



# Fludrocortisone in Pediatric Vasovagal Syncope: A Retrospective, Single-Center Observational Study

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**Background and Purpose** The purpose of this study was to determine the effect of fludrocortisone in patients with pediatric vasovagal syncope (VVS).

**Methods** This retrospective observational single-tertiary-center study based on chart reviews included 74 patients who were newly diagnosed with VVS in the head-up tilt-table test (HUTT). Some of the patients had been treated with fludrocortisone. All patients were assessed using a brain and cardiac workup before treatment to rule out the syncope being due to other causes, which resulted in seven of them being excluded: two for epilepsy and five for brain pathologies. The remaining 67 patients were analyzed. The effect of fludrocortisone was evaluated based on the results of a follow-up HUTT, with a response to the treatment considered to be present if there was a negative change at the follow-up HUTT. Univariate logistic regression were used for statistical analyses, with the criterion for significance being  $p < 0.05$ .

**Results** There were no significant differences in the characteristic of the patients between the no-medication ( $n=39$ ) and fludrocortisone ( $n=28$ ) groups, including age, sex, and duration of treatment. The recurrence rate of syncopal or presyncopal events was significantly lower in the fludrocortisone group (39.3%, 11 of 28) than in the no-medication group (64.1%, 25 of 39) ( $p=0.044$ ), as was the rate of negative change at the follow-up HUTT: 57.1% (16 of 28) and 28.2% (11 of 39), respectively ( $p=0.017$ ).

**Conclusions** Our findings suggest that fludrocortisone is more effective than no medication in pediatric patients with VVS.

**Key Words** children, vasovagal syncope, fludrocortisone, head-up tilt-table test.

## INTRODUCTION

Syncope is a symptom of sudden, temporary, self-limited loss of consciousness that is attributed to cerebral hypoperfusion. Vasovagal syncope (VVS) is a reflex syncope induced by emotional or orthostatic stress, and is typically preceded by autonomic symptoms such as sweating, pallor, or nausea.<sup>1,2</sup> Previous studies in North America have found that 15% of children aged <18 years present with syncope,<sup>3</sup> and that VVS can cause financial losses and decrease the quality of life.<sup>4</sup> This condition therefore needs to be managed appropriately. Definitive guidelines for treatment remain to be established, but the current treatment guidelines for managing VVS are as follows: the first step is educating patients about the causes and measures that can help prevent further damage.<sup>1,5</sup> The required lifestyle modifications include increased water and salt intakes,<sup>6</sup> while medications such as alpha agonists, beta blockers, or paroxetine may be administered. However, the efficacy of such drugs remains unclear. Meanwhile, fludrocortisone was recently found to be effective in adults,<sup>7</sup> but its efficacy in pediatric patients with VVS has not been validated previously.

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**Received** November 15, 2019  
**Revised** September 11, 2020  
**Accepted** September 14, 2020

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Therefore, the present study compared the efficacy of fludrocortisone with no treatment. Whether other factors can improve the results obtained in the head-up tilt-table test (HUTT) was also analyzed.

## METHODS

### Patients

This was a retrospective observational single-tertiary-center study based on chart reviews that involved 74 pediatric patients up to 18 years of age who had been newly diagnosed with VVS at the Department of Pediatrics of Jeonbuk National University Hospital from January 2014 to July 2019. The patients were diagnosed with syncope when there was a temporary, self-limited loss of consciousness or if presyncope symptoms were caused by specific triggers based on history-taking and a physical examination. Only patients with positive HUTT results in the initial examination were enrolled. All patients were tested to rule out other causes of syncope, using electrocardiography (ECG) to screen for cardiac causes, with echocardiography or 24-hour Holter monitoring performed if indicated, and either electroencephalography (EEG) or brain magnetic resonance imaging (MRI) to screen for central causes. This screening process identified 7 patients with syncope that could have been caused by other causes (2 with epilepsy and 5 with brain pathologies), and so 67 patients were finally enrolled in the study.

