Cureus
Part of SPRINGER NATURE

Open Access Original Article

# Clinical Outcomes Following Intravenous Saline Infusion in Adolescents With Refractory Postural Orthostatic Tachycardia Syndrome: A Retrospective Study

**Review began** 10/10/2026
**Review ended** 10/24/2026
**Published** 10/27/2026

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**DOI:** 10.7759/cureus.118695

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## Abstract

### Background

Postural orthostatic tachycardia syndrome (POTS) can substantially impair daily functioning and school attendance in adolescents. Evidence regarding intravenous (IV) saline infusion in adolescents with refractory POTS remains limited. This study evaluated short-term clinical outcomes and adverse events following IV saline infusion administered during symptom exacerbations in adolescents with refractory POTS.

### Methods

This retrospective, single-center study identified 53 adolescents with refractory POTS between April 2021 and March 2022. Of these, 42 received peripheral IV saline infusion, while 11 did not. The primary outcome was subjective treatment response assessed within one month after treatment initiation in all 42 treated patients. Paired assessments of orthostatic dysregulation (OD) physical symptom scores, school attendance and daily functioning scores, and standing heart rate were available for 22 patients at baseline and approximately one month after treatment initiation. Paired symptom and functional outcomes were compared using two-sided Wilcoxon signed-rank tests. Documented adverse events were also reviewed.

### Results

Thirty-six of 42 patients (85.7%) reported at least some subjective improvement. The 22 patients with paired one-month assessments received a total of 66 infusions, with a mean of 3.0 infusions per patient. Among these patients, the mean OD physical symptom score decreased from 7.5 ± 1.5 to 6.1 ± 2.0 (P = 0.004), and the mean school attendance and daily functioning score decreased from 2.5 ± 1.4 to 1.7 ± 1.6 (P = 0.023). The proportion of patients with some school participation increased from 54.5% to 77.3%, although the difference was not statistically significant (P = 0.125). Among 20 patients who completed paired standing tests, the mean maximum heart rate increase decreased from 41.7 to 38.2 beats/min, without statistical significance (P = 0.254). Transient adverse events included pain during needle insertion and feeling cold during infusion. No venous-access infection or thrombosis was documented among the 22 patients with available short-term follow-up assessments.

### Conclusions

In adolescents with refractory POTS, IV saline infusion administered during symptom exacerbations was followed by subjective improvement in most patients and lower physical symptom and daily functioning scores among those with paired one-month assessments. Changes in school attendance status and standing heart rate were not statistically significant. These findings suggest that IV saline may have a role in short-term symptom relief during acute exacerbations, although its efficacy cannot be established from this uncontrolled study. Long-term safety remains uncertain, and prospective controlled studies are needed to clarify the benefits, risks, and appropriate use of this approach.

**Categories:** Neurology, Cardiology, Pediatrics
**Keywords:** children and adolescents, dysautonomia/pots, intravenous saline, orthostatic intolerance, postural tachycardia syndrome, pots treatment, refractory pots

## Introduction

Postural orthostatic tachycardia syndrome (POTS) is a form of orthostatic intolerance characterized by excessive tachycardia on standing together with symptoms that are relieved by recumbency. It commonly affects adolescents and young adults and may cause lightheadedness, headache, fatigue, nausea, abdominal symptoms, sleep disturbance, and difficulty getting up in the morning [1,2]. In adolescents, these symptoms can interfere substantially with daily functioning and school attendance.

The pathophysiology of POTS is heterogeneous. Reduced effective circulating volume, impaired venous return, and excessive blood pooling in the lower extremities or splanchnic circulation may contribute to reduced stroke volume and compensatory tachycardia [1-3]. Increasing fluid and salt intake is therefore commonly used as a non-pharmacological treatment strategy. First-line non-pharmacological management of POTS includes increased fluid and salt intake, compression garments, and graded exercise training or rehabilitation programs [4,5]. In children and adolescents with difficulty waking in the morning, including those with POTS, estimated daily salt intake calculated from spot urine samples was positively associated with resting systolic blood pressure and negatively associated with school non-attendance scores [6].

