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The Study of Diffrent Therapeutic Methods of Midodrine Hydrochloride In the Treatment of Postrual Orthostatic Tachycardia Syndrome (POTS). (In Children)

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Abstract: Postural orthostatic tachycardia syndrome (POTS) is a very common and has a serious impact on children's life. The medication of Midodrine hydrochloride is an very effective treatment in Orthostatic hypotension as well as POTS. The study was designed to examine the therapeutic efficacy and strength of midodrine hydrochloride by quantifying changes in blood pressure during the head-up test (HUT) and Head up Tilt Test in children with POTS.

Midodrine hydrochloride is used clinically in children to treat postural tachycardia syndrome (POTS), but sometimes it is not effective in all patients. This study was designed to evaluate the therapeutic efficacy of midodrine hydrochloride in children with POTS to find changes in the heart rate response and its predictive value.

Postural tachycardia syndrome (POTS) can be defined by the symptoms of orthostatic intolerance in associated with excessive tachycardia. The patients of POTS experience number of problems in daily life as like shopping, playing, housework, eating, and attending work or school. As a vasoconstrictor, midodrine hydrochloride has been reported to improve symptoms and suppress permanent heart rate. Postural tachycardia syndrome is an abnormal increase in heart rate which occurs after sitting up or standing. Some typical symptoms including like dizziness and fainting. In some cases of people they have mild symptoms, while others find the condition affects their quality of life. POTS often raise up with the time, and there are some medicines and self-care remedies that can help in the treatment. In this article we studied about the some diifrent method and their conditions in the treatment of POTS.

Keywords: Posrtrual trachycardia syndrome(POTS), midodrine hydrochloride, blood pressure, dizziness and fainting, etc.

INTRODUCTION:

Postural tachycardia syndrome (POTS) is one of the general forms of chronic (at least 180 days) orthostatic intolerance (OI), and it shows in most of the cases loss of consciousness symptoms accompanied by inappropriate sinus tachycardia with normal blood pressure in an upright position. The enatvating condition of POTS is frequently accompanied by orthostatic discomforts including lightheadedness, presyncope, momentary "blackout," blurred vision, headache, giddiness, pale complexion, cognitive difficulties, sleep disturbances, fatigue, and even sudden syncope. Sometime patient of postural tachycardia syndrome shows signs of excessive sympathoexcitation such as chest tightness, palpitations, inappropriate vasomotor skin changes, excessive sweat. For children and teenaged, the diagnostic criteria of POTS include discomforts of orthostatic Iintolerance together with a normal supine heart rate (HR) and HR increase of at least 40 beats per minute or a maximum HR gets over 130 beats per minute for children aged between 6–12 years or more than 125 bpm for teenaged aged 13–18 years in the first 10 min of an active standing test or during the passive head-up tilt test (HUTT) without orthostatic hypotension shown by a reduction in systolic blood pressure (SBP) more than 20 mmHg or a reduction in diastolic blood pressure (DBP) which is more than 10 mmHg. The Postural tachycardia syndrome is odd disorder has more possible basic causes, such as fever, anemia, dehydration, hyperthyroidism, myocardial damage, and autonomic neuropathies. Once a specific cause of disorder is identified, the POTS label should be throw out in favor of the appropriate disease term.

What happens in PoTS:

Normally when you sit up or stand, gravity pulls some of your blood down to your belly area, hands and feet. In response, your blood vessels quickly narrow and your heart rate increases slightly to maintain blood flow to the heart and brain, and prevent blood pressure dropping.

This is all done without needing to think about it, by the autonomic nervous system – the nervous system in charge of automated body functions.

In POTS, the autonomic nervous system does not function properly. When you become upright, the blood supply to the heart and brain decreases and the heart races to compensate.

