Short- and Long-Term Outcomes of Children with Cyclic Vomiting Syndrome

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Objective: *To determine the efficacy of prophylactic pharmacotherapy on the short- and long-term outcomes of children with cyclic vomiting syndrome (CVS).*

Material and Method: *Medical records were reviewed in 32 children who were diagnosed with CVS between 2000 and 2013. Efficacy of prophylactic medications was classified as good vs. no response after treatment for three to six months. Long-term outcome was evaluated in patients who had been diagnosed for ≥2 years and classified as 1) excellent: no episode, 2) good: one to two episodes, and 3) poor: three episodes or more during the past year.*

Results: *At three to six months after treatment, good response to amitriptyline was significantly higher than propranolol (73% vs. 36%, p = 0.04). Of the 24 CVS patients who had been diagnosed ≥2 years, data was available in 19 patients (mean age, 11.3±4.9; and mean duration from diagnosis to follow-up, 6.3±3.3 years). Excellent outcome was achieved in seven, good in seven, and poor in five children. Overall, the favorable long-term outcome (good and excellent) was 74%. Most children (86%) who had favorable long-term outcome had good response to the prophylactic medications in the early period of treatment.*

Conclusion: *Amitriptyline may be more effective than propranolol for prophylaxis of CVS. However, a randomized controlled trial is required to confirm this result. Children with CVS have a relatively favorable long-term outcome, particularly those who initially responded well to the prophylactic medications.*

Keywords: *Cyclic vomiting syndrome, Functional gastrointestinal disorder, Migraine, Vomiting*

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Cyclic vomiting syndrome (CVS) is a disorder characterized by recurrent episodes of severe vomiting with symptom-free intervals between the episodes and stereotypic pattern within individuals[1]. CVS can involve all age groups including adults[2] but commonly presents in childhood and occurs approximately 2% of school-aged children[3,4]. A population-based study in Ireland has shown the incidence of 3.1 per 100,000 children per year[5]. The etiologic mechanisms of CVS remain unknown but likely due to mitochondrial dysfunction, hypothalamic-pituitary-adrenal axis stimulation and autonomic dysfunction[6]. Many studies have suggested that CVS is associated with migraine headache, as many patients develop migraine headache during adolescence, and family history of migraine headache is common[7-9]. There are no specific diagnostic investigations for CVS; therefore, diagnosis is based on characteristic clinical manifestations[6,10,11]. Although CVS is a functional gastrointestinal disorder[10,11], patients and their family usually suffer from repetitive severe symptoms, frequent admissions to hospital and school absenteeism[5,6]. Moreover, delayed diagnosis is common, typically two years from the disease onset, resulting in treatment delay[6,12,13].

Key management of CVS includes supportive treatment during acute episodes and prophylactic therapy[1]. The most commonly used prophylactic medications are antimigraine agents including cyproheptadine, propranolol, and amitriptyline[1,14,15]. However, only few studies compared the efficacy of these medications for CVS in children[13,16,17]. The efficacy of other drugs including phenobarbital, sodium valproate, erythromycin, co-enzyme Q10 and L-carnitine has been reported in small studies[18-22]. Moreover, there have been only few studies on the long-term outcome of CVS in children[12,23-25]. The objectives of the present study were to determine the

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efficacy of prophylactic pharmacotherapy on the short- and long-term outcomes of children with CVS.

Study design

Retrospective cohort study.

Material and Method

Patients younger than 18 years who were diagnosed with CVS at Ramathibodi Hospital between January 2000 and December 2013 were enrolled. Medical records were comprehensively reviewed to gather demographic data, clinical manifestations, associated symptoms, medical conditions, investigations, and prophylactic medications including outcome after the initiation of treatment. In the short-term evaluation, clinical response to prophylactic medications was evaluated at three to six months after initiation of treatment and categorized as: 1) good response: either remission (no attacks after treatment) or markedly improvement, and 2) no response: decreased approximately <50% in the frequency of attack. The authors evaluated all patients who took medications for at least three months including those who received alternatives to the first-line medication. Additional medications were not evaluated if they were used as combination therapy.

Long-term outcome was evaluated in the patients who were diagnosed with CVS for ≥2 years. For those who were lost to follow-up, a questionnaire was sent to the child's guardian to verify current clinical status, severity and frequency of vomiting, age of outgrowing from CVS, an occurrence of migraine headache, and current medications. Long-term outcome was classified by the frequency of vomiting as 1) excellent (resolution): no episode, 2) good: one or two episodes, and 3) poor: three episodes or more during the past year. Patients who had no attacks in the past year but remained on prophylactic medications were classified as good. Migraine headache was diagnosed based on the third International Classification of Headache Disorder[26].