Intravenous (IV) saline provides rapid volume expansion. Acute studies have shown improvement in orthostatic hemodynamics or symptoms after saline administration in patients with POTS [7-9]. The 2015 Heart Rhythm Society expert consensus statement describes acute IV saline infusion as a reasonable rescue therapy for short-term clinical decompensation, while regular long-term IV saline infusions are not recommended because repeated venous access, particularly chronic central access, may cause harm [4].

Evidence in adolescents with refractory disease remains limited. Moak et al. reported outcomes of IV hydration in medication-resistant orthostatic intolerance among adolescents and young adults [10], and intermittent saline has also been studied in predominantly adult patients with medication-refractory POTS [11]. In Japan, pediatric orthostatic dysregulation guidelines include POTS-specific diagnostic and management criteria [12], and IV saline has been discussed as an option for temporary acute exacerbations [13]. The present study therefore evaluated short-term clinical outcomes following IV saline infusion administered during symptom exacerbations in adolescents with refractory POTS, with subjective treatment response within one month as the primary outcome and changes in OD physical symptoms, school attendance and daily functioning, and adverse events as additional outcomes.

## Materials And Methods

### Study design and participants

This was a retrospective single-center study conducted at Kobe Tokushūkai Hospital. Among 53 adolescents diagnosed with refractory POTS between April 2021 and March 2022, 42 received IV saline treatment, while 11 did not. The decision not to administer IV saline was based on the treating physician's clinical judgment, considering patient age, symptom severity, and individual circumstances, including the predominance of symptoms other than orthostatic intolerance, such as headache or abdominal pain, fear of pain associated with needle insertion, and patient preference against infusion therapy. Treatment allocation was not randomized. Subjective treatment responses were obtained from all 42 treated patients. Of these, 22 had paired symptom and functional scores recorded at baseline and within ±7 days of one month after treatment initiation and were included in the paired analysis. The remaining 20 patients did not attend a follow-up visit within this assessment window and were therefore excluded from the one-month paired analysis.

POTS was diagnosed after other organic diseases had been excluded. All 42 patients underwent complete blood count, thyroid function tests, 12-lead electrocardiography, and echocardiography to evaluate alternative causes of their symptoms. Cervicogenic and vestibular causes of dizziness were also considered during the clinical evaluation. POTS was diagnosed using a 10-minute morning standing test with a mercury-free automatic blood pressure monitor (KM-385OD). Japanese diagnostic criteria were applied. Patients were required to have at least three OD symptoms listed in Table *1* and a standing heart rate of ⩾115 beats/min or an increase in heart rate of ⩾35 beats/min from the recumbent position, sustained for more than 30 seconds. Other forms of orthostatic hypotension were excluded according to the Japanese diagnostic criteria [12].

| Symptom | Often (1 point) | Sometimes (0.5 point) | Occasionally (0 point) |
|---|---|---|---|
| Lightheadedness or dizziness | Often | Once a week | Less than once a week |
| Feeling unwell when standing or fainting | Once a week | Once a month | Once every 2 months |
| Feeling sick when bathing or seeing/hearing something unpleasant | Every bath | More than half of bath | Once every 2 months |
| Palpitations or shortness of breath with minor exertion | More than two-thirds of episodes | About half of episodes | Once every 2 months |
| Difficulty getting up, nausea or sickness in the morning | 3 or more times/week | 1-2 times/week | Less than once a week |
| Pale complexion | 3 or more times/week | 1-2 times/week | Less often |
| Anorexia | 3 or more times/week | 1-2 times/week | Less often |
| Pain around the navel | 3 or more times/week | 1-2 times/week | Less often |
| Fatigue/easily tired | 3 or more times/week | 1-2 times/week | Less often |
| Headache | 3 or more times/week | 1-2 times/week | Less often |
| Motion sickness | Every ride | About half of rides | Once every 2 months |

**TABLE 1: Orthostatic dysregulation physical symptoms, frequency categories, and scoring**

Refractory POTS was defined using the criteria reported in the 2011 Japanese pediatric orthostatic dysregulation guidelines [12]. Patients met at least one of the following: no improvement after four or more weeks of treatment; absence from school for more than one month with persistent OD symptoms; or persistent physical symptoms despite pharmacological treatment while receiving psychiatric care.

