

2017

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Sokalski, Christopher S., "Is Pharmacologic Therapy for Blood Pressure Control Effective At Reducing Symptoms and Improving Quality of Life in Patients With Postural Orthostatic Tachycardia Syndrome (POTS)?" (2017). *PCOM Physician Assistant Studies Student Scholarship*. 416.

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Is pharmacologic therapy for blood pressure control effective at reducing symptoms and improving quality of life in patients with postural orthostatic tachycardia syndrome (POTS)?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 5, 2016

Abstract

Objective

The objective of this selective EBM review is to determine whether or not pharmacologic therapy for blood pressure control effective at reducing symptoms and improving quality of life in patients with postural orthostatic tachycardia syndrome (POTS).

Study Design

Systematic review of two single blind crossover randomized control trials published in 2009 and 2012 and one retrospective case control study published in 2009.

Data Sources

Three studies were obtained using PubMed.

Outcomes Measured

Self reported symptoms of POTS and the Vanderbilt POTS symptom scoring system as well as quality of life in patients.

Results

Raj et al. (2009), Coffin et al. (2012), and Lai et al. (2009) all demonstrated improvement in symptoms and quality of life with blood pressure altering medications in patients with POTS.

Conclusion

Evidence to support effective treatment for symptom relief and quality of life improvement in patients with POTS is scarce in the current literature. This systematic review indicates that evidence is strong for efficacy of β -blockers and DDAVP to control standing HR and improve overall symptom burden in POTS patients compared to placebo and other treatment modalities. Future studies comparing the control of catecholamines vs β -adrenergic blockade in POTS would be beneficial for the understanding of underlying mechanisms, therefore provide better control of symptoms in patients

Key Words

Postural orthostatic tachycardia syndrome, POTS, beta blockers

Introduction

Postural orthostatic tachycardia syndrome (POTS) is a disorder of chronic orthostatic intolerance that occurs in patients who experience symptoms in response to postural change.¹ POTS is a disorder of the autonomic nervous system hallmarked by an excessive increase in heart rate in response to postural stress without an associated drop in blood pressure.² POTS is clinically defined as an increase in heart rate by ≥ 30 bpm in adults, by ≥ 40 bpm in children, or an absolute heart rate exceeding 120 bpm, within 10 minutes of assuming an upright posture, with no corresponding orthostatic fall in blood pressure.^{3,4} Patients with postural orthostatic tachycardia syndrome most commonly report clinical symptoms of dizziness, weakness, fatigue, mental clouding, blurred vision, palpitations, tremulousness, and anxiety.^{1,3,5} POTS is associated with a poor quality of life and has been found to have the functional impairment similar to patients who have congestive heart failure or chronic obstructive pulmonary disease.^{1,4} Although the exact cause of this disorder is not entirely understood, there are a few theories for the underlying mechanisms that lead to orthostatic instability. Hypovolemia caused by an impairment of the renin-angiotensin-aldosterone system is thought to play a major role in the disorder. Several studies in patients with POTS have noted observations of hypovolemia, reduced RBC volume, and excessive venous pooling as evidence of a decrease or redistribution of blood volume.⁵ Other theories include decreased venous return, cardiovascular deconditioning, a primary abnormality in the baroreflex, and increased sympathetic activity (including elevated arterial NE levels at rest and decreased NE clearance).⁵

POTS is estimated to affect 500,000 Americans and is disproportionately observed in women of childbearing age.^{1,2} Patients with POTS present at a relatively young age (15-45 years) and the disorder is becoming increasingly recognized in adolescents. The exact amount of

healthcare spending contributed to POTS is unknown, however the condition contributes to worsened physical health, bodily pain, and physical and social functioning in the younger population. The population affected and the lack of standardized treatment modalities contributes to the importance of recognition of POTS in the clinical setting.

No known cure or optimal therapy exists for postural orthostatic tachycardia syndrome.³ Because many patients with POTS have a low plasma volume, most patients respond rapidly and have symptomatic improvement with saline infusion.⁵ It is common practice for practitioners to advise patients to follow a high sodium diet of 200-300 mEq/day with a significant increase in water consumption, restrict caffeine, and gradually increase exercise.^{2,3,5} In addition to dietary and lifestyle changes, many patients are prescribed medication to either increase plasma volume, increase peripheral vasoconstriction, or compensate for increased catecholamine levels. Midodrine, beta-blockers, SSRIs, and fludrocortisone are medications that are frequently prescribed to POTS patients depending on the evaluation of their symptoms.³ Given that the hallmark symptom and diagnostic sign of POTS is tachycardia, β -adrenergic blockade is shown to be a logical treatment to reduce symptoms in patients.¹ This review paper examines the effectiveness in blood pressure control and fluid retention with pharmacologic therapy to reduce tachycardia, thus reducing symptoms and improving the quality of life in patients with POTS.

