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Research paper

# Short-term efficacy of ORS formulation and propranolol regimen in children with POTS

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ABSTRACT

*Background:* To evaluate the short-term effectiveness of reduced-osmolarity oral rehydration salt formulation (ORS) and propranolol in children diagnosed with postural orthostatic tachycardia syndrome (POTS) in head-up tilt testing (HUTT).
*Methods:* Children were admitted with symptoms of orthostatic intolerance (OI) occurring in a standing position and disappearing in the supine position. Patients with heart rate increments of $\geq$ 40 bpm and symptoms of OI constituted the pediatric POTS group in HUTT. A total of 70 pediatric patients with POTS were included in the study. POTS patients were divided into two groups based on whether they were prescribed reduced-osmolarity ORS and propranolol or not. The study group comprised patients on a regimen of reduced-osmolarity ORS and propranolol ($n = 34$), while the control group comprised patients who were not prescribed any medication ($n = 36$). The frequency of symptoms and standardized symptom scores were analyzed before and after 3 months of treatment in both groups.
*Results:* The post-treatment frequency of syncopal attacks was significantly reduced in both groups ($P < 0.01$ for both groups), but the post-treatment standardized symptom scores were significantly reduced in the pediatric study group compared with the control group ($P < 0.01$).
*Conclusion:* The frequency of syncopal attacks was significantly reduced and the symptom scores for OI were improved in the study group. The improvement in OI symptom scores was better in the treatment group than in the control group. The control group symptoms persisted and caused extreme difficulty in their daily activities. In view of its clinical efficacy, we strongly advocate the use of combined treatment of reduced-osmolarity ORS and low-dose propranolol in pediatric patients with POTS.


## 1. Introduction

Orthostatic intolerance (OI) and postural orthostatic tachycardia syndrome (POTS) are a cause of significant concern for children and their parents. The etiology of OI and POTS remains unexplained, and these conditions are defined as symptoms of OI occurring in standing position and disappearing in supine position. Symptoms of OI include hand tremor, vomiting, headache, palpitation, dyspnea, obscuration of vision, dizziness, chest pain, and syncope [1]. Initially, the diagnostic criteria designed for adults were also used for the diagnosis of OI and POTS in children [2]. Since children are increasingly referred to healthcare organizations for symptoms of OI causing difficulties in daily activities, there is an increased need for new and enhanced diagnostic criteria and treatment recommendations for childhood OI and POTS. Singer et al. redefined the POTS diagnostic criteria for

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children in 2012. Pediatric OI was described as the development of a heart rate increase of more than 40 bpm and OI symptoms (dizziness, obscuration of vision) within the first 5 min of head-up tilt testing (HUTT). Pediatric POTS included, in addition to the pediatric OI criteria, the following: detection of a heart rate of $\geq$ 130 bpm at age $\leq$ 13 years, or $\geq$ 120 bpm at age $\geq$ 14 years within the first 5 min of HUTT [3,4].

Today, the diagnostic criteria of POTS for pediatric patients are more complete. In 2015, Sheldon et al. defined POTS as a clinical syndrome that is usually characterized by random clinical manifestations while standing, such as lightheadedness, palpitations, tremulousness, generalized weakness, blurred vision, exercise intolerance, and fatigue. An increase in heart rate of $\geq$ 40 bpm is detected when moving from a recumbent to a standing position held for more than 30 s within the first 10 min of HUTT in the absence of orthostatic hypotension ($>$ 20 mmHg drop in systolic blood pressure) [5]. Stewart et al. confirmed the previous definitions of POTS with the alternate value of heart rate increase in adolescents. In their study, they defined POTS as daily symptoms of OI for more than 3 months and excessive postural tachycardia [6]. There are still conflicting statements in the literature on OI in HUTT with pediatric patients.

To date, various clinical studies have been conducted in search of a proper method for the treatment of OI and POTS. Regular use of low-dose beta-blockers and increased daily intake of salt and liquids are beneficial. Fludrocortisone, midodrine, octreotide, and erythropoietin have been promoted in exceptional circumstances [7–12]. There have been numerous studies that tested propranolol versus placebo in patients with POTS. Raj et al. conducted a study of 54 patients with POTS, which compared a low dose of propranolol (20 mg orally) and placebo. Low-dose oral propranolol clearly decreased tachycardia and ameliorated symptoms of POTS [10]. A further study, by Amy et al., compared the effect of placebo versus a single low dose of propranolol (20 mg) to examine possible alterations in heart rate control and exercise capacity in patients with POTS. The authors concluded that a single low dose of propranolol is effective in improving heart rate control and exercise capacity in patients with POTS [13]. All these studies were based on OI and POTS diagnostic criteria developed for adults. Therefore, it is crucial to re-evaluate the effectiveness of the treatment protocols that meet the recently revised diagnostic criteria established for children. Reduced-osmolarity oral rehydration salt formulation (ORS) alone or low-dose propranolol treatment alone has been recommended for POTS in adult patients, but the efficacy of their combined treatment for POTS remains unclear; thus, this manuscript can provide clinically valuable data.