Symptoms of PoTS

- Sometimes you can get symptoms almost immediately, or a few minutes after sitting up or standing. Lying down may relieve from the condition.
- dizziness or lightheadedness
- fainting
- problems with thinking, memory, reminding and concentration – this combination of symptoms is also called "brain fog"
- heart palpitations
- shaking and sweating
- weakness and fatigue (tiredness)
- headaches
- poor sleep
- chest pain
- feeling sick
- shortness of breath

METHODS:

- **Method I**

This potential study was approved by the Ethics Committee of Peking University First Hospital (Beijing, China). All children guardians were completely informed of the purpose and methods of our study, and informed assent was obtained. Children who has shown symptoms of orthostatic intolerance (OI) and were diagnosed as having POTS by the head-up test (HUT) or head-up tilt test (HUTT) between June 2008 to August 2011 at Peking University First Hospital were registered as POTS group. The Healthy children without a history or any record of OI and with a negative result to the HUT they were selected as the Control group. For the defining POTS the present study used the specific criteria, as like (i) A child has a normal heart rate when supine and no any record of cardiovascular or heart disease, (ii) after standing up or getting out of bed the following symptoms are shown in child viz are dizziness, chest distress, chest pain, headache, palpitations, pale face, amaurosis, fatigue, discomfort, or syncope. These symptoms should be relieved or recoverd by recumbence and should occur repeatedly for one month, (3) in addition to symptoms of OI, the child shows a increase in heart rate upto 30 beats/min or a heart rate >120 beats/min within the first 10 minutes after standing or during HUT or HUTT. Simultaneously, the decrease in blood pressure should be less than 20/10 mm Hg, and (4) children with other diseases that exhibit symptoms in the autonomic nervous system (eg., anemia, arrhythmia, hypertension, endocrine disorders) as well as cardiac or neurologic diseases that would be inspire the syncope were excluded.

Table No. 1 Baseline characteristics of study participants- (Ref no. 1)

Characteristics	POTS Group (n ¼ 108)	Control Group (n ¼ 20)	t or Chi-Square Value	P Value
Male/female	48/60	8/12	0.135	0.713
Age (yrs)	12 ±3	12 ±4	0.015	0.988
Height (cm)	151±14	146 ±20	1.021	0.318
Body weight (kg)	42 ±13	46±22	0.797	0.434
Baseline diameter of brachial artery (mm)	3.0±0.4	3.0±0.5	0.518	0.605
FMD (%)	11.0±3.3	5.6±2.2	7.057	<0.001
Mean artery pressure (mmHg)	81±8	79±10	1.090	0.278
Supine heart rate (beats/min)	76±10	77±13	0.123	0.903
Increased heart rate during HUT (beats/min)	38±9	7±7	0.107	<0.001
Symptom score	4.0±2.2	0	—	—

The protocol for HUT or HUTT was following according to the previously published literatures. Measurement of FMD was taken by using a color Doppler ultrasound system (Ultrasound Cardiograph, HP2500, Philips Healthcare, Andover, Massachusetts), and the frequency of the transducer was 7.5 MHz.

Children with POTS who gets Midodrine HCl (2.5 mg/day without other medications or drug) for treatment were followed upto 3 months by telephone or by active clinic visits. During follow up, the symptoms of POTS and frequency of occurrence of each patient were recorded at two time points (1st month and 3rd month) to evaluate and examine the therapeutic effects of MD Patients who visited the clinic after 1 month were re-evaluated for HUT and FMD of the brachial artery. Symptom scoring was applied to check or evaluate the therapeutic effect of Midodrine hydrochloride. Scorings were mainly based on the typical symptoms of OI, including dizziness or lightheadedness, syncope, nausea, chest tightness, palpitation, and headache. The score or range for every symptom was detected by its frequency according to the scoring system. If the any patient or child had never suffered from any of the mentioned symptoms, he or she gets a score 0; also symptoms shows or experienced less than once per month, a score is 1; if 2 to 4 times per week, a score is 2; if 2 to 7 times per week, a score is 3; and if symptoms shows more frequent than once per day, a score is 4. The sum of all symptom scores

was the total symptom score. Symptom scoring was performed for every patient or children at the beginning of treatment and after 1 month of therapy using MD.