### Treatment and follow-up monitoring

The 67 patients [age=14.84±2.10 years (mean±SD), age range=10–20 years; 35 males and 32 females] were allocated to the fludrocortisone ( $n=28$ ) or no-medication ( $n=39$ ) group (Fig. 1). We defined patients who took fludrocortisone during the study period as the fludrocortisone group, and those who were followed up without medication as the no-medication group. The fludrocortisone group received 0.05 mg of fludrocortisone once a day in the morning for the first week, after which the dosage was increased to 0.1 mg once a day. All patients underwent HUTT and 24-hour blood pressure (BP) monitoring before and after the follow-up period. The response to treatment was evaluated approximately 6 months after the initial diagnosis, at which time follow-up HUTT was also performed.

The patients were also classified into two groups according to the results of the follow-up HUTT, defining the response group as those in whom HUTT was converted to a negative response, and the no-response group as the other patients. We used 24-hour BP monitoring to compare several parameters between before and after the use of fludrocortisone, including the heart rate (HR) and BP.

Univariate logistic regression analyses were conducted to

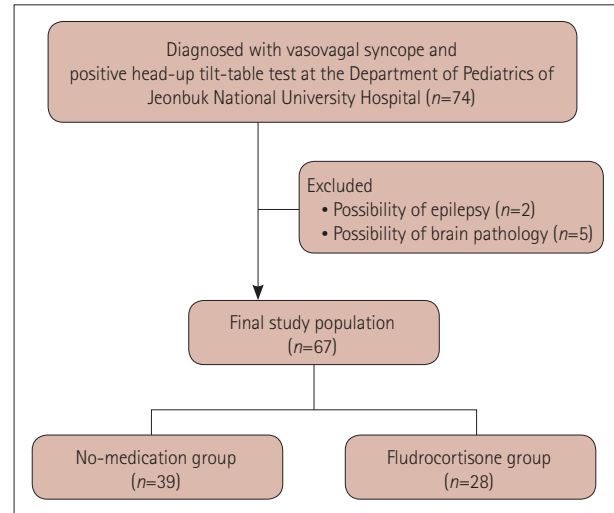


Fig. 1. Study population diagram.

identify the independent variables associated with a good response in the follow-up HUTT.

### HUTT

All patients underwent the HUTT before and after the treatment. HR and BP were recorded while the patient was in a supine position, and then the patients was tilted to 80° for 30 min or until symptomatic. We defined presyncope as the presentation of any of the following symptoms: nausea, vomiting, dizziness, pallor, diaphoresis, blurred vision, or abdominal pain without loss of consciousness. Syncope was defined as the loss of consciousness after presenting with presyncope symptoms. Vital signs were monitored, and divided into four types: cardioinhibition without asystole (HR <40 bpm for >10 s and asystole for <3 s), cardioinhibition with asystole (asystole for >3 s and hypotension coinciding or before HR <40 bpm), vasopressor (HR <10% of its peak at syncope), and mixed (HR <40 bpm for <10 s and asystole for <3 s). Test results were considered positive if presyncope or syncope occurred with the changes in vital signs, as mentioned above. According to how the HUTT was classified in this study, cases of tachycardia or BP changes without HR change were not included in the positive-result group, which allowed us to rule out cases of orthostatic hypotension and postural orthostatic tachycardia syndrome.

A follow-up HUTT was carried out after each treatment. We classified the patients into two groups according to the responsiveness to treatment: 1) the response group, in which the test result changed from positive to negative, and 2) the no-response group, in which the test result did not change.

### ECG and echocardiography

All patients were required to undergo ECG to rule out car-

diogenic causes of syncope. Most of the patients showed a normal sinus rhythm. However, there were 37 abnormal ECG findings in 28 patients, which included 9 instances of sinus arrhythmia (25%), 7 of sinus bradycardia (19%), and 5 of right axial deviation (13%), and etc. Six of the patients underwent 24-hour Holter monitoring, which revealed that none of the cases were related to syncope—all six patients had only sinus bradycardia in the 24-hour Holter monitoring. Another six patients underwent echocardiography, which was also not related to syncope: four (66%) of these patients had normal results, one (16%) presented with a post-balloon state of pulmonary valvular stenosis, and one (16%) had an almost closed ventricular septal defect. All of these findings were considered to be unrelated to syncope, and hence they were all included in the study.

### EEG and brain MRI

EEG or brain MRI was performed on each patient to rule out the central causes of syncope. Even if abnormal findings that are not related to syncope were observed in EEG or MRI, the patients were still included in the study cohort. This meant that five out of seven patients who showed abnormalities in brain MRI such as acute infarction or intracranial hemorrhage were judged as having related symptoms, and so were withdrawn from the experiment. However, the remaining two considered to be unrelated to syncope, such as choroidal fissure cyst or arachnoid cyst, were included in the study. The other two patients who showed epileptic findings in EEG were also excluded.

