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Effects of intermittent intravenous saline infusions in patients with medication—refractory postural tachycardia syndrome

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Abstract
Background The postural tachycardia syndrome (POTS) is a heterogeneous group of disorders that results in symptoms of orthostatic intolerance. Excess blood pooling has been observed to cause low effective circulating volume in the central vasculature. Consequently, acute volume loading with IV saline has emerged as a potential strategy for clinical intervention. We evaluated the impact of acute volume loading on both the signs and symptoms of patients suffering from POTS.
Methods Fifty-seven subjects screened from our population of POTS patients and assenting to participation were administered the two surveys by telephone. Subjects completed each survey twice, before, and after initiating IV hydration therapy. The Orthostatic Hypotension Questionnaire (OHQ) was used to assess change in clinical symptomatology, while the short form 36 health survey (SF-36) was employed to assess the impact of IV saline infusion on quality of life.
Results Fifty-seven patients were included in the analysis. The average number of medications trialed before referral for IV hydration was 3.6 ± 1.7 medications. Saline infusions occurred with mean frequency of 11.3 ± 8.5 days and at a mean volume of 1.5 ± 0.6 l per infusion. The mean change of the OHQ was 3.1 ± 0.3 (95% CI 2.6–3.7; $P < 0.001$), with significant improvement in all the composite scores. The mean change in the SF-36 form was 19.1 ± 2.7 (95% CI −24.6 to −13.6; $P < 0.001$).
Conclusions Intermittent IV infusions of saline dramatically reduce symptoms and improve quality of life in patients suffering from POTS. Further work should explore its efficacy as a bridge study for patients of high symptomatic severity.

Keywords POTS · Refractory POTS · IV hydration

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1 Introduction

The postural tachycardia syndrome (POTS) is a heterogeneous group of disorders that results in symptoms of orthostatic intolerance. In its most common forms, excess blood pooling has been observed to cause low effective circulating volume in the central vasculature [1]. Consequently, acute volume loading with IV saline has emerged as a potential strategy for clinical intervention [2]. Despite its growing popularity, empiric evidence supporting its usage is small. Citing this paucity of evidence, the most recent consensus guidelines have recommended against long-term use of intravenous hydration and reserve it for rescue therapy only [3]. A recent

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investigation, in 2014, showed improvement in resting cardiac output but failed to demonstrate any improvement in exercise tolerance among POTS patients [4]. Prior investigations were more supportive. A 1997 study in *Circulation* suggested that acute volume loading with IV saline is more efficacious than pharmacologic intervention [5]. The key to reconciling these two results may lie in the distinction between subjective and objective measures. While concurring with the result from Jacob et al., a later study reported that IV saline's superiority in offering symptomatic improvement was distinct from its comparatively weaker performance on observed cardiovascular parameters [6]. Similarly, a prospective study of POTS patients found that those patients who showed symptomatic improvement after any treatment regimen tended to do so without improvement in the heart rate response during tilt table testing [7].

These results are not necessarily contradictory. As suggested by a recent 5-year retrospective study by Moak et al. [8], the dramatic subjective improvement seen after acute volume loading may increase patient compliance with behavioral interventions (such as reconditioning) needed to realize long-term objective improvements. However, these findings are of uncertain generalizability, given the known changes in autonomic function over the human lifespan [9].

Examining their validity in adult populations is a research priority. We evaluated the impact of acute volume loading on both the signs and symptoms of patients suffering from POTS to properly rationalize its role in treatment. To the best of our knowledge, this is the first study in an adult population to evaluate the response to IV saline infusion in a clinical setting.

2 Methodology

This prospective observational study was approved the University of Toledo Medical Center (UTMC) Institutional Review Board.