Table No. 2 (Ref no. 1)

Comparisons of symptom scores and changes in heart rate and flow-mediated vasodilation before treatment in children with postural orthostatic tachycardia syndrome children with different responses to midodrine hydrochloride

Time of Follow-Up (months)	Subjects	Cases	Symptom Score		HR (beats/min)	FMD (%)
			Before Treatment	After Treatment		
1 (n = 108)	Responders	90	4.1 ±2.3	0.5 ±1.0	37 ± 8	12±3*
	Non-responders	18	3.8 ±1.7	3.0 ±1.8	41 ±11	9±2
3 (n ¼ 105)	Responders	95	4.1 ± 2.3	0.4 ±0.9	37 ±8	11 ±3*
	Non-responders	10	3.7 ±1.4	2.9 ± 1.6	43 ±15	8 ±2

HR = increased heart rate during Head Up Test (HUT).

Compared with the non-responders after 1 month of therapy, $p < 0.05$.

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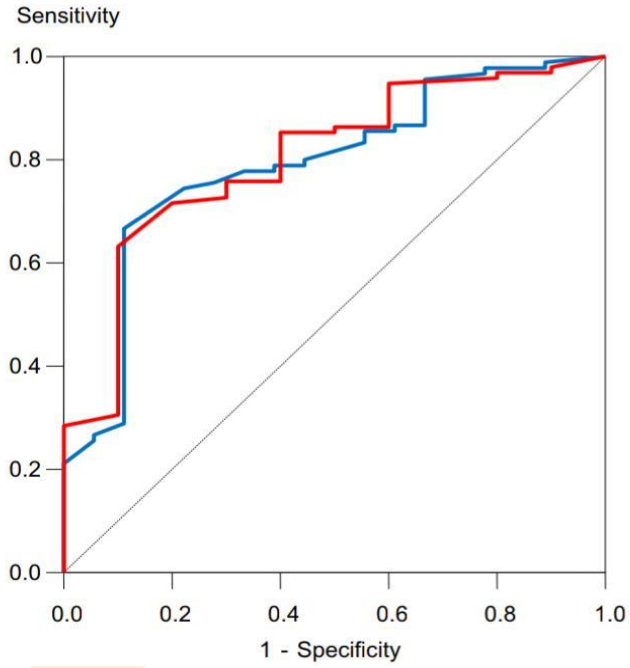

Fig. 1 Receiver operating characteristic (ROC) curve

The figure shows ROC of different cutoff values of FMD for predicting the therapeutic effect of MD treating in children with POTS. The vertical coordinates shows or indicate sensitivity of prediction as well as the horizontal coordinate indicates pseudo-positive rate (1-specificity). The dotted slope or line is a known as consulting line on which the sensitivity is equal to pseudo-positive rate, which means there is no predictive value. The red coloured curve stands for predictive value of different cut-off values also the blue coloured curve shows ROC on predictive value of FMD for 1 month therapy, and the AUC is 0.790 (95% CI: 0.679 to 0.902; p <0.01)

A receiver operating characteristic (ROC) curve was used to evaluate the value of FMD for predicting the therapeutic effect of MD. The predictive value of FMD was shown by the area under the curve (AUC). The intension that FMD is a predictor of the therapeutic effects of MD for treating children with POTS would be supported if p 0.9 reflected a high predictive value.

Conclusion of this method-

In total, there were 108 children who affected by POTS group and 20 children in the control group. Symptom scores of children in the control group were 0. Baseline data are shown in Table 1. The values for brachial arter baseline diameter and FMD detected by 2 operators were correlated, and there was no significant difference between them (Table 2). During treatment with MD, all 108 patients were re scored to assess the potency of MD after 1 month of therapy, whereas 105 were rescored after 3 months. Data on 3 children were not available at the final phase because the parents of the participanting children refused for their children to be followed up. Compared with baseline symptom scores (4.0 _ 2.2), higher symptom scores were reduced significantly after 1 of month treatment (1.0_1.5; p <0.05) and 3 months of treatment (0.6_1.3; p<0.05).HUTwas performed and FMDwas measured again for 68 patients who returned to clinic after 1 month of therapy. There was no difference in baseline characteristics (age, gender, height, weight, mean artery pressure, FMD, increased heart rates duringHUT, symptomscore) between the patients who had repeat HUT and those who did not (p >0.05, Supplementary Table 1). The increased FMD values and excessive heart rate during HUT were reduced significantly after treatment withMD(FMD: 11_3%at baseline to 8_3% after 1 month, p <0.05; delta heart rate: 38 _ 9 beats/min at baseline to 30 _ 11 beats/min after 1 month, p <0.05). The data of symptom scores, changes in heart rates during HUT/HUTT, and FMD values before treatment were compared between the responders and nonresponders to MD at various time points during follow-up (Table 3). There was a significant difference between responders and nonresponders with regard to FMD before treatment (p <0.05). The ROC curve (Figure 1, blue curve) denoting the predictive value of FMD for 1 month of therapy showed that the AUC was 0.790 (95% CI: 0.679 to 0.902; p <0.001); the ROC curve (Figure 1, red curve) for 3 months of therapy showed the AUC was 0.803 (95% CI: 0.669 to 0.936; p < 0.01), suggesting a moderate predictive value. Using an FMD value before treatment of 9.85% as a cut-off value, sensitivities