Objective

The objective of this selective EBM review is to determine whether or not pharmacologic therapy for blood pressure control is effective at reducing symptoms and improving quality of life in patients with postural orthostatic tachycardia syndrome (POTS).

Methods

This review is comprised of two single blind crossover randomized control trials and one retrospective case control study that meet specific criteria for the comparison of pharmacologic therapy for blood pressure control to reduce symptoms and improve quality of life in patients with postural orthostatic tachycardia syndrome. The first study utilized propranolol as a method of blood pressure control and symptomatic relief from POTS. The second study measured the outcomes on symptoms by using desmopressin to improve fluid status. The third study was a retrospective case control study that compared the relief of symptoms in patients treated with medications, most commonly β -blockers or midodrine. All patients used for this review met the clinical diagnostic criteria for postural orthostatic tachycardia syndrome and did not have additional comorbid conditions that could impact orthostatic intolerance.

Key words used in the research of these included studies were postural orthostatic tachycardia syndrome, POTS, beta blockers, and treatment. All articles used in this systematic review were published articles in English from peer-reviewed journals and located via PubMed. Articles had to meet several inclusion criteria such as: relevance to the proposed research question, relationship to patient oriented evidence that matters (POEMs), at least two randomized control trials, and original research published in the year 2000 or later. Exclusion criteria included articles published prior to the year 2000, articles focused on disease oriented outcomes (DOEs), and systematic review articles. Statistics reported in the articles utilized in this study include p-values. Numbers needed to treat (NNT), relative benefit increase (RBI), and absolute benefit increase (ABI) were calculated and reported for the Lai³(2009) study to determine results as a POEM. Table 1 demonstrates the demographics and characteristics of studies included in this systematic review.

Table 1 - Demographics & Characteristics of included studies

Study	Type	# PTs	Age	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Raj ¹ (2009)	Single blind RCT	54	>18 years old	PTs meeting the criteria for POTS	<ul style="list-style-type: none"> < 18 years old Use of Fludrocortisone within 5 days 	0	<ul style="list-style-type: none"> Protocol 1: propranolol 20 mg D (low dose) Protocol 2: propranolol 80 mg D (high dose)
Coffin ² (2012)	Single blind RCT	30	>18 years old	<ul style="list-style-type: none"> Patients referred to the Vanderbilt University Autonomic Dysfunction Center PTs meeting criteria for POTS >= 6 months of symptoms 	<ul style="list-style-type: none"> < 18 years old 	0	<ul style="list-style-type: none"> Desmopressin (DDAVP) 0.2 mg D
Lai ³ (2009)	Retrospective case control study	47	11-17 years	<ul style="list-style-type: none"> Adolescents with POTS seen at Mayo Clinic from 2002-2005 	<ul style="list-style-type: none"> > 18 years old 	13	<ul style="list-style-type: none"> Beta blockers vs Midodrine

Outcomes Measured

The first two studies measured outcomes using self reported symptoms and the Vanderbilt POTS symptom scoring system: POTS symptoms including mental clouding, blurred vision, shortness of breath, rapid heart beat, tremulousness, chest discomfort, headache, lightheadedness, and nausea immediately before and at 2 and 4 hours post therapy. Patients were asked to rate severity of the 9 symptoms on a scale 0-10 with 0 being absence of symptom. The

sum of the scores at each interval during the study was used to calculate total symptom burden. The third study measured outcomes using the Walker Functional Disability Inventory to assess for a change in quality of life prior to and after treatment with 15 questions to rate activity. Patients were asked to rate their activity before treatment at the Mayo Clinic and level of activity at the time of the survey. The scale rated activities from 0 (no trouble performing activity) to 4 (impossible to perform the activity). The sum of scores was added up to calculate quality of life from 0 (no disability) to 60 (inability to function).

