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Erythropoietin in the Treatment of Postural Orthostatic Tachycardia Syndrome

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Erythropoietin has been reported to improve symptoms of orthostatic intolerance in patients suffering from orthostatic hypotension. Previous reports on the use of erythropoietin in patients with postural orthostatic tachycardia (POTS) have included only a very small number of patients. In the current study, we report on the use of erythropoietin in patients with refractory POTS. The study was approved by the institutional review board. A retrospective nonrandomized analysis was performed on 39 patients evaluated at our autonomic center for POTS from 2003 to 2010. The diagnosis of POTS was based on patient history, physical examination, and response to head-up tilt-table testing. The mean follow-up period was 6 months. The patients were included in the current study if they had a diagnosis of POTS with severe symptoms of orthostatic intolerance and were refractory to the commonly used medications. All these patients were started on erythropoietin, and the response to therapy was considered successful if it provided symptomatic relief. We screened 200 patients with POTS and found 39 patients (age 33 ± 12, 37 females) to be eligible for inclusion in the current study. The response to the treatment was assessed subjectively in each patient and was obtained in a retrospective fashion from patient charts and physician communications. Eight (21%) patients demonstrated no improvement in symptoms after administration of erythropoietin. Three (8%) patients showed an improvement in symptoms of orthostatic intolerance of <3 months. Twenty-seven (71%) patients demonstrated sustained improvement in their symptoms of orthostatic intolerance at the mean follow-up of 6 months. Erythropoietin significantly improved sitting diastolic blood pressure but had no effect on other hemodynamic parameters. In a select group of POTS patients who are refractory to commonly used medications, erythropoietin may help improve symptoms of orthostatic intolerance.

Keywords: erythropoietin, postural tachycardia syndrome, orthostatic intolerance

INTRODUCTION

Postural orthostatic tachycardia (POTS) is a condition causing symptoms of orthostatic intolerance (of >6 months' duration) accompanied by a heart rate increase of at least 30 beats/min (or a rate >120 beats/min) that occurs in the first 10 minutes of the patient being in the upright posture or head-up tilt posture in the absence of other chronic debilitating disorders.[1–4] Although the exact cause is unknown, venous pooling,[5] partial dysautonomia (involving lower limbs),[6] and blood volume deficits[7–11] have been proposed as possible mechanisms involved. The resultant compensatory increase in heart rate and myocardial contractility attempts to compensate for the reduced effective circulating blood volume. There are roughly 500,000–1,000,000 people suffering from POTS in the United States.[6,7] Multiple pharmacotherapeutic agents including fludrocortisone, midodrine, bupropion, and selective serotonin reuptake inhibitors have been used to prevent symptoms of

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orthostatic intolerance in these patients. However, there are some patients who are refractory to these pharmaceutical agents. Erythropoietin has been used for ameliorating the symptoms of orthostatic intolerance in patients suffering from orthostatic hypotension[12] and pure autonomic failure.[13] Hoeldtke et al[14] reported on the use of erythropoietin in a series of 8 POTS stating that there was no improvement in orthostatic tachycardia after administration of erythropoietin. However, 3 patients in this series reported a significant improvement in their symptoms of orthostatic dizziness. In the current study, we report on the use of erythropoietin in a select group of POTS patients with refractory symptoms of orthostatic intolerance and had failed multiple other medications.

METHODS

This was a retrospective study approved by our Institutional review board. We screened 200 POTS patients who were being followed up at our autonomic center. Thirty-nine patients were found to be eligible for inclusion in the current study.

Criterion for diagnosis of postural orthostatic tachycardia

POTS was defined as chronic symptoms of orthostatic intolerance (of >6 months' duration) accompanied by a heart rate increase of at least 30 beats/min (or a rate >120 beats/min) that occurs in the first 10 minutes of the patient being in the upright posture or head-up tilt test (HUTT) posture in the absence of other chronic debilitating disorders. Symptoms include fatigue, orthostatic palpitations, exercise intolerance, lightheadedness, diminished concentration, headache, near syncope, and syncope. In a retrospective detailed chart review, we collected data including demographic information, presenting symptoms, laboratory data, tilt-table response, and treatment outcomes.