The study was approved by the Ethic Committee of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University, and conformed to the Declaration of Helsinki 1995 (revised in Seoul 2008).

Statistical analysis

Subjects were described using descriptive statistics, such as mean (standard deviation, SD), median (interquartile range, IQR). For the continuous variables, we used student t-tests. The *p*-value of <0.05 was considered statistically significant. Stata 13 (StataCorp, College Station, TX, USA) was used for calculation and statistical analyses.

Results

Between January 2000 and December 2013, 40 pediatric patients were diagnosed with CVS, but only 32 medical records were available for study. Baseline characteristics are shown in Table 1. Blood tests for complete blood count, electrolytes, blood sugar, ammonia, urinalysis, and upper GI series with or without small bowel follow-through were

Table 1. Demographic and clinical data of the study patients (n = 32)

Characteristic	Mean (SD) or numbers (%)
Male, n (%)	17 (53.1)
Age at onset (years)	3.9 (SD 2.6)
Age at diagnosis (years)	6.1 (SD 3.7)
Duration between onset to diagnosis (years)	2.2 (SD 2.8)
Duration of each episode (days)	4.5 (SD 2.3)
Severity at the time of diagnosis, n (%)	
Interval ≤4 weeks	22 (68.7)
Interval >4 to ≤8 weeks	7 (21.8)
Interval >8 to ≤12 weeks	1 (3.1)
Interval >12 weeks	2 (6.2)
Associated symptoms during episodes, n (%)	27 (84.4)
Abdominal pain	19 (59.4)
Lethargy	9 (28.1)
Headache	6 (18.8)
Hypertension	7 (21.9)
Pallor	2 (6.3)
Dizziness	1 (3.1)
Fever	1 (3.1)
Hematemesis	8 (25.0)
Identified triggering factors, n (%)	18 (54.5)
Physical stress	7 (21.9)
Psychological stress/excitement	7 (21.9)
Illness	6 (18.8)
Menstruation	1 (3.1)
Coexisting conditions, n (%)	10 (31.3)
Mental retardation	2 (6.2)
Developmental delay	3 (9.4)
Asthma	3 (9.4)
Allergic rhinitis	3 (9.4)
Growth hormone deficiency	1 (3.1)
Others (Cornelia de Lange, Noonan syndrome, Ehlers-Danlos syndrome)	3 (9.4)
Family history of migraine, n (%)	9 (28.1)

performed in all patients. Other investigations including upper gastrointestinal endoscopy, abdominal ultrasonography, computerized tomography or magnetic resonance imaging of the brain, and investigations for metabolic diseases were performed if clinically indicated. The study flow chart is shown in Fig. 1.

Short-term outcome of prophylactic pharmacotherapy

Prophylactic medications were given in 29 patients (90%) and the first-line medications were propranolol (n = 11), cyproheptadine (n = 4), and amitriptyline (n = 14) with the recommended dosages[1]. We noted 18 out of 29 patients received only the first-line treatment, while 11 patients required alternatives which four required more than two changes in 46 treatment events. The reason for changing the medications was poor response in all except one patient who experienced an adverse reaction. Ten treatments were excluded from the analysis due to treatment duration shorter than three months (amitriptyline 5, propranolol 1, topiramate 1) and the additional drugs for a combination therapy (valproate 1, co-enzyme Q10/L-carnitine 2). Response to treatment (Table 2) was evaluated in the eligible patients receiving the following medications: amitriptyline (n = 15), propranolol (n = 14), cyproheptadine (n = 4), and sodium valproate (n = 3). Proportion of patients who had good response to amitriptyline was significantly higher than propranolol (73.3% vs. 35.7%, $p = 0.04$). Good response to valproate was 33.3%.

Long-term outcome

Of the 24 patients who were diagnosed for ≥2 years, seven patients continued follow-up in our clinic, 12 patients answered the questionnaire, five patients did neither answer the questionnaire nor were reachable, therefore the data for long-term outcome were available in 19 patients. The mean age of the patients at the time of study was 11.3 (SD 4.9) years and the mean duration from diagnosis to last follow-up/contact was 6.3 (SD 3.3) years.

