The predictive value of low urine specific gravity in the diagnosis of vasovagal syncope in children and adolescents

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Research article

Keywords: Urine specific gravity, Vasovagal syncope, Children, Adolescents

Posted Date: June 15th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-33823/v1>

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Version of Record: A version of this preprint was published at Italian Journal of Pediatrics on April 17th, 2021. See the published version at <https://doi.org/10.1186/s13052-021-01043-2>.

Abstract

Background

Vasovagal syncope (VVS) is a kind of common neurogenic syncope in children and adolescents. Decreased blood volume is one of the pathogenesis of VVS. The study will explore the predictive value of low urine specific gravity (USG) in the diagnosis of VVS in children and adolescents.

Methods

97 cases, 43 males and 54 females, aged 4 to 16 years old, with an average age of 10.91 ± 2.18 years old, due to unexplained premonitory syncope or syncope were selected. They were diagnosed with VVS through head-up tilt table test. During the same period, 91 cases of children and adolescents, including 45 males and 46 females, aged from 5 to 15 years old, who underwent a healthy examination were matched as a control (control group). USG was measured in both groups.

Results

The USG of VVS group was significantly lower than that of the control group ($P < 0.01$). The sensitivity and specificity of USG prediction in the diagnosis of VVS were evaluated by ROC curve. The area under the ROC curve was 0.751, standard error was 0.035, and 95% CI (0.683, 0.819) suggested that USG was of moderate predictive value in the diagnosis of VVS. Setting USG as < 1.0185 , the sensitivity and specificity and diagnostic coincidence rate of VVS were 74.39%, 66.04% and 69.68%, respectively.

Conclusion

Low USG has predictive value in the diagnosis of VVS in children and adolescents.

1. Background

Vasovagal syncope (VVS) is a kind of common neurogenic syncope in children and adolescents, tends to occur in the long standing, a sudden position change (eg. from the squat or sitting position suddenly to the standing position), and stuffy environment, etc. The process of syncope can lead to falling blood pressure and/or slow heart beat, characterized by transient and self-limited consciousness disorders due to transient cerebral insufficiency of blood supply, accompanied by falling down to the ground because of loss of muscle tone which maintains body posture [1]. The incidence of VVS is closely related to the low blood volume in patients [2], and low blood volume can cause vasovagal reflex. When VVS happens, volume load of left ventricular is reduced, returned blood volume is decreased and ventricle is underfilling, causing hyperexcitability of sympathetic nerves, excess shrinking of cardiac ventricle, stimulation of the mechanical baroreceptor in the posterior inferior wall of the left ventricle, transmitting excitement to the

brain stem, triggering diminished sympathetic activity and raised vagal activity, leading to abnormal bradycardia, decreased peripheral vascular resistance, fall of blood pressure and cerebral hypoperfusion, finally resulting in syncope. Generally, 24 h-urinary sodium of VVS patients decreased [3], and 24 h-urinary sodium is correlated with the severity of VVS. The lower the 24 h-urinary sodium is, the more severe the VVS symptoms are [4]. Therefore, measures to increase water and salt intake should be taken in treatment [5–7]. The diagnosis of VVS is mainly based on head-up tilt table test (HUTT), but temporary aphasia, severe arrhythmia, convulsions, psychological fear and other complications may easily occur when HUTT induces syncope [1], and thus HUTT could only be carried out in larger hospitals. To find a simple and safe VVS diagnosis method can improve the VVS diagnosis efficiency of children and adolescents in primary hospitals.

Urine specific gravity (USG) is under the condition of 4°C the ratio weight of the urine to the pure water with the same volume, it depends on the concentration of the urinary solute, and is proportional to the total solids. The USG of normal people may fluctuate due to differences in diet, water drinking, sweating and urination. The USG of infants is usually lower than that of adults. Under pathological conditions, urine contains more proteins, glucose, ketone bodies and various cells, which increase the USG. Clinically, the USG can be used to judge the fluid status in human body [8], predict the incidence of acute ischemic stroke [9], early evaluate the hydration status of workers in extremely low humidity environment [10], identify diabetes patients with polyuria or diabetes insipidus and also as a monitoring index for the risk of urinary calculi, for example [11], the occurrence of urinary calculi can be reduced if the USG is maintained at a low level [12]. Given that the relationship between urinary specific gravity and VVS in children and adolescents has not been reported, the objective of this study was to discuss the predictive value of USG in the diagnosis of VVS in children and adolescents.

