* value <0.05.

Results

Demographic, clinical and hemodynamic characteristics

Seventy-eight patients (41 females, aged 5–17 years; and 37 males, aged 6–16 years) with VVS receiving ORS treatment were included in the study, but four of them were subsequently lost to follow-up. Finally, 74 eligible patients (38 females, aged 6–17 years; and 36 males, aged

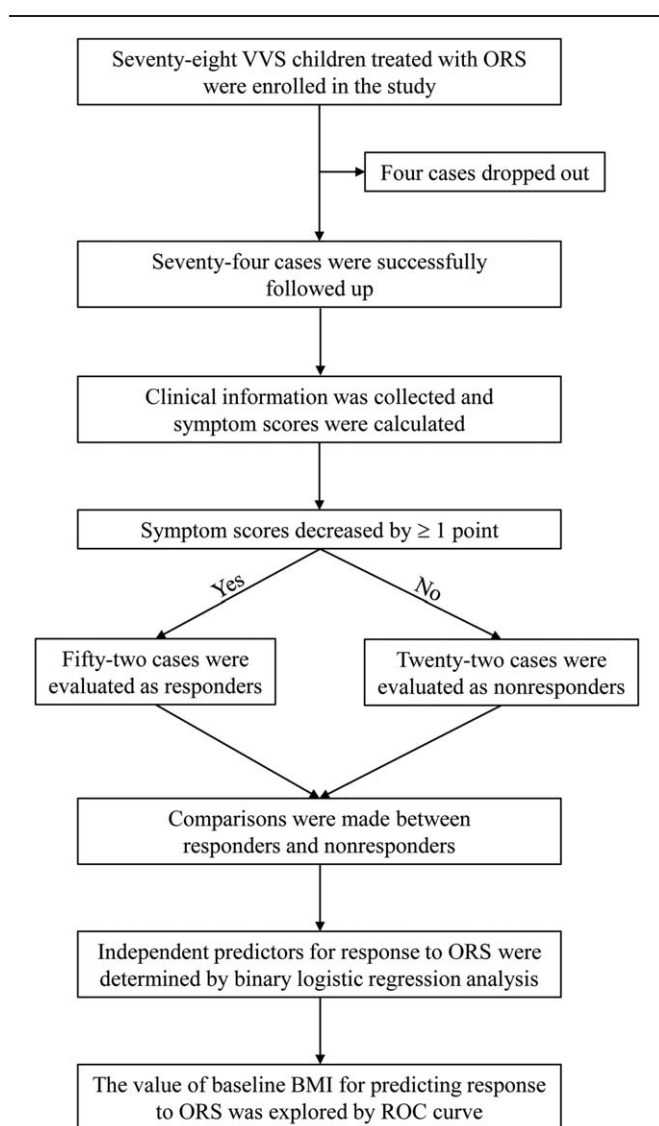


Figure 1: Flow chart and statistical analysis procedures for this study. VVS: Vasovagal syncope; ORS: Oral rehydration saline; BMI: Body mass index; ROC curve: Receiver operating characteristic curve.

6–16 years) were enrolled with a median treatment duration of 3.0 (2.0, 3.0) months. Of them, 48 (65%) patients had a vasoinhibitory response, 24 (32%) patients had a mixed inhibitory response and the remaining 2 (3%) patients had a cardioinhibitory response. No adverse effects were reported according to follow-up data. Based on the changes in symptom scores, 52 patients were defined as responders, and the other 22 were defined as non-responders. Between responders and non-responders, no difference was found in the symptom scores before treatment ($P = 0.886$). However, the responders had much lower symptom scores at follow-up than the non-responders ($P < 0.001$). No differences existed in sex, age at the first syncope event, age at HUTT, duration of treatment, hemodynamic characteristics in HUTT or hemodynamic types of VVS between responders and non-responders ($P > 0.05$). Compared with the non-responders, the responders had short duration of symptoms before treatment ($P = 0.001$) and low baseline BMI ($P < 0.001$) [Table 1].

Predictor of the therapeutic efficacy of ORS treatment

Items with P values < 0.1 in the univariate analysis (age at HUTT, duration of symptoms before treatment, baseline BMI and positive systolic blood pressure in HUTT), were included in the binary logistic regression analysis, and only the baseline BMI was determined to be an independent predictor of response to ORS treatment (odds ratio = 0.629, 95% Confidence interval [CI]: 0.500–0.792, $P < 0.001$).

Correlation between baseline BMI and response time in HUTT

To further explore whether the baseline BMI was associated with the severity of VVS, we performed a partial Spearman correlation test after adjusting for sex and found that the baseline BMI was positively correlated with response time in HUTT ($r = 0.256$, 95% CI: 0.067–0.439, $P = 0.029$) [Figure 2].