Reduced-osmolarity ORS is commonly used, especially in developing countries, for the treatment of dehydration states. Since medical personnel are accustomed to this practice, its utilization in the treatment of POTS may prove to be inexpensive and convenient. We hypothesized that a treatment regimen of reduced-osmolarity ORS and propranolol would be effective in the short term for children who are diagnosed with POTS in HUTT. In this study, we evaluated the short-term effectiveness of reduced-osmolarity ORS and propranolol in children diagnosed with POTS in HUTT in light of the revised criteria.

## 2. Materials and methods

The present prospective study was initiated after approval from the local ethics committee. The Department of Pediatric Cardiology was mainly in charge of the patients with POTS included in this study. Patients diagnosed with disease states capable of autonomic system disturbances were excluded from the study. The study consisted of 102 patients with POTS. All patients gave their written informed consent. The patients were children with complaints of OI during daily activities and/or at least one syncopal attack during the past 3 months. Patients with heart rate increments of $\geq$ 40 bpm and symptoms of OI within the first 10 min of HUTT were recruited in the study ($n$ = 102). First, a questionnaire for symptom scoring of OI and frequency of syncopal attacks in the past 3 months was administered to all the patients and their responses were recorded. POTS patients were divided into two groups based on whether they were prescribed reduced-osmolarity ORS and propranolol or not. The study group comprised patients on a reduced-osmolarity ORS and propranolol ($n$ = 56) treatment regimen, while the control group comprised patients who were not prescribed any medication ($n$ = 46). All of the POTS patients were contacted every 10 days to ensure they were complying with the treatment protocol and to ask whether they experienced any OI symptoms. During the 3-month follow-up, POTS patients who did not comply with the rules of the study, such as not taking their medication on time or not being available when they were contacted, were excluded from the study (22 patients from the study group and 10 from the control group). Thus, 70 patients were finally included in this study. Most of the excluded patients were female (approximately 80%). The final number of patients in the study group was 34 and in the control group it was 36. Only patients in the study group were given reduced-osmolarity ORS and propranolol, and their response rates were evaluated after a follow-up of $\geq$ 3 months. At the end of the 3 month-follow-up, HUTT was performed in both groups of patients, and the patients' initial responses to the OI symptom scoring questionnaire were compared with their last responses. Any change in symptom score was recorded and calculated as mean $\pm$ standard deviation. The reduced-osmolarity ORS utilized in the study (Ge-Oral rehydration salt, Kansuk Laboratories, Istanbul, Turkey) was made up of sodium chloride 2.6 g, trisodium citrate 2.9 g, potassium chloride 1.5 g, and anhydrous glucose 13.5 g, to be dissolved in 1 L of water for oral intake. Patients were advised to ingest at least 1 L of the solution daily. The same amount of 1 L reduced-osmolarity ORS was given to every patient regardless of their body mass. Propranolol was given orally in low single doses (20 mg/day).

### 2.1. The head-up tilt test protocol

The test protocol was a slightly modified version of the Kenny et al. [14] protocol. Patients were required to discontinue any drugs capable of affecting the autonomic nervous system for at least 5 days before testing. The test was performed in a dim, heat-controlled, and quiet environment, a minimum of 4 h after the last food intake. Tilt-table testing consisted in supine resting for at least 25 min, followed by a 70° passive head-up tilt, without any medications. Electrocardiogram (ECG) and blood pressure changes were recorded automatically with a bedside monitor every 5 minutes during the tilt test (Dash 2000 Multi-lead Physiological Monitor; General Electric, NY, USA).

### 2.2. Assessment of therapeutic efficacy

The patients' response patterns were assessed using both symptom scoring and frequency of syncopal attacks before and after treatment. The frequency of typical symptoms of OI (hand tremor, nausea, vomiting, dyspnea, obscuration of vision, dizziness, palpitations, headache, chest pain, and syncope) and/or syncopal episodes per month were recorded using a slightly modified version of the questionnaire by Winker et al., before and 3 months after the initiation of therapy (Tables 1–3) [15].