All patients with POTS seen in the Syncope and Autonomic Disorders clinic between January 1, 2010, and February 1, 2016, were screened for possible inclusion. Inclusion criteria was a diagnosis with POTS, made or confirmed by the UTMC Syncope and Autonomic Disorders clinic, failure of at least one pharmacologic intervention to control symptoms, and referral for IV hydration therapy. Diagnosis was made as per the recent consensus guidelines for POTS which states the following: symptoms of orthostatic intolerance associated with a heart rate increase of 30 beat per minute (bpm) that occurs within the first 10 min of standing or upright tilt test in the absence of other secondary causes of orthostatic intolerance [1, 3]. Those who met all inclusion criteria were contacted by phone and offered the opportunity to participate in the study. Attempts to contact each potential participant were made until they were reached or three calls were placed. Patients declining participation or who could not be reached after three attempts were excluded from the study.

Each subject underwent a comprehensive chart review to extract baseline demographic data, comorbidities, and objective correlates of disease severity, as well as attempted procedural, pharmacologic, and behavioral interventions to ameliorate the disease.

3 Study outcomes

Subjects assenting to participation were administered the Orthostatic Hypotension Questionnaire (OHQ) by telephone. This tool, validated for clinical use in the longitudinal measurement of the symptomatic severity of orthostatic hypotension [10], is routinely employed in our clinic. Patients' responses were compared before and after initiating IV hydration therapy. The questionnaire consists of ten composite scores, six items evaluate symptoms and four assess the impact of symptoms on daily activities. Each item is scored on a Likert scale from zero to ten with zero indicating the absence of the symptom in question and ten implicating the worst expression of said symptom or impact on quality of life.

We also assessed quality of life using the short form 36 health survey (SF-36). The questionnaire contains 36 items that yield eight category scales divided into two major components: mental health and physical health. The scale ranges from 0 to 100, with lower scores indicating higher disability and lower quality of life. This questionnaire has been validated and used to assess quality of life in several medical conditions [11]. In 2002, Benrud-Larson et al. showed that the diminished quality of life suffered by POTS patients is comparable to those with chronic obstructive pulmonary disease and congestive heart failure [12].

4 Statistical analysis

All data extracted underwent descriptive statistical analysis using the SPSS 21.0 software (SPSS Inc.). Each patient's serial response on the OHQ and SF-36 was analyzed for statistical significance using a Student's t test in a paired sample design.

A two-tailed P value of <0.05 was considered to be statistically significant.

5 Results

Of the 382 patients with POTS who were screened, 72 patients were prescribed the IV saline infusions and 57 assented to participation in this retrospective study (Diagram 1).

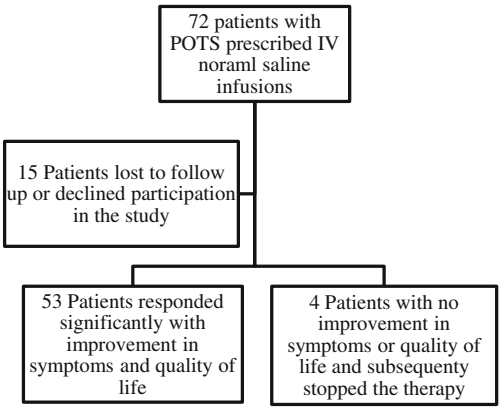

Diagram 1 Outline of t he study

The population of the study was prominently young females (96.5%) with a mean age of 35.0 ± 12.9 years and no significant comorbidities. Three had diabetes mellitus, 10 had hypertension, 4 had other cardiovascular diseases, and none had kidney impairment. These demographics reflect those commonly described in patients with POTS [3].

The fifty-seven patients included in our study had a follow-up time ranging from 3 to 12 months. The average number of medications trialed before referral to IV hydration was 3.6 ± 1.7 medications.

The baseline characteristics of these patients are summarized in Table 1.

6 Therapy protocol

Patients received IV hydration with normal saline through peripheral IV starts (42 [73.7%]), peripherally inserted central catheter (PICC) line inserted by certified nurse or interventional radiologist (12 [21.1%]), or subcutaneously implanted ports (3 [5.3%]). The initial treatment consisted of 1 l of IV normal saline infused over 1–2 h every week. Therapy was then titrated up (2 l per week) or down (1 l every 2–4 weeks) depending on the patient's response and desire.

1.5 ± 0.6 l were received per infusion with a mean frequency of 11.3 ± 8.5 days.