## Intravenous saline administration

All patients received 0.9% saline through peripheral venous access. The initial infusion volume was generally 1,000 mL, administered over one to two hours, but was adjusted according to body weight and clinical condition. Subsequent infusion volumes could be adjusted according to clinical response, adverse effects, and patient preference; however, the infusion volume remained unchanged for each patient throughout the treatment period. IV saline infusions were administered primarily during symptom exacerbations, based on patient preference and the treating physician's clinical judgment. The frequency and timing of infusions were determined according to each patient's clinical condition.

## Outcome assessment

The primary outcome was subjective treatment response, assessed in all 42 treated patients through direct interviews conducted by the treating physician during post-treatment outpatient visits within one month after treatment initiation. The timing of assessment varied among patients. Responses were classified into four categories: “very much better,” “better,” “a little better,” and “no effect.” The first three categories were classified as subjective improvement; “no effect” was classified as no subjective improvement.

OD physical symptoms were assessed using the 11 items and symptom-specific frequency categories in Table *1*. A simplified scoring method adapted from Gomi et al. [14] was used. Each item was scored as 1 point for “often,” 0.5 point for “sometimes,” and 0 points for “occasionally,” giving a total score from 0 to 11.

School attendance and daily functioning were assessed using a seven-stage ordinal scale (stages 0-6) based on the Japanese Society of Pediatric Psychosomatic Medicine guidelines for pediatric orthostatic dysregulation [12] (Table *2*). This scale includes school participation, leaving home, and interaction with family. Higher scores indicate greater functional limitation. For a separate analysis of school attendance status, stages 0-2 were classified as indicating some degree of school participation, whereas stages 3-6 were classified as indicating no school participation.

| State | School attendance | Leaving home | Description |
|---|---|---|---|
| Stage 0 | Can go to school | Can go out | Almost no late arrivals or absences |
| Stage 1 | | | Often late or absent; frequent use of the school infirmary |
| Stage 2 | | | Absent, or in the infirmary/counseling room, more than half of the time |
| Stage 3 | Can't go to school | | Regular participation in activities outside school |
| Stage 4 | | | Can go out relatively easily |
| Stage 5 | | Can't go out | Stable at home but finds it difficult to go out |
| Stage 6 | | | Stays in own room and rarely interacts with family |

**TABLE 2: Evaluation of school attendance and daily functioning**

Stages 0-2 indicate some degree of school participation, whereas stages 3-6 indicate no school participation. Higher stages indicate greater limitations in daily functioning.

Both scores were recorded before treatment and, when follow-up assessments were available, approximately one month after treatment initiation (within ±7 days).

Standing heart rate measurements were also retrospectively evaluated in the 22 patients with one-month follow-up assessments. Heart rate was measured during a 10-minute standing test, both before treatment and approximately one month after treatment initiation (within ±7 days). The maximum heart rate increase was calculated as the highest recorded standing heart rate minus the resting heart rate. In patients who developed vasovagal syncope during the standing test, the test was discontinued for safety reasons. Measurements after discontinuation were treated as missing. The analysis of maximum heart rate increase was restricted to patients who completed the standing test at both assessments.

Adverse events were assessed from medical records and available follow-up information. Documented adverse events during infusion and venous-access complications were reviewed.