2. Methods

2.1 Study population

From September 2014 to September 2018, 97 cases of children and adolescents (43 males and 54 females, aged from 4 to 16 years old, with an average age of 10.9 ± 12.18 years old, including 5 cases aged from 4 to 6 years old, 70 cases aged from 7 to 12 years old, and 22 cases aged over 13 years old), hospitalized in the Department of Pediatric Cardiology, The Second Xiangya Hospital, Central South University, due to unexplained premonitory syncope or syncope were selected. After detailed enquiry of medical history, physical examination, blood biochemical examination (including fasting blood glucose, myocardial enzyme, etc.), routine electrocardiogram, dynamic electrocardiogram, chest X ray film, echocardiography, EEG and head MRI examination, etc. excluding the organic diseases of nervous system and circulatory system, and drug influences, etc. They were diagnosed with VVS through HUTT which was carried out after adequate communication with and written informed consent from the receivers or guardians (VVS group). During the same period, 91 cases of children and adolescents were randomly examined for health in the Outpatient Department of Child Health Care in our hospital were

matched as the control group, 45 males and 46 females, aged from 5 to 15 years old, among which 3 were less than 7 years old, 64 were from 7 to 12 years old, and 24 were more than 13 years old.

The informed consent was obtained from all the subjects directly or their guardians prior to enrollment. The study protocol was approved by the Ethics Committee of The Second Xiangya Hospital, Central South University.

2.2 Data source

2.2.1 USG: 10 ml morning urine was retained, and the USG was detected by strip method.

2.2.2 HUTT

2.2.2.1 Basic head-up tilt table test (BHUT): children need lay on the tilt bed for at least 10 min with band fixed to avoid buckling of ankle joint and knee joint. HR, BP and ECG recordings are performed during the period. Then, they are tilted upward at an angle of 60° with the simultaneous monitoring of HR, BP and EEG. Tests are stopped when the subjects have a positive response or finish the whole 45 minutes' process. Children should be placed in the supine position (from the standing position) as soon as a positive response occurred [1].

2.2.2.2 Sublingual nitroglycerin HUTT (SNHUT): if syncope does not develop in BHUT, the subjects are suggested to undergo SNHUT keeping the same position for a further 20 min after given a sublingual nitroglycerin 4–6 µg/kg (maximum ≤ 300 µg). The end points of the test are positive response or completion of the protocol. The simultaneous monitoring of HR, BP, EEG and clinical performance should be performed after taking the medicine [1].

2.2.2.3 Standards for positive response of VVS: children with syncopal episodes or presyncope with any of the following responses in HUTT are considered positive: (1) systolic BP (SBP) ≤ 80 mmHg (1 mmHg = 0.133 kPa) or diastolic BP (DBP) ≤ 50 mmHg or mean pressure decrease ≥ 25%; (2) HR < 75 beats/min for 4–6 years old children; HR < 65 beats/min for 7–8 years old children; HR < 60 beats/min for those older than 8 years; (3) electrocardiogram showed sinus arrest, premature junctional contractions; and (4) atrioventricular block and cardiac arrest ≥ 3 seconds. The responses are classified as vaso-inhibitory, cardio-inhibitory, or mixed type. The vaso-inhibitory type is characterized by a significant BP decrease without obvious HR reduction, the cardio-inhibitory type is characterized by a marked HR decrease without marked decrease in systolic pressure, and the mixed type is characterized by both HR and BP decrease [1].

2.3 Statistical methods

The SPSS 22.0 software was used for statistical analysis, the measurement data were expressed as mean ± standard deviation ($\bar{x} \pm s$), and t test was used for comparison between groups. The receiver operating characteristic curve (ROC) was adopted to evaluate the sensitivity and specificity of urinary specific gravity in predicting VVS and area under the curve (AUC) indicated the predictive ability of USG. AUC of

0.5 ~ 0.7 indicates low predictive ability, 0.7 ~ 0.9 is moderate predictive ability, and > 0.9 indicates high predictive ability. $\alpha = 0.05$ was used as the test standard, then $P < 0.05$ was considered statistically significant in difference.

3. Results

3.1 There was no statistical significance difference in age (10.91 ± 2.18 years vs. 11.07 ± 2.02 years, $t = 0.517$, $P > 0.05$) between the VVS group and the control group, and the USG of VVS group was significantly lower than that of the control group (1.0159 ± 0.0067 vs. 1.0225 ± 0.0069 , $t = 6.747$, $P < 0.01$), as shown in Fig. 1.

3.2 ROC curve: The receiver operating characteristic curve (ROC) was used to evaluate the sensitivity and specificity of urinary specific gravity in predicting VVS. The area under the ROC curve was 0.751, standard error was 0.035, and 95% confidence interval (0.683, 0.819) suggested that USG had a moderate predictive value for the diagnosis of VVS. Setting USG as < 1.0185 , the sensitivity and specificity and diagnostic coincidence rate of VVS were 74.39%, 66.04% and 69.68%, respectively. as shown in Fig. 2.