7 Study outcomes

The average OHQ score before initiating IV hydration therapy was 6.6 ± 1.5. Dizziness and fatigue were reported as the most disabling symptoms, with scores of 7.3 ± 2.5 and 8.2 ± 1.6, respectively.

The mean change of the OHQ was 3.1 ± 0.3 (95% CI 2.6–3.7; $P < 0.001$), with significant improvement in all the composite scores, Fig. 1.

Figure 2 shows the mean SF-36 for each category at baseline and after the intervention. As illustrated, IV saline infusion leads to significant improvement in quality of life with mean difference of 19.1 ± 2.7 (95% CI −24.6 to −13.6; $P < 0.001$). This significant improvement was valued across all the domains appraised by the SF-36.

Most patients reported an immediate improvement in symptoms that lasted for 3.3 ± 2.2 days.

Four patients reported no improvement in symptoms or quality of life to our intervention. This subgroup was entirely Caucasian with a mean age of 19. Three of them had POTS secondary to hypermobility syndrome. Mean OHQ and SR-36 before intervention were 6.6 and 47.3, respectively. Hypermobility and young age were the only factors found to predict poor response to IV hydration, $P = 0.015$ and $P = 0.009$, respectively. However, given our small total sample, it is unclear that this finding is generalizable.

During the study period, the overwhelming majority of subjects saw sufficient symptomatic improvement to discontinue IV saline infusion altogether. Of the 50 patients who successfully weaned from saline infusion during the study period, all had done so in less than 6 months, and 44% did so in less than 3 months. There was no clear demographic, behavioral, or treatment characteristic common to this group

Table 1 Characteristics of patients in our study ($N = 57$)

Females, *N* (%)	55 (96.5%)
Age in years (mean ± SD)	35.0 ± 12.9
Ethnicity	
White	55 (96.5%)
Other, *N* (%)	2 (3.5%)
Cause of orthostatic intolerance, *N* (%)	
Idiopathic	41 (71.9%)
Hypermobility	14 (24.6%)
Hyperadrenergic	2 (3.5%)
Previous medication failed, *N* (%)	
Beta-blockers	35 (61.4%)
Midodrine	28 (49.1%)
SSRIs and SNRIs	25 (43.9%)
Desmopressin	24 (42.1%)
Fludrocortisone	17 (29.8%)
Bupropion	14 (24.6%)
Pyridostigmine	14 (24.6%)
Octreotide	10 (17.5%)
Dextroamphetamine/amphetamine	9 (15.8%)
Other	9 (15.8%)
Northera	8 (14.0%)
Epoetin alfa	4 (7.4%)
Ivabradine	2 (3.5%)

N number, *SD* standard deviation, *SSRI* selective serotonin reuptake inhibitor, *SNRI* serotonin–norepinephrine reuptake inhibitor