and specificities of 1-month therapy and 3-month therapy to predict the therapeutic effects of MD for treating POTS were calculated (1 month sensitivity 74.4% and specificity 77.8%; 3-month sensitivity: 71.6% and specificity: 80%).

- **METHOD II-**

Fifty-three children having symptoms of POTS were divided into four groups. Group I (Midodrine hydrochloride + Methods and Results: conventional therapy), group II (metoprolol + conventional therapy) and group III (conventional therapy). Standing test was conducted for all childrens. The improvement rate, cure rate, effective rate and symptoms scoring were compared among the three groups. A Kaplan–Meier survivorship curve was used to For describe the proportion of symptom-free cases during a long term follow-up. Before the standing test, all participants underwent diagnostic tests that were unable to determine their etiology. The diagnostic protocol consist of a full record history, physical examination, chest X-ray, electrocardiography, electroencephalography, and biochemical screening of participants. When the results of all of the aforesaid determinations were negative and the patient was diagnosed as POTS by standing test,1 he or she was included in our study. Patients with central nervous system disorders, metabolic disorders hypertension, orthopedic ailments, systemic disease, and cardiogenic diseases were excluded.

Protocol of Method II-

In this method 53 childrens are involved as patients who was between October 2007 to June 2010, (included 22 boys and 31 girls; age 12.2±2.4 years; range, 6 to 17 years) with the symptoms of POTS were admitted into the Department of Pediatrics, Peking University First Hospital. The symptoms included exercise intolerance, visual blurring or tunneling, nausea, lightheadedness, palpitation, chest wall pain, tremulousness, headache, occasionally syncope, and near syncope. A total of 53 patients were divided into three groups. Group I consist of 19 patients given midodrine hydrochloride as first-line therapy along with conventional therapy, involving increased intake of water and salt, evasion of predisposing situations, artifice to prevent blood from pooling in the lower extremities (leg crossing) and to abort the episode (supine posture) and reassurance regarding the condition's non-life-threatening nature, and the dose of midodrine hydrochloride was 2.5mg once in day. Six Patients took midodrine hydrochloride at 6 o'clock in the morning. Group II consists 19 patients given metoprolol as first-line therapy along with conventional therapy, and the dose of metoprolol was 0.5mg twice a day. Group III comprised 15 patients who only treated with conventional therapy. The course of this treatment was upto 3 to 6 months.

Standing Test Protocol-

All patients was also treated with the standing test. The test was occured in the same quiet room with the temperature of 25°C and mild light in the morning. It was preceded by 10min of observation in the supine position, electrocardiogram, blood pressure and heart rate were recorded before the test by using the Dash 2000 Multileads Physiological Monitor (GE company, U.S.A). The tilt angle during orthostatic stress was 90°. Then blood pressure and heart rate were monitored as well as electrocardiogram was recorded simultaneously during the test. However, the patients were settled in the supine from the standing position as soon as the positive response or symptoms of OI occurred. A sustained heart rate increase with >30 beats/min or a sustained heart rate reached upto 120beats/min in the first 10min of passive upright tilt is considered diagnostic.