4. Discussion

USG and urine color are widely used in clinical practice [13]. USG can monitor the internal fluid status of athletes. And Wilcoxson et al [8] reported that dynamic monitoring of USG had a good effect on fluid retention and hydration in male runners. Osterberg et al [14] covered that USG was used to determine the pregame fluid intake of American Basketball Association (NBA) athletes, when pregame USG was ≤ 1.020 , athletes should be ensured to supply adequate water. Zubac et al [15] also took USG as the most commonly used biochemical index to monitor athletes' fluid deficiency. And Stover et al [16] found that the USG of exercisers did not change with time and place before physical exercise. If the USG of exercisers was ≥ 1.020 , it suggested that 46% of exercisers might be dehydrated.

Patients with VVS are at low blood volume status. El-sayed et al [17] conducted a double-blind randomized controlled study with oral rehydration salts (ORS) treatment on 20 VVS adult patients and found that, after more than 2 months of follow-ups, the clinical symptoms of VVS patients were significantly improved, especially in patients with previous salt intake < 170 mmol/d, their blood volume increased and so did their tolerance to erectness, with more apparent symptoms improvement. Younoszai et al [18] gave oral isotonic saline intervention to 58 VVS children, and 90% (52/58) of the children had complete relief of symptoms, suggesting that oral liquid therapy was effective in treating VVS children. Li et al [19] reported that 178 cases of children with neurally-mediated syncope were followed up after non-drug treatment (health education, ORS, vertical training, etc.) as the main intervention measure, and found that subjective symptoms were significantly improved (100%). The rate of HUTT's conversion to negative or improvement was 72.47% (129/178 cases), and 98.88% (176/178 cases) of children had good treatment compliance. Zhu et al [20] reported 146 cases of children with orthostatic intolerance. On the basis of health education, ORS treatment was given for 14 ~ 180 days [mean (39.77 ± 31.92) days], the

total clinical subjective efficacy was 78.8% (115/146 cases), and HUTT's total conversion rate was 39.0% (57/146 cases), suggesting that ORS treatment could extend the time of orthostatic intolerance in children with neurally-mediated syncope.

5. Conclusion

This study showed that the urinary specific gravity of VVS children and adolescents was significantly lower than that of healthy control children ($P < 0.01$). The receiver operating characteristic curve (ROC) was used to evaluate the sensitivity and specificity of the predictive value of urinary specific gravity in the diagnosis of VVS, and the area under the ROC curve was 0.751, indicating that the USG had a moderate predictive value in the diagnosis of VVS in children and adolescents. $USG < 1.0185$ was as the boundary point, the sensitivity and specificity and diagnostic coincidence rate of VVS were 74.39%, 66.04% and 69.68%, respectively. The results of this study suggested that the urine specific gravity index could better reflect the amount of water in VVS children and adolescents, and the decrease of USG of VVS children reflected the previous research results on the pathogenesis of insufficient capacity load in the body, which guided patients to increase the intake of water and salt in clinical practice, and the effect of supplemental water and salt could be monitored by the USG [21]. Therefore, it appeared the monitoring method of USG is simple, practical and has certain predictive value for the diagnosis of VVS in children and adolescents.

Declarations

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Availability of data and materials

There are no linked research data sets for this submission. The following reason is given: Data will be made available on request.

Ethical Approval and consent to participate

The informed consent was obtained from all the subjects directly or their guardians prior to enrollment. The study protocol was approved by the Ethics Committee of the Second Xiangya Hospital, Central South University.

Consent for publication

Participants agreed in writing to publish the data without personal privacy.

Competing interests

The authors have no conflicts of interest to disclose.

Authors' contributions

PL and CW conceived the study. PL, XZ, HY, WM, YW and JZ collected and reviewed patient data. RZ performed statistical analysis. PL drafted the manuscript, and all authors contributed to its revision.

Acknowledgements

The authors thank the research personnel and study volunteers involved with the project.

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Figures

Figure 1

Comparison of Urine Specific Gravity Between the Research Group and the Control Group

Figure 2

ROC Curve on the Predictive Value of USG in the VVS Diagnosis in Children and Adolescents. Notes: ROC curve on the predictive value of VVS diagnosis in children and adolescents with USG as the cut-off value. The vertical axis denotes the sensitivity of USG to the predictive value of VVS diagnosis, and the horizontal axis indicates the false positive rate (1-specificity), the solid line of 45° coordinate in the figure is criterion-referenced line, indicating that the sensitivity and the false positive rate is equal, no predictive value. The farther the curve is to the upper left of the reference line, the higher the predictive value is. The area under the curve (AUC) represents the predictive value of USG in the diagnosis of VVS. The AUC value of 0.5 ~ 0.7 is low, 0.7 ~ 0.9 is medium, and > 0.9 is high.