Results

The Raj¹(2009) study, a single-blind RCT, compared a low dose of 20 mg propranolol vs placebo in POTS patients to measure symptom burden immediately before and at 2 and 4 hours post drug administration. The study included patients referred to the Vanderbilt University Autonomic Dysfunction Center with POTS between November 2003 and September 2008. Patients met the diagnostic criteria for POTS and had at least 6 months of symptoms and were at least 18 years of age. Exclusion from the study included patients with existing comorbid conditions, taking medications that could alter autonomic tone, and the administration of fludrocortisone within 5 days of testing. Patients were predominately female with a mean age of 34 years. There was no difference in symptoms scores at baseline between the propranolol and placebo groups.¹ The decrease in total symptom burden was shown to be significantly greater with 20 mg propranolol from baseline to 2 hours post treatment ($p = 0.044$). At 4 hours post treatment, symptom burden was significantly lower after administration of propranolol vs placebo ($p = 0.045$). The study revealed that propranolol decreased each component symptom of the Vanderbilt POTS symptom score more than placebo.¹ The study also revealed that there was

no significant difference between low dose (20mg) and high dose (80 mg) of propranolol in lowering total symptom score, revealing that a low dose is sufficient to improve symptom burden of POTS. This trial was safe and there were no reported adverse effects to treatments.

Table 2. Symptom Score with Propranolol 20 mg and Placebo in POTS patients (n=54)

Symptom Score	Before	2 Hours After	4 Hours After
Propranolol 20 mg	17	9.5	10
Placebo	16	15	12.5
P-Value (between Propranolol 20mg and placebo)	0.385	0.012	0.007

*Values expressed as a group of means

The Coffin²(2012) study, a single-blind RCT, compared 0.2 mg of desmopressin (DDAVP) to placebo in POTS patients to measure changes in symptom burden immediately before, 2, and 4 hours post drug administration. The study included patients referred to the Vanderbilt University Autonomic Dysfunction Center with POTS between November 2003 to September 2008. Patients met the clinical diagnostic criteria for POTS with at least 6 months of symptoms and were at least 18 years of age. Patients with an existing comorbid condition known to cause orthostatic intolerance, on prolonged bed rest, and under 18 years of age were excluded from this study. The study included 30 patients who met the previous criteria, the majority female (26) with a mean age of 37 years. Symptom ratings were similar between the DDAVP and placebo prior to treatment ($p = 0.99$). Symptom score was significantly better at 2 hours post treatment for patients treated with DDAVP versus placebo ($p < 0.001$).² DDAVP also led to a significantly better symptom score at 4 hours post treatment vs placebo ($p = 0.006$).²

There was a significant reduction of palpitation with DDAVP ($p = 0.023$) and a strong, but not statistically significant reduction of visual disturbance with the drug vs placebo ($p = 0.086$).²

This study was safe and there were no reported adverse reactions to therapy in either group.

Table 3. Symptom Score with desmopressin (DDAVP) 0.2 mg vs placebo

Symptom Score	Before	2 Hours Post	4 Hours Post
DDAVP 0.2 mg	18 ± 18	13 ± 15	13 ± 16
Placebo	18 ± 17	19 ± 16	19 ± 18
P-value (between DDAVP 0.2mg and placebo)	0.587	0.001	0.009

*Values expressed as means ± standard deviation

The Lai³(2009) study, a retrospective case control study, surveyed POTS patients seen at the Mayo clinic and prescribed medication for symptom relief. The most commonly prescribed medications compared in this study were midodrine (n=13) and β -blockers (n=14). The study included patients seen at the Mayo Clinic from 2002 through 2005 for POTS and excluded patients over the age of 18. Patients treated with midodrine vs β -blockers in this study were not statistically different in terms of age, gender, and change of baseline heart rate from initial evaluation to survey completion.³ On the Walker Functional Disability Inventory (WDFI) survey, patients had more functional disability prior to receiving treatment at the Mayo Clinic. Initial scores were similar before evaluation at the clinic in patients treated with midodrine vs a β -blocker ($p = 0.126$).³ Patients who were given a β -blocker reported a greater improvement in functional ability than patients who were treated with midodrine ($p = 0.004$).³ When compared

to patients who were not given a β -blocker or midodrine, patients in the β -blocker group had a significant improvement in their WDFI score ($p = 0.046$), whereas midodrine compared to the same group showed no significant difference.³ This study indicated that overall improvement in functional ability and quality of life in patients with POTS appears to be greater when patients are treated with a β -blocker. The absolute benefit increase (ABI) was calculated to be 10.9% in patients treated with midodrine or β -blocker compared to other existing treatments for POTS. This study also revealed a calculated numbers needed to treat (NNT) of 9. This study was safe and there were no reported adverse effects from medication treatment. A total of 13 patients were lost to follow up during this study.