### Statistical analysis

Continuous variables are presented as means ± standard deviations, and categorical variables as counts and percentages. Baseline characteristics of the subjective improvement and no-effect groups were compared using two-sided unpaired Student's t-tests assuming equal variances. Baseline and one-month OD physical symptom scores and school attendance and daily functioning scores were compared using two-sided Wilcoxon signed-rank tests in patients with available paired assessments. Changes in school attendance status (stages 0-2 versus stages 3-6) were assessed using the two-sided exact McNemar test. Baseline characteristics were compared between patients with and without one-month follow-up data using the two-sided Mann-Whitney U test for continuous and ordinal variables. Available observations were analyzed for each variable. Statistical analyses were performed using Python with SciPy (Python Software Foundation, Wilmington, DE, USA). A two-sided P-value of less than 0.05 was considered statistically significant. Paired heart rate measurements and maximum heart rate increases were compared using two-sided Wilcoxon signed-rank tests. Each analysis included only patients with complete paired measurements for the corresponding outcome. These analyses were exploratory.

### Ethics

The study was approved by the Tokushukai Group Ethics Committee (approval number: TGE01910-014) and was conducted in accordance with the Declaration of Helsinki. The treating physician explained the study to both the patients and their parents in the presence of family members, and written informed consent was obtained from both the patients and their parents.

## Results

### Participant characteristics

Among the 53 patients identified, 42 received IV saline infusion, while 11 did not. The 42 participants had a mean age of 15.0 ± 1.6 years (range, 11-18 years); 14 (33.3%) were male and 28 (66.7%) were female. Fifteen of the 42 patients also met the international diagnostic criteria for POTS, including symptom duration of at least three months and a heart rate increase of ⩾40 beats/min upon standing.

Twenty-two patients (52.4%) were classified as stages 0-2 and 20 (47.6%) as stages 3-6 on the school attendance and daily functioning scale. The mean school attendance and daily functioning score was 2.5 ± 1.3.

Mean body weight was 49.9 ± 7.7 kg, with a minimum of 31 kg. The mean saline dose was 20.1 ± 3.8 mL/kg per infusion, with a maximum recorded dose of 27.8 mL/kg. The 11-year-old patient weighed 41 kg and received an initial infusion of 1,000 mL (24.4 mL/kg), whereas the patient with the lowest body weight (31 kg) received an initial infusion of 500 mL (16.1 mL/kg).

Over an approximately one-month treatment period, patients received a median of 4 infusions per patient (range, 1-5), with a total of 127 infusions. The mean cumulative infusion volume was approximately 3.0 L per patient. Table *3* summarizes participant characteristics, including baseline scores and infusion volumes.

| Participant characteristics | |
|---|---|
| Gender | |
| Male | 14 (33.3%) |
| Female | 28 (66.7%) |
| Age | 15.0 ± 1.6 (range, 11-18) |
| 11-12 years | 1 (2.4%) |
| 13-15 years | 24 (57.1%) |
| 16-18 years | 17 (40.5%) |
| OD physical symptom score (points) | 7.3 ± 1.7 |
| School attendance and daily functioning score | 2.5 ± 1.3 |
| School attendance states: 0-2 | 22 (52.4%) |
| School attendance states: 3-6 | 20 (47.6%) |
| Body weight (kg) | 49.9 ± 7.7 |
| IV saline dose | |
| 500 mL/infusion | 3 (7.1%) |
| 1,000 mL/infusion | 37 (88.1%) |
| 1,500 mL/infusion | 2 (4.8%) |
| Dose per body weight (mL/kg/infusion) | 20.1 ± 3.8 |
| Infusions per patient, median (range) | 4 (1-5) |
| Cumulative infusion volume per patient (L), mean | 3 |

**TABLE 3: Clinical and demographic characteristics of participants (n = 42)**

Values are presented as n (%), mean ± SD, or median (range), as appropriate. Infusion volumes were adjusted according to body size and clinical condition.

OD: orthostatic dysregulation, IV: intravenous.