**Table 1**
Questionnaire for symptom scoring for orthostatic intolerance (OI).

| Score | Score frequency of OI symptoms |
|---|---|
| 0 | Once every 3 months |
| 1 | Once a month |
| 2 | Twice to seven times per month |
| 3 | At least two times per week |
| 4 | More often than once daily |

**Table 2**
Baseline characteristics of the groups.

| | Study group | Control group | *P* |
|---|---|---|---|
| Cases (*n*) | 34 | 36 | – |
| Male/female (*n*) | 11/23 | 12/24 | NS |
| Age (years) | 13.26 ± 2.55 | 13.37 ± 2.22 | NS |
| Body mass index | 18.66 ± 2.22 | 19.21 ± 1.73 | NS |
| Supine systolic BP (mmHg) | 110.02 ± 7.9 | 108.34 ± 6.2 | NS |
| Supine diastolic BP (mmHg) | 62.88 ± 4.7 | 63.27 ± 4.9 | NS |
| Supine heart rate (bpm) | 77.98 ± 11.7 | 78.34 ± 5.1 | NS |
| Change in symptom scores | 1.84 ± 1.32 | 0.42 ± 0.98 | < 0.001 |

BP: blood pressure; NS: not significant; bpm: beats per minute. All data expressed as mean ± standard deviation.

**Table 3**
Post-treatment supine blood pressure and heart rate.

| | Study group | Control group | *P* |
|---|---|---|---|
| Cases (*n*) | 34 | 36 | – |
| Supine systolic BP (mmHg) | 106.01 ± 6.8 | 108.34 ± 6.2 | NS |
| Supine diastolic BP (mmHg) | 60.70 ± 4.7 | 62.40± 5.5 | NS |
| Supine heart rate (bpm) | 70.83 ± 9.5 | 77.23 ± 6.2 | < 0.001 |

BP: blood pressure; NS: not significant; bpm: beats per minute. All data expressed as mean ± standard deviation.

### 2.3. Statistical analyses

Statistical analyses were performed using SPSS software version 13.0 (SPSS, Chicago, Ill., USA). Measurement data are presented as mean ± standard deviation. Comparisons between groups were performed using the independent Student *t*-test. Pre- and post-treatment symptom scores were compared using the paired *t*-test. A *P*-value of $< 0.05$ was considered statistically significant.

## 3. Results

There were no statistically significant differences between the groups regarding age, gender, body mass index (BMI), supine systolic and diastolic blood pressure, or pre-treatment frequency of syncopal attacks ($P > 0.05$; Table 2). After the 3-month treatment, post-treatment supine blood pressure and heart rate were also evaluated in both groups. There was no significant difference in post-treatment supine blood pressure between the two groups. However, the post-treatment supine heart rate in the study group was significantly lower than in the control group (Table 3). Changes in symptom scores in the study group were statistically significantly higher than in the control group ($P < 0.001$). This result showed the clinical efficacy of the combined treatment of reduced-osmolarity ORS and low-dose propranolol in the study group. The pre-and post-treatment OI symptom scores and the frequencies of syncopal attacks were compared in the two groups. The frequency of syncopal attacks decreased significantly and the OI symptom scores improved markedly in the study group. However, in the control group, while the frequency of syncopal attacks was markedly reduced, the OI symptom scores did not improve. The improvement in OI symptom scores in the study group was statistically significant (Table 4). In other words, patients in the study group responded well to the reduced-osmolarity ORS and low-dose propranolol treatment regimen in a short-term period.

## 4. Discussion

Orthostatic intolerance, which is defined as symptoms of OI occurring in standing position and disappearing in the supine position, is common in pediatrics. Beta-blockers, especially propranolol, limit an excessive increase in heart rate [7,8]. By controlling the heart rates, these agents increase diastolic cardiac filling and stroke volume and aid in the elimination of POTS symptoms [9]. Case reports and open-label studies alike have reported beneficial effects of beta-blockers in patients with POTS [10,11]. In our study, propranolol decreased the frequency of syncope, but this also occurred in the control group. There was a significant reduction in symptoms in the study group; however, in the control group, there was no statistically significant reduction in symptoms.

It has been reported that the use of propranolol in patients with POTS reduces the tachycardia during HUTT and improves OI symptoms. Gordon et al. performed HUTT on 21 patients with POTS and observed that their heart rates during supine position and in the 1st and 5th min of the upright stage were lowered with a single dose of propranolol and yet their symptoms were not eliminated [7]. For the treatment of orthostatic symptoms, lower rather than higher doses of beta-blockers are advocated [16]. Raj et al. showed that the use of low doses of propranolol (20 mg) significantly improved symptoms and lowered the heart rate during the upright stage of HUTT. However, it was noted during the same study that a higher dose of propranolol (80 mg) lowered the heart rate even further but failed to eliminate the symptoms and made them even worse [8]. We used low doses of propranolol in our study and did not observe any adverse effects in any patient.