Table 3. Baseline Clinical Data of Children in 3 Groups- (Ref no. 2)

Points	Group I	Group II	Group III	F	X2	P value
N	19	19	15			
Age (years)	12.5±2.2	12.4±1.9	11.5±3.1	0.922		0.404
Baseline SBP (mmHg)	104±9	109±11	110±7	2.463		0.095
Baseline DBP (mmHg)	64±9	68±10	70±6	2.135		0.129
Baseline HR (beats/min)	77±12	79±10	73±10	1.015		0.37
Short term follow-up (months)	4.9±1.4	4.4±1.9	5.6±0.9	2.844		0.068
Long term follow-up (months)	14.8±4.1	15.6±3.6	14.4±5.6	0.357		0.702
Baseline symptom score	5.2±0.8	5.0±0.9 0.683	5.0±0.8	0.384		
Symptom score after treatment	1.1±2.2*,	2.8±2.4*	3.7±2.0	6.021		0.005
Improvement	4	3	5			
Cure	13	8	3			
Cure rate (%)	68.42%*,	42.11%	20.00%		8.053	0.018

Effective	17	11	8			
Ineffective	2	8	7			
Effective rate(%)	89.47%*	57.89%	53.33%		6.393	0.041

Clinical Curative Outcome:

We used the criterion of symptoms scoring in assesment the symptom severity of children with POTS. The standard of scoring symptom is that 0–4 score represents the severity of syncope, dizziness, palpitation, chest distress, nausea, headache and blur, respectively. A score of 0 represents no symptoms shown in patient. A score of 1 represents one episode of one symptom per month. A score of 2 represents 2 to 4 episodes of one symptom per month. A score of 3 represents 2 to 7 episodes of 1 symptom in every single week. A score of 4 represents more than 1 episode of 1 symptom in a single day. We examined and scored the OI symptoms before therapy and 3 months to 6 months after treatment, respectively. Then, we compared the clinical data and standing test results of post-treatment with pre-treatment. Cure was defined by disappearing the symptoms of OI. The OI symptoms decreased by 50 percent or more were regarded as betterment, and if they decreased less than 50 percent, it indicated as inefficacy. The cure rate was determined as (the number of patients who were cured or curative at short term follow-up)/(the total number of patients). The improvement rate of patient was equal to (the number of patients who were improved or at short term follow-up)/(the total number of the patients). The effective rate of patient was equal to (the number of patients who were curative + the number of patients who were improved at short term follow-up)/(the total number of patients). The Inefficacy was such that patients could not recover or curative nor improved during short term follow-up.

Follow-up

All patients underwent short-term follow-up after treated for 90 to 180 days and long-term follow-up for calculate their potential efficacy. The long term follow-up period upto 15.0±4.3 months (range, 5 to 24 months). It involved eliciting information about symptom re-examination, recurrence of standing test and obtaining information about adverse events of drug. All patients were followed up by an experienced interviewer.

Table No. 4

Midodrine and POTS in Children: (Ref no. 2)

	Group I	Group II	Group III
Number of patients (n)	19	19	15
Systolic BP			
Difference before treatment	2.8±2.3	4.3±1.7	1.1±1.0
Difference after treatment	4.3±1.5	3.3±1.3	3.3±1.5
T	–0.694	0.454	-1.101
P Value	0.496	0.655	0.289
Diastolic BP			
Difference before treatment	3.0±1.7	7.0±2.4	2.5±1.2
Difference after treatment	7.5±1.2	4.4±1.2	5.5±2.0
T	–2.050	1.132	–1.345
P Value	0.055	0.273	0.200
Heart rate			
Difference before treatment during standing test	38±2.4	36±1.3	35±1.9
Difference after treatment during standing test	21±1.4*	** 25±1.9**	28±2.6**
T	6.037	5.377	2.189
P Value	0.000	0.000	0.046