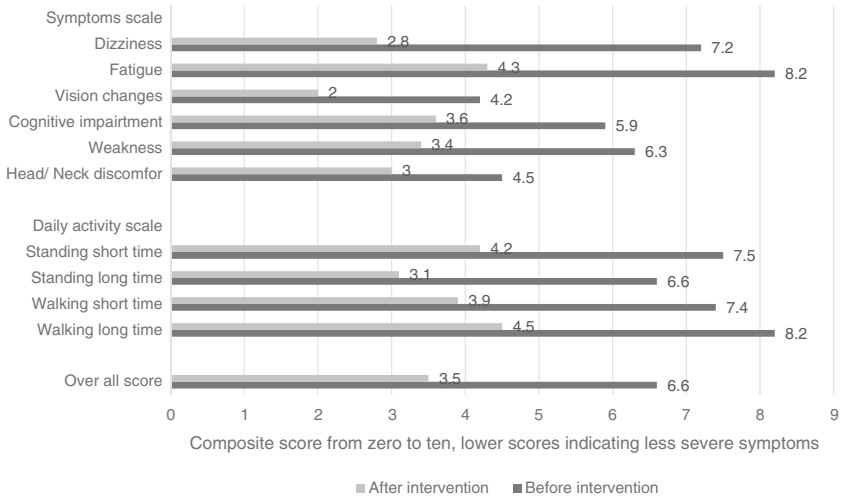

Fig. 1 Difference in OHQ before and after IV hydration therapy

of high-responders. Eventually, four would suffer relapse, requiring transition back to saline infusion therapy. However, even in these cases, relapsed subjects showed dramatically reduced need for intervention, with average frequency of infusion lowering from 9.25 ± 4.65 to 20.13 ± 7.88 days. Among subjects that successfully weaned from saline infusion for any length of time, some return to therapy during episodes of acute exacerbation or for limited periods of annual peak symptomology. There was no clear demographic, behavioral, or treatment characteristic that allowed discrimination between those who would could be weaned from therapy and those who remained on therapy for at least one year's time.

There were no hospitalizations attributable to IV saline infusion during the period studied. One patient discontinued the therapy due to development of hypertension. There were no reported cases of deep vein thrombosis or soft tissue infection. Despite the apparent gulf in complication rate, these results are in line with the major trends seen in comparable studies. As compared with our own study population, where 73.7% of subjects received therapy via peripheral IV starts, this same modality of represented only 25.6% of the subjects studied by Moak [8]. Significantly, the entirety of their reported complications was among subjects employing peripherally inserted central catheter (PICC) lines or infusion ports. Risks associated with IV saline infusion may be more particular to the modality of administration than intrinsic to the therapeutic intervention.

8 Discussion

In line with other recent publications, this study offers support for the safety and efficacy of medium-term IV saline infusion in the treatment of POTS. The principle distinction between the recently published work of Moak et al. [8] and this work is the population under study. There are a number of behavioral and physiologic changes with age which might predispose to worsening of the disease.

Unambiguously, a recent systematic review on sedentary behavior found a positive correlation between age and total sedentary time in 70% of all studies reviewed [13]. Deconditioning after prolonged bed rest is associated with a decline in stroke volume [14]. Exercise is a first-line intervention in POTS, with even short-term regimens demonstrating

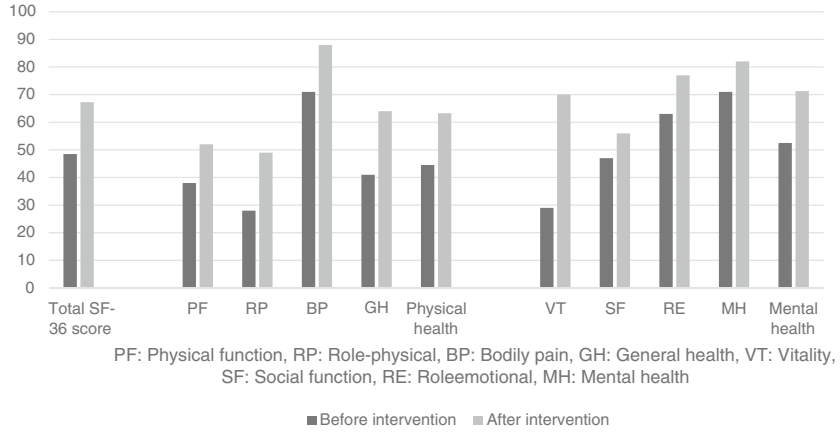

Fig. 2 SF-36 point score before and after the intervention, lower score indicating lower quality of life

up to 8% augmentation of stroke volume [15]. This combination of physiological and behavioral changes over the life cycle would be expected to render persistent adult cases of POTS more refractory to treatment than their juvenile counterparts. Our results were supportive of such a finding; our subjects having failed a mean of [3.6 ± 1.7] medications as opposed to the 3.1 trials reported by Moak [8].

There is no clear consensus in medical literature as to the role and efficacy of intermittent intravenous fluid loading in POTS patients. While contemporary treatment protocols for intravenous hydration space interventions in days to weeks, responsiveness to crystalloid bolus is usually understood over a much shorter time frame. Studying healthy volunteers, Grothwohl reported a complete reversal of the peak expansion in plasma volume in only 8 h [16]. In critically ill postoperative patients, hemodynamic benefits were reversed in 2 h [17].