Capability of baseline BMI to predict the response to ORS treatment in children with VVS

To explore whether baseline BMI could predict the therapeutic efficacy of ORS, we applied ROC curve analysis. The area under the curve was 0.818 with a 95% CI of 0.704 to 0.932 ($P < 0.001$) [Figure 3]. A baseline BMI of 18.9 kg/m^2 was determined to be the cut-off value for the maximum Youden index, with a sensitivity of 83% and a specificity of 73%.

Discussion

In this study, we observed that the baseline BMI of responders was much lower than that of non-responders. The baseline BMI showed a positive correlation with the response time in the HUTT. More importantly, a baseline BMI cut-off value of 18.9 kg/m^2 produced a relatively high value in predicting the response of children with VVS to ORS treatment.

Although the administration of ORS is relatively safe, we do not advise pediatricians to prescribe it nonselectively. Inappropriate ORS treatment would greatly limit its therapeutic efficacy, prolong the duration of symptoms, and increase the economic burden of the families. Therefore, it has been important to determine a useful measure for predicting the therapeutic efficacy of supplementation with fluid and salt in pediatric VVS and to identify a more individualized treatment.

ORS is effective for VVS patients likely through the restoration of hypovolemia.^[8] After standing, an instantaneous shift of blood from the thorax to the lower extremities and splanchnic organs occurs. Decreased venous return to the heart is overt once the total blood volume is low, which leads to the decompensation reaction. Obviously, supplementing with fluid and salt can reverse the situation in patients whose predominant mechanism is hypovolemia. Disappointingly, heterogeneous and overlapping multifactorial mechanisms greatly reduce the value of this treatment. Blood volume can be

Table 1: Comparisons of characteristics of responders and non-responders in 74 patients with vasovagal syncope.

Characteristics	All patients (n = 74)	Treatment response		Statistics	P values*
		Responders (n = 52)	Non-responders (n = 22)		
Sex (female/male, n)	38/36	26/26	12/10	0.128 [†]	0.721
Age at the first syncope event (years)	8.7 ± 2.8	8.7 ± 3.0	8.7 ± 2.5	-0.019 [‡]	0.985
Age at HUTT (years)	10.0 (8.0, 13.0)	10.0 (8.0, 13.0)	11.5 ± 3.0	-1.776 [§]	0.076
Duration of symptoms before treatment (months)	12.0 (3.8, 36.0)	9.5 (2.0, 24.0)	34.3 ± 23.6	-3.283 [§]	0.001
Duration of treatment (months)	3.0 (2.0, 3.0)	2.5 (2.0, 3.0)	3.0 (2.0, 3.0)	-0.043 [§]	0.966
Body mass index (kg/m ²) at baseline	17.1 (15.9, 19.4)	16.4 (15.5, 17.8)	20.7 ± 3.6	-4.305 [§]	< 0.001
Symptom scores before treatment (points)	1 (1, 1)	1 (1, 1)	1 (1, 1)	-0.143 [§]	0.886
Symptom scores at follow-up (points)	0 (0, 1)	0 (0, 0)	1 (1, 1)	-7.777 [§]	< 0.001
Supine heart rate in HUTT (bpm)	75 (68, 80)	75 (70, 82)	71 ± 11	-1.640 [§]	0.101
Supine systolic BP in HUTT (mmHg)	104 ± 9	104 ± 9	104 ± 8	-0.069 [‡]	0.945
Supine diastolic BP in HUTT (mmHg)	60 ± 8	61 ± 8	58 ± 8	-1.310 [‡]	0.195
Positive heart rate in HUTT (bpm)	75 (64, 114)	77 (63, 115)	73 (63, 114)	-0.325 [§]	0.745
Positive systolic BP in HUTT (mmHg)	75 (66, 83)	74 (65, 82)	80 ± 14	-1.698 [§]	0.089
Positive diastolic BP in HUTT (mmHg)	42 ± 9	42 ± 9	44 ± 11	1.116 [‡]	0.268
Response time in HUTT (minutes)	14 (10, 26)	14 (9, 26)	14 (10, 28)	-0.563 [§]	0.574
Hemodynamic type ratio of VVS (VI/[MI+CI], n)	48/26	31/21	17/5	2.115 [†]	0.146

Normally distributed data are presented as the mean ± standard deviation, otherwise as the median (25th, 75th percentiles). Categorical data are expressed as frequencies. * Comparisons between responders and non-responders. [†]χ² value. [‡]t value. [§]Z value. HUTT: Head-up tilt test; BP: Blood pressure; VVS: Vasovagal syncope; VI: Vasoinhibitory response; MI: Mixed inhibitory response; CI: Cardioinhibitory response.