### Outcome measures

The efficacy of fludrocortisone was evaluated based on both symptoms and HUTT results. Regarding symptoms, we compared the number of patients who experienced either syncopal or presyncopal events during the follow-up period. In the HUTT, we compared the number of patients with negative follow-up HUTT results between the fludrocortisone and no-medication groups.

We also compared the effects of fludrocortisone in 24-hour BP monitoring by analyzing the following nine parameters: the overall HR, systolic BP, and diastolic BP values over 24 hours and during daytime and nighttime. Moreover, we defined the response group as the group in which HUTT converted to a negative result and the no-response group as the other group, and compared the results of 24-h BP monitoring after treatment between the response and no-response groups.

Finally, we used univariate logistic regression to analyze the associations between the following factors and negative follow-up HUTT results: sex, age, height, weight, body mass

index (BMI), initial HR, systolic BP, and diastolic BP.

### Statistical analyses

The Statistical Package for the Social Sciences software (version 22.0 for Windows) was used for the statistical analyses. The two-sample *t*-test was used to compare continuous variables between two groups, and the chi-square test was used to assess proportions between two groups. Univariate logistic regression analyses were performed to identify the factors associated with negative HUTT results. However, multivariate analysis was not carried out due to the lack of significant variables. A *p* value < 0.05 was considered statistically significant.

This study was performed with approval from the Institutional Review Board of Jeonbuk National University Research Council (approval no. CUH 2018-12-007-003).

## RESULTS

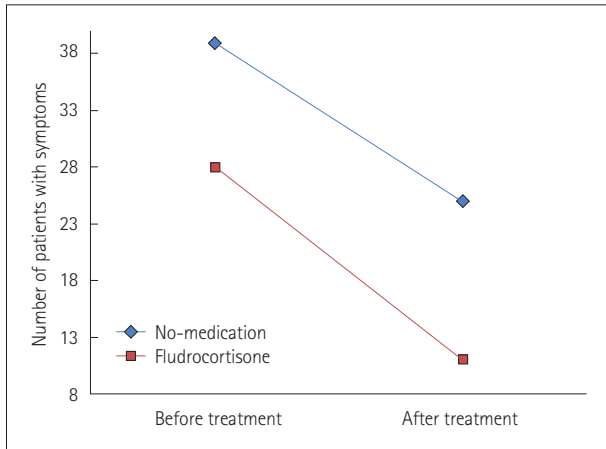
### Characteristics of the patients

None of the characteristics of the patients differed significantly between the no-medication (*n*=39) and fludrocortisone (*n*=28) groups, including age, sex, height, weight, BMI, presence of loss of consciousness, systolic BP, diastolic BP, HR, and treatment duration (Table 1). The mean durations of treatment in the no-medication and fludrocortisone groups were 221.4 and 146.9 days, respectively (*p*=0.233), while the numbers of outpatient visits were 2.6 and 2.4 days, respectively (*p*=0.679). No side effect such as gastrointestinal trouble, headache, or hypertension was reported.

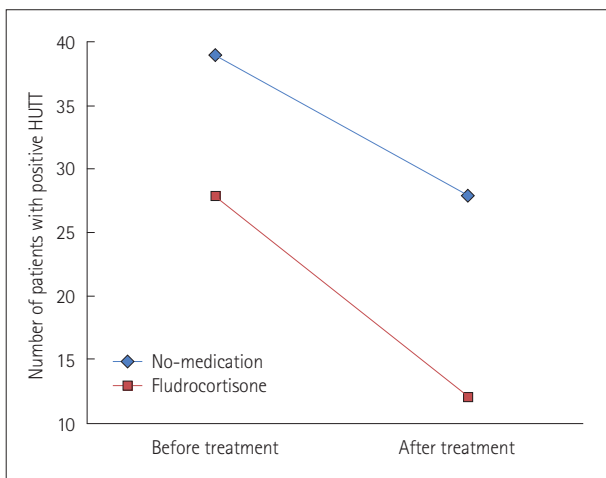
**Table 1.** Characteristics of the patients