Table 2. Efficacy of prophylactic medications in the short-term study

Medications	Response rate (%)
Amitriptyline (n = 15)	11 (73.3)
Propranolol (n = 14)	5 (35.7)
Cyproheptadine (n = 4)	0
Valproate (n = 3)	1 (33.3)

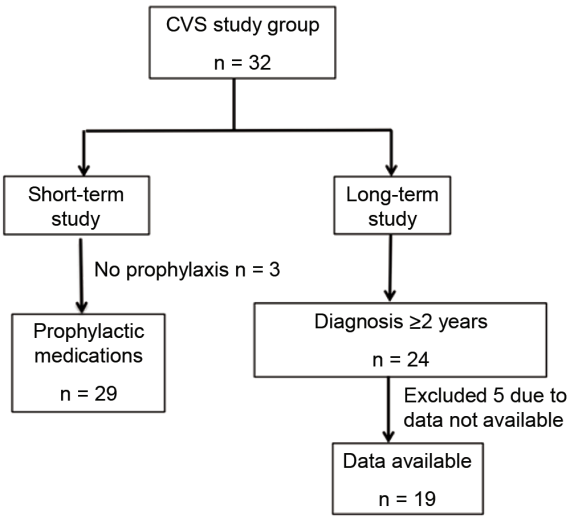

Fig. 1 Flow chart of the study.

Seven patients (37%) had excellent outcome, while seven patients (37%) had good, and five (26%) had poor outcome. The favorable long-term outcome (excellent combined with good outcomes) was then documented in 74% in this cohort. Three patients with good outcome remained on prophylactic medications at the time of study. Among seven patients who had resolution, median age of resolution was seven years (IQR 6-14), median duration of illness was 2.7 years (IQR 1.6-11.2), and one patient developed migraine headache.

Among 14 patients who had favorable long-term outcome, all except two had good response to the first or second-line medications in the early period of treatment (Table 3). Clinical characteristics of the patients with poor outcome are shown in Table 4. Four of the five patients had early onset before two years of age. Four patients had poor response to prophylactic medications and required various alternatives. One patient (case 5) had long-standing course and continued to suffer from frequent episodes. She had poor compliance with treatment and lost to follow-up shortly after diagnosis.

Discussion

The present study demonstrated the outcome of short-term and long-term treatment of children with CVS. The clinical manifestations of CVS in the present study were not different from the previous reports[9,12,13,16]. However, the mean age at onset (3.9 years) was younger and the mean duration of each episode (4.5 days) was longer than previous

Table 3. Patients with good and excellent long-term outcomes and their response to pharmacotherapy in the short-term evaluation

Case	Age at onset (Y)	Age at Dx (Y)	Current age (Y)	1st line Rx		2nd line Rx		Duration of Rx (M)	Long-term outcome
				Drug	Response at 3-6 M	Drug	Response at 3-6 M		
1	8.3	8.5	17.7	Amt	G	-	-	32	Excellent
2	4.6	6.1	14.9	Amt	G	-	-	5	Excellent
3	2.0	14.6	17.2	Amt	G	-	-	12	Excellent
4	2.8	6.4	16.0	Pro	P	Amt	G	33	Excellent
5	1.1	2.5	10.5	Pro	P	Amt	P	6[a]	Excellent
6	4.1	4.3	7.6	Pro	G	-	-	15	Excellent
7	2.1	3.1	13.2	Pro	G	-	-	11	Excellent
8[b]	8.0	8.3	14.5	Amt	G	Estrogen	G	9/24[b,c]	Good
9	6.5	7.2	15.7	Amt	G	-	-	23	Good
10	6.0	8.6	12.7	Amt	G	-	-	43[c]	Good
11	8.0	11.9	16.0	Amt	NA	-	-	NA	Good
12	5.0	6.7	8.7	Pro	G	-	-	3	Good
13	0.5	1.5	10.5	Pro	G	-	-	3	Good
14	5.2	5.8	12.6	Pro	P	Val	G	60[c]	Good

Y = years; M = months; Dx = diagnosis; Rx = treatment; Amt = amitriptyline; Pro = propranolol; Val = valproate; G = good; P = poor; NA = not available (due to less than 3 months of treatment)

[a] Continue treatment in another hospital with unknown duration of treatment.

[b] Patient had remission for 3 years after amtriptyline treatment and subsequently developed recurrent symptoms, triggered by menstruation, which responded well to low-dose estrogen therapy. The duration of treatment was 9 months for amitriptyline and 24 months for estrogen.

[c] Patients remained on treatment at the time of study.