## Subjective treatment response

Thirty-six patients (85.7%) reported at least some subjective improvement, and 6 (14.3%) reported no effect. Two reported feeling “very much better,” 24 “better,” and 10 “a little better.” When improvement was restricted to the categories “better” and “very much better,” 26 of 42 patients (61.9%) met this more restrictive definition. Baseline characteristics by subjective treatment response are presented in Table *4*.

| Variable | Improvement group (n = 36; 85.7%) | No-effect group (n = 6; 14.3%) | t | P-value |
|---|---|---|---|---|
| Age, years | 14.9 ± 1.5 | 15.2 ± 2.0 | -0.359 | 0.721 |
| OD physical symptom score | 7.3 ± 1.6 | 7.2 ± 2.6 | 0.146 | 0.885 |
| School attendance and daily functioning score | 2.3 ± 1.1 | 3.3 ± 1.9 | -1.831 | 0.074 |

**TABLE 4: Baseline characteristics according to subjective treatment response (n = 42)**

Values are presented as mean ± SD. Comparisons used two-sided unpaired Student's t-tests assuming equal variances.

OD: orthostatic dysregulation.

## One-month outcomes

Paired assessments at baseline and one month were available for 22 patients. The remaining 20 patients did not attend an outpatient visit within 1 month ± 7 days after treatment initiation and were therefore excluded from the paired analysis. No statistically significant differences in age, sex, body weight, baseline OD physical symptom scores, or baseline school attendance and daily functioning scores were observed between the 22 patients with paired assessments and the 20 patients without paired assessments (all P > 0.05).

The mean OD physical symptom score decreased from 7.5 ± 1.5 to 6.1 ± 2.0 (Wilcoxon signed-rank test, W = 16.5, P = 0.004), with a decrease in score observed in 14 of 22 patients (63.6%). The mean school attendance and daily functioning score decreased from 2.5 ± 1.4 to 1.7 ± 1.6 (Wilcoxon signed-rank test, W = 17.0, P = 0.023), with a decrease in score observed in 12 of 22 patients (54.5%). Both changes were statistically significant.

Regarding school attendance status, 12 patients (54.5%) were classified as stages 0-2 at baseline, compared with 17 patients (77.3%) at one month. Although the proportion of patients with some school participation increased, the difference was not statistically significant (exact McNemar test, P = 0.125) (Table *5*).

| Outcome | Before IV saline | One month after IV saline | P-value |
|---|---|---|---|
| OD physical symptom score | 7.5 ± 1.5 | 6.1 ± 2.0 | 0.004 |
| School attendance and daily functioning score | 2.5 ± 1.4 | 1.7 ± 1.6 | 0.023 |
| School attendance status | | | |
| Stages 0-2: Some school participation | 12 (54.5%) | 17 (77.3%) | 0.125 |
| Stages 3-6: No school participation | 10 (45.5%) | 5 (22.7%) | |

**TABLE 5: Changes in orthostatic dysregulation symptoms and school attendance and daily functioning scores after IV saline therapy (n = 22)**

Values are presented as mean ± SD or n (%), as appropriate. Changes in OD physical symptom scores and school attendance and daily functioning scores were analyzed using the two-sided Wilcoxon signed-rank test. Changes in school attendance status were analyzed using the two-sided exact McNemar test.

OD: orthostatic dysregulation, IV: intravenous.

## Changes in standing heart rate

Standing heart rate was retrospectively evaluated in the 22 patients with one-month follow-up assessments. Mean resting heart rate decreased from 69.5 to 65.5 beats/min (n = 22, P = 0.149). Among the 20 patients who completed the standing test at both assessments, the mean maximum heart rate increase decreased from 41.7 to 38.2 beats/min (P = 0.254). Neither change was statistically significant (Table *6*).

| Measurement | n | Before IV saline | One month after IV saline | P-value |
|---|---|---|---|---|
| Resting heart rate | 22 | 69.5 | 65.5 | 0.149 |
| Maximum heart rate increase from rest | 20 | 41.7 | 38.2 | 0.254 |

**TABLE 6: Changes in heart rate during the standing test before and one month after IV saline infusion**

Values are presented as means (beats/min). Comparisons were performed using two-sided Wilcoxon signed-rank tests. Only patients with paired measurements were included in each analysis. The analysis of maximum heart rate increase was restricted to patients who completed the standing test at both assessments.