Parameter	No medication ( <i>n</i> =39)	Fludrocortisone ( <i>n</i> =28)	<i>p</i>
Age, years	15.05±2.37	14.36±1.62	0.122
Sex, male	19 (48)	16 (57)	
Height, cm	165.10±13.00	166.32±9.72	0.333
Body weight, kg	59.80±16.92	57.97±13.10	0.217
Body mass index, kg/m <sup>2</sup>	21.67±4.16	20.83±3.57	0.334
Loss of consciousness	35 (89)	21 (75)	
Initial systolic BP before treatment, mm Hg	116.75±11.29	118.36±9.18	0.237
Initial diastolic BP before treatment, mm Hg	66.25±4.78	67.41±5.12	0.923
Treatment duration, days	221.40±306.09	146.85±93.47	0.233
Number of outpatient visits	2.64±0.52	2.39±0.39	0.679

Data are mean±SD or *n* (%) values. *p* values are from *t*-tests. BP: blood pressure.



**Fig. 2.** The x-axis was set before and after each treatment with fludrocortisone and no medication, and the y-axis was set to the occurrence of either syncopal or pre-syncopal events for each period. Occurrence of either syncopal or presyncopal events after treatment with fludrocortisone or no medication.  $p=0.044$  from Pearson's chi-square test.



**Fig. 3.** The x-axis was set before and after each treatment with fludrocortisone and no medication, and the y-axis was set to the number of patients with positive HUTT results for each period. Number of patients with positive HUTT results before and after the treatment with fludrocortisone or no-medication.  $p=0.017$  from Pearson's chi-square test. HUTT: head-up tilt-table test.

### Efficacies of fludrocortisone and no medication on symptoms

Repeated syncopal and/or presyncopal symptoms appeared in 25 (64.1%) of the 39 patients in the no-medication group, but in only 11 (39.3%) of the 28 patients in the fludrocortisone group ( $p=0.044$ ) (Fig. 2).

### Comparison of efficacies of fludrocortisone and no medication in the HUTT

The results in the follow-up HUTT improved in 16 (57.1%) of the 28 patients in the fludrocortisone group, but in only 11

**Table 2.** Comparison of BP and HR between before and after taking fludrocortisone ( $n=20$ )

	Before fludrocortisone	After fludrocortisone	<i>p</i>
Overall HR, bpm	72.10±5.89	74.10±7.19	0.078
Daytime HR, bpm	74.50±6.09	77.10±8.14	0.071
Nighttime HR, bpm	63.10±7.43	61.80±6.35	0.924
Overall systolic BP, mm Hg	119.40±10.20	117.60±9.85	0.159
Overall diastolic BP, mm Hg	67.90±5.49	67.90±5.49	0.257
Daytime systolic BP, mm Hg	121.30±10.17	120.00±10.17	0.226
Daytime diastolic BP, mm Hg	69.90±5.74	72.20±4.34	0.521
Nighttime systolic BP, mm Hg	112.10±12.31	109.20±11.69	0.058
Nighttime diastolic BP, mm Hg	60.70±6.05	57.40±7.41	0.228

Data are mean±SD values. *p* values are from paired *t*-tests. BP: blood pressure, HR: heart rate.

**Table 3.** Differences in BP between the response and no-response groups in the head-up tilt-table test

	Response group ( $n=18$ )	No-response group ( $n=22$ )	<i>p</i>
Overall systolic BP, mm Hg	121.18±8.43	114.90±8.28	0.620
Overall diastolic BP, mm Hg	69.89±4.19	66.77±3.68	0.849
Daytime systolic BP, mm Hg	123.86±8.52	116.84±8.54	0.873
Daytime diastolic BP, mm Hg	72.83±4.44	68.79±4.09	0.766
Nighttime systolic BP, mm Hg	111.97±9.39	106.46±8.24	0.840
Nighttime diastolic BP, mm Hg	59.14±7.01	58.10±5.66	0.671

Data are mean±SD values. *p* values are from paired *t*-tests. BP: blood pressure.

(28.2%) of the 39 patients in the no-medication group ( $p=0.017$ ) (Fig. 3).

### Comparison of 24-h BP and HR between before and after treatment with fludrocortisone

There were no significant changes between before and after treatment in the drug treatment group in any of the nine analyzed 24-hour BP and HP parameters ( $p>0.05$ ) (Table 2).