Head-up tilt test protocol

The protocol used for tilt-table testing has been described elsewhere, but basically consisted of a 70° baseline upright tilt for a period of 30 minutes, during which time the heart rate and blood pressure were monitored continually. If no symptoms occurred, the patient was lowered to the supine position and an intravenous infusion of isoproterenol started with a dose sufficient to increase the heart rate to 20–25% above the resting value. Upright tilt was then repeated for a period of 15 minutes.

Patients were included in the study if they had a POTS pattern on HUTT (rise in heart rate independent of any change in blood pressure).

Treatment protocols

The treatment protocols that were initially employed were based on our previous experiences with orthostatic disorders and are described in detail elsewhere.[2–4,15] We identified 39 patients of POTS who were refractory to other commonly used medications. Briefly, a sequence of therapies were employed that included physical countermaneuvers and aerobic and resistance training and increased dietary fluids and sodium. If these were ineffective, pharmacotherapy was initiated in a sequence generally consisting of fludrocortisone, midodrine, selective serotonin reuptake inhibitors, either alone or in combination. A trial of stimulants including methylphenidate or dextroamphetamine failed to provide symptomatic relief in these patients. All these patients were subsequently tried on Erythropoietin. We did not employ a formal questionnaire to assess the response to treatment nor did we assess the response to the treatment with HUTT testing. The information about the subjective symptoms and sense of well-being from each patient were collected from the patient charts, physician communications, and direct patient inquiry. A treatment was considered successful if it provided symptomatic relief.

RESULTS

We screened 200 patients of POTS who followed our syncope and autonomic center clinic. We found 39 patients (age 33 ± 12, 37 females) who met the inclusion criterion for this study. Table 1 summarizes the clinical characteristics of the study population.

Erythropoietin administration

Before administration of Erythropoietin, patients underwent serum determination of Hematocrit, hemoglobin, white and red cell count, iron, total iron-binding capacity, and ferritin levels. Patients were started on Erythropoietin as long as their Hematocrit was <50%. Patients then received 10,000 international units (IU) of erythropoietin per week. A complete blood count was repeated every 3–4 weeks. If there was no response either clinically or hematologically, the dose was increased to 20,000 IU/wk. No patient received a dose >20,000 IU/wk. If the Hematocrit was >50%, the erythropoietin dose was held until the Hematocrit fell below 50. The hematocrit value of most patients was maintained in the range of 43–46%.

Response to the treatment

The response to the treatment was assessed subjectively in each patient and was collected in a retrospective fashion from patient charts and physician communications and patient inquiry. Response to Erythropoietin was assessed

Table 1. Baseline clinical characteristics of the study population (N = 39).

Age	33 ± 12
Sex (females)	37 (95%)
Symptoms of orthostatic intolerance	
Orthostatic palpitations	13 (33%)
Dizziness	36 (92%)
Inability to concentrate	7 (18%)
Syncope	38 (97%)
Fatigue	22 (56%)
Presyncope	39 (100%)
Medications	
Betablockers	28 (71%)
SSRI	13 (33%)
NERI/SSRI	23 (59%)
Midodrine	29 (74%)
Modafinil	12 (30%)
Fludrocortisone	
Comorbid conditions	
Hypertension	3 (8%)
Migraine	25 (64%)
Precipitating factor	
Surgery	2 (5.2%)
Viral infection	7 (17%)

SSRI, selective serotonin reuptake inhibitor; NERI/SSRI, combined norepinephrine and serotonin reuptake inhibitor.

at a mean follow-up of 6 months. Eight percent demonstrated no sustained beneficial response of <3 months, and 71% patients demonstrated a sustained positive response of >6 months. Twenty-one percent failed to demonstrate any positive response to erythropoietin at all (Fig. 1). The symptoms that improved most in the responders were orthostatic tachycardia, dizziness, and palpitations. Syncope occurred in 38 (97%) of the patients before starting erythropoietin. Syncope frequency decreased in 26 patients, 15 had no syncope at 6 months of follow-up, and 9 had a significant decrease in the frequency of their syncope episodes. No patient reported any serious side effect.