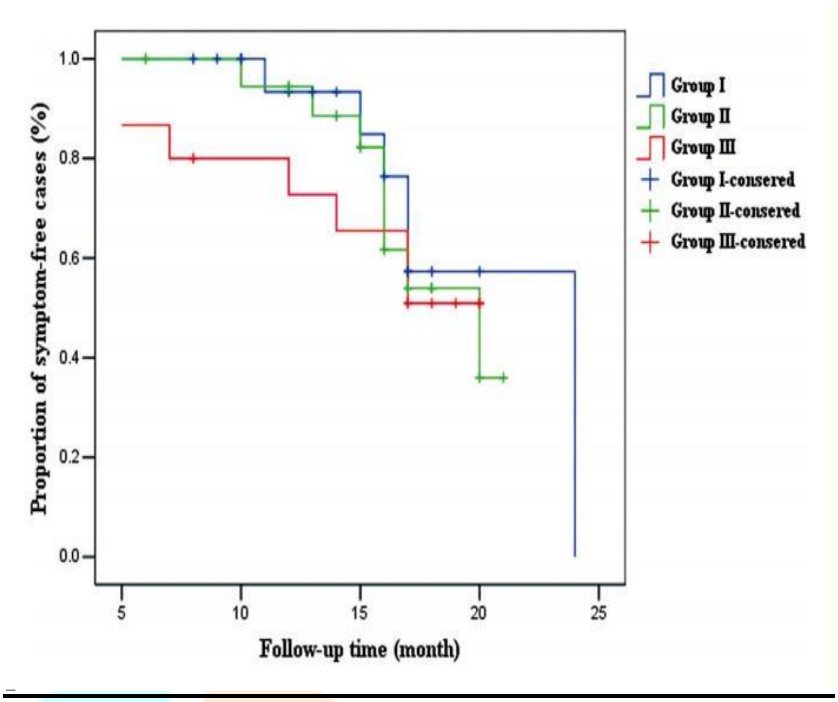

Fig.2 Kaplan–Meier survivorship

Figure. curve with follow-up rate as an assesment of symptom improvement. The proportion of symptom-free cases in group II and group III was significantly lower than group I respectively, during follow-up.

Statistical Analysis-

Results which are found to be normally distributed are expressed as mean±standard deviation. If results are not normally distributed, they are reported as median and range. Continuous variables were compared using Student's t-test and differential analysis; specific variables were compared using Fisher's exact test. A Kaplan–Meier survivorship curve and log-rank test were used to describe the long term follow-up rates of symptom-free cases every month. All content were analyzed using SPSS version 10.0 (SPSS Inc, Chicago, IL, USA) for Windows.

Side Effects During Treatment

The blood pressure of three patients slightly increased during taking midodrine hydrochloride, and systolic blood pressure increased by 5mmHg compared to that before therapy, but they did not have relevant symptoms. One child had side effect such as pain in stomach during taking midodrine hydrochloride. These children could keep on taking midodrine hydrochloride and did not shows to have any side effects while taking metoprolol.

Results-

The baseline characteristics of children in the three groups were listed in Table 3. The age, There was no significant difference in age, baseline symptom score, baseline systolic blood pressure, baseline diastolic blood pressure, baseline heart rate, short-term follow-up, and long-term follow-up. Group I, Group II and Group III (P>0.05) (Table 3).

The Outcome After Short-Term Follow-up, in group I, the OI symptoms in 13 out of 19 children disappeared and in 4 (4/19) children improved after treatment. In group II, the OI symptoms in 8 children out of 19 improved after treatment, and the treatment for 6 children out of 19 children was ineffective compared to pre-treatment. In group III, the OI symptoms in 5 (5/15) children improved after treatment, and the therapy for 7 (7/15) children was ineffective compared to pre-therapy (Table 3). The cure rate at the end of short-term follow-up in group II and group III was significantly lowert than that of group I (68.42% vs. 42.11% and 20.00%, P0.05) (3 Table). The systolic blood pressure difference and diastolic blood pressure difference after

therapy did not vary from those before therapy in every group (P>0.05). The heart rate difference after treatment during standing test was lower than that before treatment (P is less than 0.05)

The Symptom Score Outcome After treatment, the symptom score in group I was significantly lower than group II and group III, respectively (1.1±2.2 vs. 2.8±2.4 vs. 3.7±2.0, (P>0.05) (Table no 3)

The result of Long-Term Follow-up During long-term follow-up, we founded that the symptom recurrent rate in group I was significantly lower than group II and group III, respectively (P>0.05) , but it did not differ significantly between group II and group III. Meanwhile, the results showed that the time of symptom improvement in group I was shorter than group II and III (Figure 2).

Conclusion:

From the study of both method we can say that Midodrine hydrochloride is effective and useful in the treatment of Postrual orthostatic tachycardia syndrome in children.

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