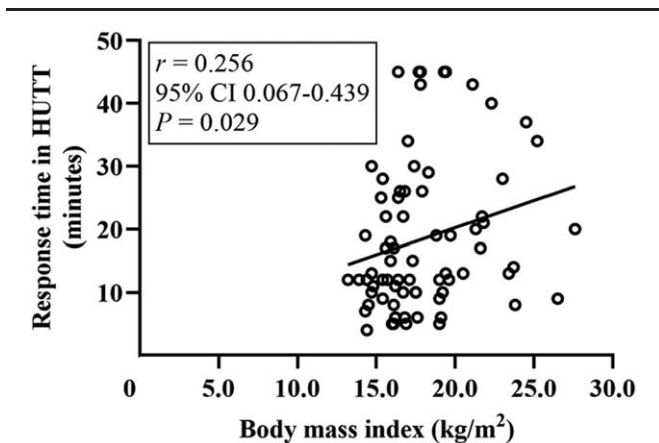


Figure 2: Correlation between baseline body mass index and response time in HUTT. CI: Confidence interval; HUTT: Head-up tilt test.

calculated using isotopic or dye dilution techniques. However, the procedures for these techniques are complex and invasive.^[22] Two decades ago, Younoszai *et al*^[23] investigated the value of an intravenous injection of 1 L of isotonic fluid during tilting to predict the efficacy of oral fluid therapy. A negative response to the tilt table test after intravenous injection predicted good efficacy of oral fluid therapy, with a sensitivity of 85% and a specificity of 20%. However, this method is invasive, time-consuming, and has the risk of inducing heart failure. Twenty-four-hour urinary sodium was reported to be correlated with blood volume and the severity of VVS.^[24,25] Recently, Zhang *et al*^[7] observed that 109.5 mmol of 24-hour urinary sodium excretion had a sensitivity of 100% to predict the therapeutic efficacy of ORS, but its specificity was low (30.8%). Further study is required to determine its predictive value.

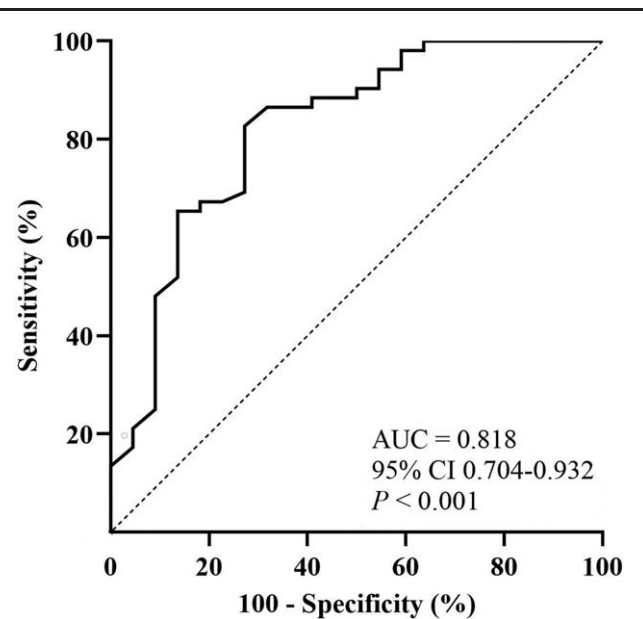


Figure 3: Receiver operating characteristic curve of baseline body mass index for predicting the therapeutic efficacy of oral rehydration saline in vasovagal syncope patients. AUC: Area under the receiver operating characteristic curve; CI: Confidence interval.

Previous studies have shown that BMI is positively related to blood volume^[11-13] and can predict the therapeutic efficacy of ORS in children diagnosed with postural orthostatic tachycardia syndrome, another common cause of pediatric syncope.^[26] Furthermore, people with lower BMI are more prone to experience syncope or respond positively to a HUTT than those with higher values.^[14-16] Therefore, we conducted the present study to evaluate whether baseline BMI had the capacity to predict the therapeutic efficacy of ORS treatment.

In the present study, we found that the baseline BMI of the responders was much lower than that of the non-responders. Furthermore, we used response time in HUTT as a reasonable indicator of the severity of VVS,^[27,28] and it showed a positive correlation with baseline BMI, which suggested that baseline BMI was reasonably capable of reflecting the severity of this disease. With the help of ROC curve analysis, we found out for the first time, that baseline BMI was a promising predictor prior to treatment.

However, body blood volume is influenced by many cofactors aside from weight and height (which were used in calculating BMI), such as age, physical activity, climatic environment, hematocrit and autonomic nervous activity. All these cofactors codetermine the actual state of blood volume.^[29-33] Therefore, the value of application of BMI in predicting the efficacy of supplementation with fluid and salt could be lowered by such cofactors.

Some limitations should not be neglected in this study. The small sample size could have led to bias in the study conclusions. Additionally, the retrospective case-control study design could have resulted in an inevitable recall bias. In the future, prospective and larger sample multicenter studies seeking better indicators are needed for the implementation of individualized therapy in VVS patients.

Conclusions

Baseline BMI is a promising and practical way to predict the therapeutic response of children with VVS to ORS treatment, not only for its predictive capacity but also for its ease of measurement and inexpensiveness. Our findings could help pediatricians implement individualized therapy efficiently and conveniently.

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Conflicts of interest

None.

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