### Differences in 24-h BP after treatment between the response and no-response groups in the HUTT

There were also no significant changes in any of the analyzed 24-hour BP parameters between the groups that did and did not respond in the follow-up HUTT ( $p>0.05$ ) (Table 3).

### Factors associated with negative HUTT results

Only 23 of the 67 patients who were enrolled in this study underwent the 24-hour monitoring of BP and HR after each treatment. With the inclusion of the measurements mentioned above, other factors that might be associated with the negative HUTT results were analyzed using univariate logis-

**Table 4.** Results from univariate logistic regression analyses of the factors associated with negative conversion in the head-up tilt-table test in patients with vasovagal syncope ( $n=18$ )

	OR (95% CI)	<i>p</i>
Age, years	0.816 (0.279–1.353)	0.459
Sex, male	7.513 (5.143–9.883)	0.095
Height, cm	0.628 (0.011–1.245)	0.140
Body weight, kg	2.014 (1.110–2.918)	0.129
Body mass index, kg/m <sup>2</sup>	0.126 (–2.563––2.815)	0.131
Treatment with fludrocortisone	1.786 (0.167–3.405)	0.483
Measurements after the treatment		
Overall systolic BP, mm Hg	1.057 (0.935–1.179)	0.370
Overall diastolic BP, mm Hg	0.994 (0.769–1.219)	0.957

*p* values are from paired *t*-tests. None of the variables were significant in the multivariate analysis (except those from the equation).

BP: blood pressure, CI: confidence interval, OR: odds ratio.

tic regression. None of parameters including sex, age, height, weight, BMI, initial HR, systolic BP, or diastolic BP were significant (Table 4).

It was found that the negative conversion rate of HUTT results increased 1.057-fold each time the overall systolic BP increased by 1 mm Hg, but the effect was not statistically significant [odds ratio (OR)=1.057, 95% confidence interval (CI)=0.935–1.179,  $p=0.370$ ]. Treatment with fludrocortisone was not an independent factor associated with the negative HUTT results (OR=1.786, 95% CI=0.167–3.405,  $p=0.483$ ) (Table 4). Multivariate analysis could not be conducted due to the lack of significant variables.

## DISCUSSION

Syncope is a symptom of sudden, temporary, self-limited loss of consciousness that is caused by cerebral hypoperfusion.<sup>1</sup> It is categorized into three groups: 1) reflex syncope, 2) syncope due to orthostatic hypotension, and 3) cardiac syncope. VVS is a reflex syncope induced by emotional or orthostatic stress, and is typically preceded by autonomic symptoms such as sweating, pallor, or nausea.<sup>1</sup> Previous studies in North American have found that 15% of children aged <18 years present with syncope.<sup>3</sup> VVS is not usually life-threatening, but it causes financial loss and decreases the quality of life.<sup>4</sup> This condition therefore needs to be managed properly.

No independent gold-standard tool is available for diagnosing syncope. However, according to the European Society of Cardiology 2018 guidelines for syncope, VVS is more likely to occur if syncope is precipitated by pain, fear, or standing and is associated with typical progressive prodrome (class I, level C); thus, routine ECG should be carried out to rule out cardiac syncope.<sup>1</sup> Meanwhile, echocardiography, blood tests, brain MRI, and EEG are applied when clinically indicated. Among

the examinations, the HUTT is the most widely recognized and useful diagnostic tool for unexplained syncope.<sup>8</sup> Vdani et al.<sup>9</sup> showed that the HUTT is sensitive in diagnosing VVS not only in adults but also in children and adolescents.

There is no drug of choice for VVS. Besides avoiding triggers, another possible intervention is to increase the salt and water intakes in order to increase the blood volume. Claydon and Hainsworth<sup>10</sup> showed that such therapy is effective for VVS since it improves orthostatic cerebral and peripheral vascular control. The use of medications such as alpha agonists, beta blockers, and paroxetine can be considered in addition to lifestyle modification, but their efficacy remains to be fully elucidated. Meanwhile, recent studies have found fludrocortisone to be effective. Sheldon et al.<sup>7</sup> showed that fludrocortisone had significant benefits compared with placebo treatment in decreasing the recurrence of syncope in young adults (median age=30 years) with normal arterial BP and without comorbidities in a randomized, placebo-controlled trial.