Table 4. Clinical characteristic of the patients with poor long-term outcome

Case	Sex	Age at onset (Y)	Age at diagnosis (Y)	Current age (Y)	Co-existing condition(s)	Previously used medications	Recent medications
1	M	4.5	5.5	9.8	Cornelia de Lange, ADD, developmental delay	Amt, Val	No
2	M	0.5	0.7	2.8	No	Cypro, Pro	Pro, Val, L-carnitine, Co-enzyme Q10
3	M	0.6	2.3	4.4	Developmental delay	Cypro, Amt, Val	Topiramate
4	F	1.0	1.4	3.4	No	Cypro, Pro	Pro, L-carnitine, Co-enzyme Q10
5	F	1.5	2.1	13.3	No	Pro	No

M = male; F = female; ADD = attention deficit disorder; Y = years; Amt = amitriptyline; Pro = propranolol; Val = valproate; Cypro = cyproheptadine

reports[14]. A delay in diagnosis of 2.2 years was relatively similar to previous reports[6,12,13].

No effective abortive or specific treatments are currently available for CVS[1]. Therefore, the goal of treatment is to reduce the frequency and severity of vomiting episodes by life-style modifications, avoidance of triggering factors and prophylactic pharmacotherapy[1]. Our study showed that amitriptyline was more effective than propranolol (73% vs. 36%). Aanpreung et al. reported the efficacy of amitriptyline and pizotifen was not statistically different (83% vs. 50%, $p = 0.14$)[16]. Anderson et al reported the response rate of amitriptyline and cyproheptadine was 91% and 83%, respectively[17]. However, a prospective study

in Iranian children[13] showed that the efficacy of propranolol was significantly higher than amitriptyline (92% vs. 56%). A recent systematic review of prophylactic therapy in CVS children has concluded the response rate of amitriptyline (n = 244) and propranolol (n = 91) was 67% and 86%, respectively[14]. Nevertheless, almost 90% of data on propronalol derived from Haghighat et al report[13] and most studies were retrospective with small numbers of patients. Moreover, differences in inclusion criteria and qualitative measured outcomes in these studies preclude a comparison of efficacy. In addition, an impact of non-medical treatment could also contribute to the results. Due to the limitation of this retrospective study, prospective randomized controlled trials are crucial to compare the efficacy of prophylactic medications.

In contrast with previous report[17], the present study showed that all patients receiving cyproheptadine had no response but the numbers of the patients were small. These patients continued to have frequent episodes despites of various prophylactic medications and were classified in the poor outcome group in the long-term study (case 2, 3, and 4 in Table 4).

There have been only few reports of long-term outcome and most were small studies. About 69% of 26 children reported by Dignan et al[24] and 50% of 18 children reported by Liao et al eventually resolved from CVS[12]. The present study demonstrated the favorable (good to excellent) long-term outcome of CVS children of 74%. Among seven patients who had CVS resolution, duration of illness and age of resolution were 2.7 and seven years, respectively. Recent study by Lee et al[25], of the 28 CVS patients including childhood-onset and adult-onset diseases, 38% had improvement and 23% had resolution by 7.8 years, regardless of prophylactic treatment. Fitzpatrick et al reported that 61% of 41 children with CVS had a resolution of symptoms after diagnosis for four years but the rest continued to experience episodes of vomiting[23]. The authors concluded that the prognostic factors could not be identified since there were no differences in age at onset, age at diagnosis, duration of follow-up, severity at presentation and medication use between the two groups. The present study demonstrated that most patients (12/14, 86%) who had favorable long-term outcome had good response to the first or second-line medications in the early period of treatment. In contrast, four of the five patients who had poor long-term outcome had poor response to prophylactic medications and required various alternatives. It was noted that four of these patients (Table 4) had early onset before two years of age. The association between the early age of onset and poor long-term outcome remains inconclusive due to small sample size. Our findings suggest that poor response to initial treatment might predict a poor long-term outcome; however, further studies with larger sample size and longer duration of follow-up are required to confirm our speculation.

In conclusion, amitriptyline may be more effective than propranolol for prophylaxis of CVS. However, a randomized controlled trial is needed to confirm this result. Children with CVS have a long-standing course, however, they achieve relatively favorable outcome. Poor response to an initial prophylactic medication may lead to a less favorable long-term outcome.

What is already known on this topic?

Cyclic vomiting syndrome (CVS) is mainly a childhood disorder characterized by severe recurrent vomiting with symptom-free periods. Amitriptyline, propranolol, and cyproheptadine are useful for prophylaxis of CVS but comparative studies are rarely reported. Previous studies have suggested that CVS eventually resolves in 50 to 70% of patients.