It has been suggested that the tachycardia and elevated catecholamine levels associated with orthostatic tachycardia are principally due to hypovolemia and loss of adequate lower-extremity vascular tone [17,18]. Intravenous saline infusions lower the heart rate both in supine and upright positions [19]. Increased electrolyte and water intake reduce the heart rate during HUTT in

**Table 4**
Comparisons of pre- and post-treatment symptom scores in both groups.

| Pre-treatment | | Post-treatment | | |
|---|---|---|---|---|
| Frequency of syncopal attacks median (range) | Symptom score (mean ± SD) | Frequency of syncopal attacks median (range) | Symptom score (mean ± SD) | *P* |
| Study group 3 (2–5) | 3.85 ± 1.20 | 0 (0–1) | 2.03 ± 0.47 | < 0.001 |
| Control group 3 (2–4) | 3.83 ± 1.16 | 0 (1–2) | 3.28 ± 0.33 | > 0.05 |

POTS. Reduced-osmolarity ORS is as safe and efficacious as standard ORS [20], but hyponatremia is one of the expected adverse events of reduced-osmolarity ORS [21]. We did not detect any hyponatremia in any of the patients in this study. In our study, we believe we obtained the maximum effect of propranolol by establishing a daily and regular intake of sodium and water thereby correcting the heart rate increase caused by hypovolemia and change of position.

Renin and aldosterone levels are low in some patients with POTS [22]. These hormones increase plasma volume by retaining sodium. It has been suggested that the etiopathogenesis of POTS involves the inability to retain sufficient amounts of urinary sodium, and thus an increased salt intake (ingestion of 10–15 mg of sodium daily, in the form of salt tablets or electrolyte solutions) is especially beneficial in these patients. In our study, regular salt ingestion in the form of rehydration solution helped to eliminate symptoms in the study groups, in whom the complaints were primarily an excessive increase in the heart rate. Although the mechanism of OI and POTS are not clearly understood, it is probably multifactorial and involves increased microvascular filtration, insufficient venous return to the right heart, hypovolemia, changes in plasma renin activity and aldosterone levels, and altered adrenergic receptors [23,24]. Since most authors link hypovolemic and hyperadrenergic states to OI, we planned to study the effects of reduced-osmolarity ORS and propranolol. With this regimen, we were able to eliminate heart rate increases and symptoms in patients with study groups. In patients in the control group, however, although the frequency of frank syncope was reduced without treatment, their symptoms during daily activities persisted. We speculate that different unexplained pathophysiological mechanisms may be responsible for the symptom of syncope in POTS patients.

The role of non-pharmacological measures is also of interest, in particular measures aimed at correcting the cardiovascular deconditioning that is a standard feature of POTS syndrome. Qi Fu et al. performed a study in 2011 and demonstrated that physical activity is a better treatment than propranolol for patients with POTS for restoring upright hemodynamics, normalizing renal–adrenal responsiveness, and improving quality of life [25]. George et al. reported that a physical training program in adults with POTS resulted in remission of the syndrome in 71% of the 103 patients studied [26]. Bruce et al. carried out a study of 33 adolescents diagnosed with POTS. They aimed to evaluate the impact of an interdisciplinary rehabilitation program on functional impairment and psychological distress. Their findings were quite intriguing. They concluded that patients with POTS could manage their depression much better and the program had a significant beneficial effect on their psychological disorders [27].

The frequency of syncopal attacks was significantly reduced in both groups in our study; an improvement in the frequency of syncopal attacks was found even in patients without any treatment. As mentioned, our team speculated that different unexplained pathophysiological mechanisms might affect the development of syncope in pediatric POTS. For example, Low et al. reported that paradoxical vasoconstriction occurs in POTS because of an increased depth of respiration, resulting in hypocapnic cerebrovascular vasoconstriction. Respiration, which is not directly influenced by intravascular blood volume or regulation of the sympathetic nervous system, may affect cerebral blood flow in POTS [28].

## 5. Conclusion

In conclusion, we suggest that reduced-osmolarity ORS and propranolol can be used for the treatment of patients with POTS. The post-treatment frequency of syncopal attacks was reduced in the pediatric control group of our study. However, there was no change in the symptoms of OI, which caused difficulty in daily activities. We suggest the use of this regimen for patients diagnosed with OI symptoms during HUTT. Elucidation of the long-term benefits and further refinements of the method await larger-scale studies. We believe that the treatment regimen of reduced-osmolarity ORS and propranolol would be useful in the short term for children who are diagnosed with POTS during HUTT.

## 6. Study limitations

The major limitation in this study was that although an improvement in symptom scores was recorded, there was no difference in the number of syncopal attacks between the two groups. However, caution should be exercised in interpreting these findings as the study did not include a placebo control group. It was possible that the placebo effect in the treatment group played an important role in this pathology where psychological factors are commonly present. Thus, the absence of a placebo control group did not allow us to make a definite conclusion on the efficacy of the proposed treatment.

## Ethical approval

As this study involved human participants, Institutional Review Board approval was required for this research article and was obtained from the hospital's local ethics committee.

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### Disclosure of interest

The authors declare that they have no competing interest.

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