However, the efficacy of fludrocortisone in pediatric patients with VVS has not been validated. A small randomized double-blind trial in children found that fludrocortisone was not effective.<sup>11</sup> Two open-label uncontrolled studies found significantly low incidence rates of syncope and presyncope in children who were taking fludrocortisone.<sup>12</sup> In the present study, fludrocortisone was significantly more effective in improving symptoms than no medication (recurrence rate=39.3% vs. 64.1%,  $p=0.044$ ) (Fig. 2). Moreover, the follow-up HUTT results also showed significant differences between the two groups, with greater effectiveness in the fludrocortisone groups (rate of negative conversion of follow-up HUTT=57.1% vs. 28.2%,  $p=0.017$ ) (Fig. 3).

VVS is thought to be triggered by moving to an upright position or exercising. These specific triggers decrease venous return and cardiac filling and output, thereby lessening the blood flow to the brain. Fludrocortisone is thought to address these mechanisms underlying VVS by increasing renal sodium reabsorption and expanding the plasma volume. We therefore examined whether fludrocortisone increases the BP, but found no significant increase (Table 2), although this was probably due to the drug dosage being inadequate. Sheldon et al.<sup>7</sup> found that the recurrence of syncope decreased significantly in their fludrocortisone group compared with their placebo group when the analysis was restricted to patients who received a dosage of 0.2 mg/day for 2 weeks. In the present study, the fludrocortisone group received 0.05 mg of fludrocortisone once a day in the morning for the first week, which was then increased to 0.1 mg once a day, and this might have been insufficient compared to the capacity established in adults. The appropriate dosage



of fludrocortisone in pediatric patients with VVS has not been validated yet. In this study, fludrocortisone treatment was applied at 0.1 mg/day in order to obtain similar effects in adults when using 0.2 mg/day.

Another possible mechanism underlying the effectiveness of fludrocortisone in VVS is in the prevention of paradoxical vasodilatation by increasing renal sodium reabsorption and expanding the plasma volume. In other words, previous studies demonstrating the efficacy of fludrocortisone in adult patients with VVS did not prove the exact mechanism. This may be due to fludrocortisone acting via other mechanisms, or BP not being an appropriate indicator. Therefore, further studies are needed to determine the relationship between urinary sodium excretion and the use of fludrocortisone, or other pharmacologic mechanisms of fludrocortisone.

The controversy regarding whether medications are effective means that caution is required when considering their usage. Some authors have opined that taking medicines throughout the year is not reasonable because extreme frequent fainting typically occurs only six times per year.<sup>11</sup> In particular, the need to take the alpha agonist midodrine more frequently (two or three times a day) reduces long-term compliance,<sup>1,13</sup> and so only needing to take fludrocortisone once a day is advantageous by improving compliance. Additionally, most medications have side effects. For example, the important side effects associated with the use of beta blockers and alpha agonists are symptomatic bradycardia and urinary retention, respectively,<sup>14,15</sup> which may reduce the quality of life and eventually lead to poor compliance. The possible side effects of fludrocortisone include hypertension,<sup>1,14,15</sup> although the risk is low if it is selectively administered to patients without hypertension, heart failure, or other comorbidities. The present study found that no adverse effects of fludrocortisone were reported during the follow-up. When comparing the electrolyte levels between before and after treatment, no findings such as hypernatremia or hypokalemia were observed.

There were no significant findings when the independent variables of the group with a good response were examined during the follow-up HUTT (Table 4). Moreover, multifactor analysis was not carried out due to the lack of significant factors, which might have been due to the smallness of the sample.

The most important limitation of this study was the lack of a placebo group. Another limitation is that we did not compare the severity of syncope between the two groups, which was due to the retrospective study design. Additionally, whether the HUTT is suitable for assessing therapeutic efficacy is questioned by the low reproducibility of HUTT results, ranging from 64% to 90%.<sup>16</sup> Furthermore, the smallness of the sample and open-label design might have induced further

bias. However, this study was advantageous in that it included pediatric patients and analyzed objective indicators of improvement as well as symptoms.

In summary, treatment with fludrocortisone appears to be more effective than no medication in improving HUTT results in pediatric patients with VVS.

#### Author Contributions

Writing—original draft: all authors. Writing—review & editing: all authors.

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#### Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

#### Acknowledgements

Writing assistance was provided by <https://www.enago.co.kr/academy/>.

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