Table 4. Effects on POTS symptoms in patients treated with Midodrine vs β -Blocker

Symptoms	Midodrine (n=13)	β -blocker (n=14)
Improved	6	8
Worsened	3	4
No Change	4	2

Discussion

This systematic review compared the use of pharmacologic therapy used for blood pressure control for the use in patients with POTS to relieve symptoms and improve the quality of life in these patients. Currently, β -blockers are considered in the treatment for POTS patients, however there is no gold-standard treatment in existence and patients are treated with a “trial and error” approach. The review of the 3 studies used in this review reveal that β -blockers, including propranolol at a low dose of 20 mg daily, show a statistically significant improvement in patient

reported symptoms. Another method of treatment to relieve symptoms in POTS includes desmopressin at a low dose of 0.2 mg. When comparing methods of blood pressure control, it was also proven that β -blockers show a more significant improvement than midodrine in the relief of patient reported symptoms. These studies found that medications that have the ability to reduce HR can be effective in reducing standing HR and improvement of symptoms in patients with POTS.¹ Beta-adrenergic blockade is a relatively safe treatment modality to use in patients with POTS of the risk profile of the medication class is understood. Based on side effect profile, β -blockers could safely be used in POTS patients without the existence of an additional comorbid condition such as heart failure, reactive airway disease, diabetes, or peripheral artery disease, as β -adrenergic blockade can all exacerbate these illnesses. It is also important to note the effects of acute withdrawal from β -blockers caused by increased sympathetic activity. Acute withdrawal from the drug could worsen POTS since it is thought to be associated with an increased sympathetic tone at baseline.

Desmopressin as another treatment possibility for POTS patients studied in this review shows promising results for reduction in standing HR and improvement of symptoms. DDAVP has a major potential side effect of hyponatremia based on increasing free-water retention.² Once daily dosing of desmopressin at a low dose of 0.2 mg did not show any harm in the study, however practitioners should be cautious to prescribe DDAVP as a daily medication in POTS patients due to the risk of hyponatremia.² Serum sodium levels should be routinely checked in patients taking DDAVP for hyponatremia. Based on overall evaluation, β -blockade appears to be a safer and more effective treatment for symptoms in patients with POTS.

Limitations of this systematic review include the lack of research on POTS and effective treatment modalities. A major limitation to consider is that the Raj and Coffin studies were both performed at Vanderbilt University, utilizing their scoring system for POTS symptoms. A short follow up time is another limitation to consider concerning 2 of the studies used in this review. A 4 hour follow up window makes it difficult to assess and predict the long-term efficacy of the treatment modalities studied. It is also difficult to predict the long-term safety and tolerability of β -blockers and DDAVP for the treatment of POTS.^{1,2} The Coffin study also had a relatively small sample of patients.² The Lai study states that a patient selection bias may have occurred because the sample population included only POTS patients willing to take a survey. These patients may have only completed and returned the survey because they had a good experience at the Mayo Clinic or actually had improvement of the symptoms.³ The Lai study also had a high dropout of patients who participated in the study. Of the 121 adolescents seen at the Mayo Clinic for POTS, only 47 patients returned completed surveys.³ Other limitations of the study include the restrictions involved in a retrospective survey, the survey basis on subjective patient feedback, and the relatively small sample size.³

Conclusion

Pharmacologic therapy for blood pressure control is an effective treatment to improve symptoms and quality of life in patients with POTS. Two studies showed evidence in symptom improvement compared to placebo and one showed effectiveness of β -blockers over the use midodrine. Two studies indicated that symptom relief occurs as soon as 2 and 4 hours post treatment with either a β -blocker or desmopressin. The Lai study indicated that symptom relief and improvement in functional ability also occurs over the longer term with treatments such as

β -blockers and midodrine, also revealing that β -blockers are the more effective treatment option in POTS patients. The studies also revealed that the use of low dose propranolol (20 mg) and DDAVP (0.2 mg) is safe and shows no concerning adverse effects for the treatment of POTS in the absence of comorbidities.

Due to the relatively small sample size used in these studies and the short follow up time, it would be beneficial for future studies to follow patients over a longer period of time to observe symptom improvement over the long-term. This would also be helpful in assessing the safety of the treatment modalities for chronic treatment for POTS symptoms. Future studies could also show benefit by comparing multiple treatment options against each other rather than simply observing one option compared to a placebo. Lastly, future studies comparing the control of catecholamines vs β -adrenergic blockade in POTS would be beneficial for the understanding of underlying mechanisms, therefore provide better control of symptoms in patients. With the lack of research available for the treatment of postural orthostatic tachycardia syndrome, it seems that β -adrenergic blockade and DDAVP are safe and effective treatment options for improving symptom burden and quality of life in POTS patients.

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