What this study adds?

Amitriptyline appears to be more effective than propranolol for prophylaxis of CVS in children. Long-term study reveals overall favorable outcome of 74%. Poor response to the initial prophylactic medications may lead to a less favorable long-term outcome.

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Potential conflicts of interest

None.

References

1. Li BU, Lefevre F, Chelimsky GG, Boles RG, Nelson SP, Lewis DW, et al. North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition consensus statement

on the diagnosis and management of cyclic vomiting syndrome. J Pediatr Gastroenterol Nutr 2008; 47: 379-93.
2. Yang HR. Recent concepts on cyclic vomiting syndrome in children. J Neurogastroenterol Motil 2010; 16: 139-47.
3. Ertekin V, Selimoglu MA, Altnkaynak S. Prevalence of cyclic vomiting syndrome in a sample of Turkish school children in an urban area. J Clin Gastroenterol 2006; 40: 896-8.
4. Abu-Arafeh I, Russell G. Cyclical vomiting syndrome in children: a population-based study. J Pediatr Gastroenterol Nutr 1995; 21: 454-8.
5. Fitzpatrick E, Bourke B, Drumm B, Rowland M. The incidence of cyclic vomiting syndrome in children: population-based study. Am J Gastroenterol 2008; 103: 991-5.
6. Li BU, Misiewicz L. Cyclic vomiting syndrome: a brain-gut disorder. Gastroenterol Clin North Am 2003; 32: 997-1019.
7. Li BU, Murray RD, Heitlinger LA, Robbins JL, Hayes JR. Is cyclic vomiting syndrome related to migraine? J Pediatr 1999; 134: 567-72.
8. Lin YP, Ni YH, Weng WC, Lee WT. Cyclic vomiting syndrome and migraine in children. J Formos Med Assoc 2011; 110: 382-7.
9. Fleisher DR, Matar M. The cyclic vomiting syndrome: a report of 71 cases and literature review. J Pediatr Gastroenterol Nutr 1993; 17: 361-9.
10. Hyman PE, Milla PJ, Benninga MA, Davidson GP, Fleisher DF, Taminiau J. Childhood functional gastrointestinal disorders: neonate/toddler. Gastroenterology 2006; 130: 1519-26.
11. Rasquin A, Di Lorenzo C, Forbes D, Guiraldes E, Hyams JS, Staiano A, et al. Childhood functional gastrointestinal disorders: child/adolescent. Gastroenterology 2006; 130: 1527-37.
12. Liao KY, Chang FY, Wu LT, Wu TC. Cyclic vomiting syndrome in Taiwanese children. J Formos Med Assoc 2011; 110: 14-8.
13. Haghighat M, Rafie SM, Dehghani SM, Fallahi GH, Nejabat M. Cyclic vomiting syndrome in children: experience with 181 cases from southern Iran. World J Gastroenterol 2007; 13: 1833-6.
14. Lee LY, Abbott L, Mahlangu B, Moodie SJ, Anderson S. The management of cyclic vomiting syndrome: a systematic review. Eur J Gastroenterol Hepatol 2012; 24: 1001-6.
15. Forbes D, Withers G. Prophylactic therapy in cyclic vomiting syndrome. J Pediatr Gastroenterol Nutr 1995; 21 (Suppl 1): S57-9.
16. Aanpreung P, Vajaradul C. Cyclic vomiting syndrome in Thai children. J Med Assoc Thai 2002; 85 (Suppl 2): S743-8.
17. Andersen JM, Sugerman KS, Lockhart JR, Weinberg WA. Effective prophylactic therapy for cyclic vomiting syndrome in children using amitriptyline or cyproheptadine. Pediatrics 1997; 100: 977-81.
18. Hikita T, Kodama H, Nakamoto N, Kaga F, Amakata K, Ogita K, et al. Effective prophylactic therapy for cyclic vomiting syndrome in children using valproate. Brain Dev 2009; 31: 411-3.
19. Gokhale R, Huttenlocher PR, Brady L, Kirschner BS. Use of barbiturates in the treatment of cyclic vomiting during childhood. J Pediatr Gastroenterol Nutr 1997; 25: 64-7.
20. Vanderhoof JA, Young R, Kaufman SS, Ernst L. Treatment of cyclic vomiting in childhood with erythromycin. J Pediatr Gastroenterol Nutr 1995; 21 (Suppl 1): S60-2.
21. Van Calcar SC, Harding CO, Wolff JA. L-carnitine administration reduces number of episodes in cyclic vomiting syndrome. Clin Pediatr (Phila) 2002; 41: 171-4.
22. Boles RG, Lovett-Barr MR, Preston A, Li BU, Adams K. Treatment of cyclic vomiting syndrome with co-enzyme Q10 and amitriptyline, a retrospective study. BMC Neurol 2010; 10: 10.
23. Fitzpatrick E, Bourke B, Drumm B, Rowland M. Outcome for children with cyclical vomiting syndrome. Arch Dis Child 2007; 92: 1001-4.
24. Dignan F, Symon DN, AbuArafeh I, Russell G. The prognosis of cyclical vomiting syndrome. Arch Dis Child 2001; 84: 55-7.
25. Lee LY, Abbott L, Moodie S, Anderson S. Cyclic vomiting syndrome in 28 patients: demographics, features and outcomes. Eur J Gastroenterol Hepatol 2012; 24: 939-43.
26. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013; 33: 629-808.