IV: intravenous.

### Adverse events and short-term safety observations

Adverse events documented during or after the first infusion included feeling cold during infusion in three patients and pain during needle insertion in one. Feeling cold improved after the saline was warmed. Pain during needle insertion did not recur during subsequent infusions. Among the 22 patients assessed approximately one month after treatment initiation, no soft tissue infection, deep vein thrombosis, or other complication attributed to venous access was documented during the observation period. Routine post-treatment laboratory testing was not performed; therefore, post-treatment electrolyte abnormalities could not be systematically assessed.

## Discussion

In this retrospective cohort, most adolescents reported at least some subjective improvement after IV saline infusion. Among patients with paired one-month assessments, both OD physical symptom scores and functional scores decreased significantly, reflecting lower reported symptom burden and better daily functioning at follow-up. The uncontrolled design prevents attribution of these changes to saline infusion. The observed improvements may also have been influenced by placebo effects and nonspecific therapeutic factors, including patient expectations and interactions with healthcare professionals during infusion visits. Furthermore, because the subjective improvement group included patients who felt only “a little better,” the response proportion represents any perceived improvement rather than a validated threshold for clinically important benefit.

Improvement in daily functioning is particularly relevant in adolescents with POTS, as the impact of the condition extends beyond orthostatic symptoms to school participation and everyday activities. The functional scale includes school participation, leaving home, and interaction with family. A lower score may therefore reflect greater activity outside school without a return to school. Twelve of the 22 patients with paired assessments had a lower functional score at one month. Although the proportion of patients with some school participation increased, the change in school attendance status was not statistically significant. Improvements in daily functioning may not necessarily be accompanied by a return to school.

Although subjective symptoms and daily functioning improved, no statistically significant change in the maximum heart rate increase during standing was detected at one month. Given the transient effects of intravascular volume expansion, IV saline may provide short-term symptom relief during acute exacerbations. However, this study cannot determine whether IV saline has sustained effects on autonomic function.

Volume-related mechanisms provide a biologically plausible explanation for short-term benefit. POTS can involve reduced effective circulating volume, reduced venous return, and decreased stroke volume [1-3]. Acute IV saline expands intravascular volume, and previous studies have shown acute hemodynamic or symptomatic improvement after volume loading [7-9]. The Heart Rhythm Society consensus statement therefore considers acute IV saline a reasonable rescue intervention for clinically decompensated POTS, while discouraging routine long-term infusions because repeated venous access and chronic central lines may create additional risk [4].

Our findings are broadly consistent with earlier reports in treatment-resistant populations. Moak et al. retrospectively studied 39 adolescents and young adults with medication-resistant orthostatic intolerance and reported improvement in quality of life in 79% of patients receiving IV hydration [10]. That cohort included patients treated through peripheral IV catheters, peripherally inserted central catheters, or ports, and upper-extremity deep vein thrombosis and infection were reported. Ruzieh et al. also reported symptomatic improvement with intermittent IV saline in patients with medication-refractory POTS [11]. In contrast to the mixed venous-access methods used in the study by Moak et al., all infusions in the present

study were administered through peripheral venous access.

An additional feature of this study is the use of Japanese pediatric diagnostic criteria for POTS, reflecting clinical practice in Japan. Differences between Japanese and international diagnostic thresholds should be considered when comparing these findings with previous studies, particularly because not all patients met the international criteria.

Oral rehydration and graded exercise or rehabilitation programs may provide clinical benefits with lower risks than repeated IV saline infusion [4,5,15]. Medow et al. reported that both oral rehydration solution and IV saline improved short-term orthostatic tolerance in patients with POTS [15]. Oral rehydration should generally be prioritized as a less invasive treatment option, while IV saline infusion may have a role in selected patients with refractory POTS during acute symptom exacerbations.