While a comprehensive mechanism for this disparity in time course is as yet unarticulated, suggestive evidence has begun to emerge in understanding factors controlling blood pressure [18]. In normal human physiology, responsiveness to sympathetic neural activity seems to vary inversely with CVP [19, 20]. This relationship serves as a compensatory homeostatic mechanism during hypovolemia. The particular defects of POTS may compromise this function. An experimental model using nitroprusside-induced hypotension found that in comparison to controls, these patients could increase the frequency but not amplitude of sympathetic neural activity [21]. This has been interpreted in light of extant evidence as attributable to sympathetic denervation. Though even these results are inconsistent [22], and other defects seem responsible for some symptomatic complaints in this patient population [23], saline infusion may be effective insofar as it decreases reliance on pathologically influenced system. Further complicating this picture, our study joins a sizable preceding body of work that failed to identify clinically significant hemodynamic changes to correlate with the subjects' self-reported improvements.

The present results nonetheless present a powerful role for saline infusion as a bridge therapy in the treatment of POTS. Deconditioning creates a vicious cycle of symptomatic worsening in this patient population and represents a major challenge in treatment. For instance, one exercise-based regimen reported both an excellent response rate of 71% disease remission and that a full 23.6% of all enrollees withdrew from therapy as they found the required exercise too difficult [24]. It stands to reason that bridge therapies which alleviate acute symptomatic complaints might facilitate increased compliance. This effect has already been observed in a major study of adolescent POTS patients [8]. Researchers found no instrument ideal for tracking compliance during the present study. However, the sustained independence from saline infusion in the majority of our subjects, all of whom were treatment refractory upon enrollment, suggests a similar dynamic wherein short-term symptom relief facilitates long-term disease control. In the context of both acute exacerbations and medication-refractory initial presentations, IV saline infusion seems an effective method for breaking the positive feedback between deconditioning and symptom severity.

The first major study of this kind was published in 2015 [8]. Both that study and this one are single center using self-reported scales as a primary outcome. Results were of a consistent magnitude and statistical robustness. Their findings might also be considered complimentary. While the former employed a non-specific quality of life questionnaire, with implicitly presumed attribution to improvement in disease state, our study added a validated instrument for tracking disease severity and consequent improvement in quality of life.

A number of limitations were inherent in the nature of this study. The relatively young age of the subjects [mean age of 35.0 ± 12.9] without significant comorbidities may have led to a more favorable outcome and reduced complications. Moreover, compliance to other medical therapy and exercise programs was not accounted for, which could have altered the course of the disease. This may also have allowed the development of psychological dependence to saline infusion to go undetected.

As a non-blinded non-controlled observational study, placebo effect cannot be excluded. A blinded study protocol comparing sham and actual saline infusions is justified clarify this point. Nonetheless, these results provided a preliminary evidence for the efficacy of IV hydration therapy and thereby provide justification for larger better controlled studies. As a whole, our sample was highly responsive to IV fluid loading, with improvement reported in 93.0% of subjects. It is worth examining whether this represents a particular subset of the disease by etiology or presentation, and which medications might be synergistic with IV fluid loading. The present study, like other existing literature, suggests a wide variability in the duration of intravenous hydration therapy. With increasing clinical experience, the contours of a regimen for timing and method of discontinuation IV therapy should emerge. While increased compliance with behavioral interventions such as reconditioning has been informally observed, it is unclear whether these or some alternative mechanism are the driver of the long-term improvements observed.

This study examined the validity of IV infusion as a second-line therapy without regard to defining the efficacy of any first-line treatment program. For the first-line therapy, patients should be treated in accordance with our previously published recommendations [1, 3].

In, conclusion, intermittent IV infusions of saline dramatically reduce symptoms in patients suffering from postural tachycardia syndrome. Paired with its relative safety and low cost, this quality makes it an ideal candidate for bridge therapy to allow the implementation of long-term interventions in highly symptomatic patients. Further studies will be necessary to better refine this application.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Disclosures None.

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