ผลการรักษาระยะสั้นและระยะยาวของภาวะ cyclic vomiting syndrome ในเด็ก

สุพร ตรีพงษ์กรุณา, เชาวพงศ์ จรัสวราพรรณ, พรเทพ ตั่นเผ่าพงษ์, ฉัตต์มณี เลิศอุดมผลวณิช

วัตถุประสงค์: เพื่อศึกษาผลการใช้ยาป้องกันในเด็กที่เป็น cyclic vomiting syndrome (CVS) ในระยะสั้นและระยะยาว

วัสดุและวิธีการ: ทบทวนเวชระเบียนของผู้ป่วยเด็กที่ได้รับการวินิจฉัยว่าเป็น CVS ระหว่าง พ.ศ. 2543 ถึง พ.ศ. 2556 ประสิทธิภาพของการใช้ยาระยะสั้นประเมินหลังการรักษา 3-6 เดือน โดยแบ่งเป็น 2 กลุ่ม คือ ตอบสนองดีและไม่ตอบสนอง ส่วนผลระยะยาวศึกษาในเด็กที่ได้รับการวินิจฉัยมานานกว่าหรือเท่ากับ 2 ปี โดยแบ่งเป็น 3 กลุ่ม คือ 1) ดีมาก (ไม่มีอาการ), 2) ดี (มีอาการเพียง 1-2 รอบ), 3) ไม่ดี (อาการมากกว่าหรือเท่ากับ 3 รอบ) ในปีที่ผ่านมา ผู้ป่วยที่ไม่ได้มาติดตามการรักษาได้มีการส่งแบบสอบถามเพื่อถามอาการในปัจจุบัน

ผลการรักษา: ผลการศึกษาในระยะสั้นผู้ป่วยมีการตอบสนองดีต่อยา amitriptyline สูงกว่า propranolol อย่างมีนัยสำคัญ (ร้อยละ 73 เทียบกับร้อยละ 36, p = 0.04) มีผู้ป่วย 24 ราย ที่ได้รับการวินิจฉัยนานกว่าหรือเท่ากับ 2 ปี และมีข้อมูลครบถ้วนใน 19 ราย โดยเด็กกลุ่มนี้มีอายุเฉลี่ย 11.3±4.9 ปี และระยะเวลาเฉลี่ยจากวินิจฉัยถึงช่วงศึกษา คือ 6.3±3.3 ปี ผลดีมากพบในเด็ก 7 ราย ผลดีพบ 7 ราย และผลไม่ดีพบ 5 ราย รวมแล้วผลน่าพอใจคือระดับดีถึงดีมากคือ ร้อยละ 74 ส่วนใหญ่ของเด็กที่มีผลน่าพอใจในระยะยาว (ร้อยละ 86) มีตอบสนองดีต่อยาในช่วงการศึกษาระยะสั้น

สรุป: การศึกษานี้พบว่ายา amitriptyline น่าจะมีประสิทธิภาพดีกว่า propranolol ในการป้องกัน CVS อย่างไรก็ตามควรมีการศึกษาแบบสุ่มและมีกลุ่มควบคุมเพื่อยืนยันผลดังกล่าว ในระยะยาวเด็กเหล่านี้ส่วนใหญ่มีผลการรักษาที่น่าพอใจโดยเฉพาะกลุ่มที่ตอบสนองดีต่อยาป้องกันในระยะแรก