The treatment protocol reflected individualized clinical practice rather than a standardized intervention. IV saline infusions were administered primarily during symptom exacerbations based on patient preference and the treating physician's clinical judgment. Although the treatment was intended for symptom relief during acute exacerbations, some patients received repeated infusions. This distinction is important because the benefits and cumulative risks of repeated IV saline administration remain uncertain. Further studies are needed to determine the appropriate indications and frequency of treatment.

No venous-access infection or deep vein thrombosis was documented among the 22 patients with available short-term follow-up assessments. Infusion volumes were adjusted according to body size and clinical condition, rather than uniformly fixed at 1,000 mL. Nevertheless, relatively large infusion volumes in pediatric patients may pose risks of fluid overload and electrolyte disturbances. Adverse events documented during the first infusion were transient. The short observation period and incomplete follow-up limit the assessment of uncommon or cumulative complications.

### Limitations

This study has several limitations. First, it was a retrospective, single-center study without a control group, so placebo effects, regression to the mean, concurrent treatments, natural recovery, and other confounding factors cannot be separated from the association with IV saline. The 11 patients who did not receive IV saline were excluded from treatment based on the treating physician's clinical judgment, including relatively mild orthostatic intolerance symptoms or the predominance of other symptoms, such as headache or abdominal pain. Comparable follow-up outcome data were unavailable; therefore, these patients could not be used as an untreated control group.

Second, only 22 of 42 patients had one-month reassessment data, which may have introduced selection bias. Although no statistically significant baseline differences were observed between patients with and without paired assessments, differences in unmeasured characteristics or treatment response cannot be excluded.

Third, the small sample size and lack of multivariable adjustment limit the assessment of factors associated with treatment response. Although the OD physical symptom score was adapted from previously published Japanese assessments and the school attendance and daily functioning scale was based on Japanese clinical guidelines, the modified symptom scoring method has not been formally validated. Japanese diagnostic criteria were used, which may limit comparability with studies using other POTS definitions.

Fourth, treatment dose and frequency were individualized rather than standardized. Standing heart rate was reassessed at approximately one month, but blood pressure responses and direct measures of autonomic nervous system function were not systematically analyzed. The exploratory heart rate analyses were based on a small sample and may have been underpowered to detect clinically relevant changes. Prior and concomitant treatments and seasonal variations may have influenced the observed outcomes. Psychiatric comorbidities and psychotropic medications were not systematically documented and may have influenced heart rate and symptom severity. In addition, the primary outcome was based on subjective treatment responses assessed by the treating physician at variable time points within one month after treatment initiation, which may have introduced assessment bias and limited comparability across patients.

Finally, follow-up was limited to approximately one to two months. The absence of documented serious venous-access complications during this short period cannot establish long-term safety, particularly for uncommon events such as infection or thrombosis.

## Conclusions

Peripheral IV saline infusion administered during symptom exacerbations in adolescents with refractory POTS was followed by subjective symptom improvement in most patients and lower mean symptom and functional scores among those with available one-month assessments. These findings suggest that IV saline may have a role in short-term symptom relief during acute exacerbations, although its efficacy cannot be established from this uncontrolled study. Improvement in school attendance was not statistically significant,

and long-term safety remains uncertain. Prospective controlled studies are needed to clarify the benefits and risks of this approach.

# Additional Information

## Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

**Concept and design:** Masafumi Izui

**Acquisition, analysis, or interpretation of data:** Masafumi Izui

**Drafting of the manuscript:** Masafumi Izui

**Critical review of the manuscript for important intellectual content:** Masafumi Izui

**Supervision:** Masafumi Izui

## Disclosures

**Human subjects:** Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Tokushukai Group Ethics Committee issued approval TGE01910-014. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

## Acknowledgements

The author thanks Dr. H. Tanaka for reviewing the manuscript and providing helpful comments; I. Miura, Dr. M. Noshi, and N. Wakabayashi, RN, for their assistance with treatment planning and data collection; and Dr. Ayaka for providing valuable advice and support throughout the study.

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