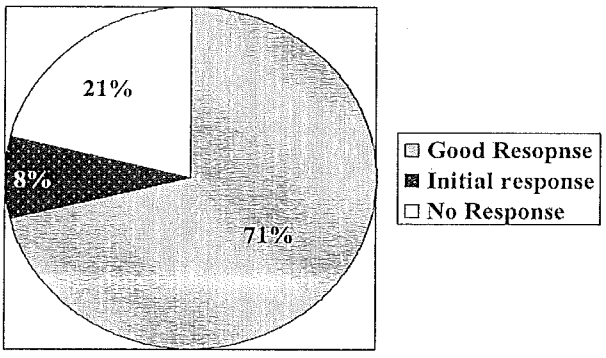

FIGURE 1. Symptomatic response to erythropoietin as assessed at a mean follow-up of 9 ± 3 months. Eight percent demonstrated no sustained response of <3 months, and 71% patients demonstrated a sustained response of >6 months. Twenty-one percent failed to demonstrate any response to erythropoietin at all.

Effect on hemodynamic parameters

Erythropoietin improved sitting diastolic blood pressure (70 ± 10 vs. 76 ± 12; $P = 0.010$) but had no effect on systolic blood pressure and heart rate (Table 2).

DISCUSSION

Erythropoietin has been used for the treatment of orthostatic intolerance in patients suffering from orthostatic hypotension[12] and pure autonomic failure.[13] In another report, erythropoietin was tried in a series of 8 POTS patients.[14] In addition to increasing the mean Hematocrit from 37 to 46, erythropoietin also increased the supine and standing mean blood pressure. However, in this report, erythropoietin administration failed to reverse orthostatic tachycardia. In this report, there was little if any information provided about the effect of erythropoietin on the symptoms of orthostatic intolerance, although the authors report that 3 patients reported a significant improvement in symptoms of orthostatic dizziness, and among these 3, only 1 showed an improvement in orthostatic tachycardia. Thus, from this report, 3 of 8 patients reported an improvement in their symptoms of orthostatic dizziness.

The current study included patients who were refractory to other commonly used medications including mineralocorticoids, betablockers, SSRI, and stimulants. Almost 70% of patients demonstrated significant improvement in their symptoms when erythropoietin was added to their pre-existing regimen. In our study population, erythropoietin significantly increased the sitting diastolic blood pressure. In addition to its effects on the red call mass and plasma volume, erythropoietin also has a direct vasoconstrictive effect that can lead to hypertension.

Erythropoietin has been shown to increase the levels of endothelin, a potent vasoconstrictor.[16,17] Also,

Table 2. Effect of erythropoietin on SBP, DBP, and heart rate.

	Before treatment	After treatment	*P*
Sitting SBP	106 ± 15	109 ± 17	0.4
Sitting DBP	70 ± 10	76 ± 12	0.012
Sitting heart rate	84 ± 26	88 ± 17	0.8
Standing SBP	100 ± 13	104 ± 15	0.09
Standing DBP	68 ± 8	72 ± 12	0.1
Standing heart rate	128 ± 26	111 ± 14	0.5

SBP, systolic blood pressure; DBP, diastolic blood pressure.

erythropoietin, by elaborating hemoglobin, inhibits nitric oxide's vasodilating effect and increases blood pressure.[18,19] In addition, erythropoietin increases tubular reabsorption of sodium,[20] and increases intracellular calcium in vascular smooth muscles thus increasing vascular resistance.[21]

The results of the current study are interesting and clinically important as well. The use of erythropoietin was associated with improvement in the clinical symptoms of orthostatic intolerance in patients suffering from POTS. The results of this study can lay a foundation for a larger randomized controlled trial of erythropoietin in the treatment of POTS.

Having said this, there are certain important limitations in the design of the current study. The study group itself was small, and it was not a randomized controlled trial. Rather, each patient was used as his or her own control. In addition, patients with POTS may exhibit spontaneous variations in symptom severity. Hence, we cannot be absolutely sure that the beneficial effects noted can be wholly attributed to the actions of the drug. However, this group of patients was highly symptomatic who had not responded to any other therapeutic modality. Also, from the results of the current study, it is unclear as to which patient will be responding the most to erythropoietin. Finally, the patients presented here all tended to have unusually severe forms of the disorder and therefore may not be representative of the majority of patients with POTS. Another important limitation of the study was the small number of patients that were included in the analysis. Erythropoietin therapy was initiated in only a small number of patients because of cost issues and the need for parenteral administration. For these reasons, erythropoietin is not a first-line medication; however, it is usually reserved for those who fail other first-line medications.

CONCLUSIONS

Erythropoietin may be useful in ameliorating symptoms of orthostatic intolerance in patients suffering from refractory POTS.

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