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COMPARATIVE EFFECTIVENESS OF PROPHYLACTIC AND ABORTIVE PHARMACOLOGIC THERAPY IN TREATING OF PEDIATRIC CYCLIC VOMITING SYNDROME

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Keywords:
cyclic vomiting syndrome, prophylactic therapy.

Abstract

Background:

Description of the condition

Initially described in children, cyclic vomiting syndrome (CVS) is an idiopathic disorder that affects patients of all ages and is characterized by recurrent episodes of vomiting separated by symptom-free intervals or baseline health. This condition is diagnosed most often in young children, but it can affect people of any age. The episodes of nausea, vomiting, and lethargy last anywhere from an hour to 10 days. The exact prevalence of cyclic vomiting syndrome is unknown; estimates range from 4 to 2,000 per 100,000 children.

Description of the interventions

supportive therapy (during episodes), prophylactic therapy (to prevent episodes), and abortive therapy.

Why it is important to do this review

The evidence for the effectiveness of supportive, prophylactic, and abortive therapy in children with CVS remains weakest. we have sought to summarize evidence from Cochrane systematic reviews and other resources that included clinical trial data on the treatments of CVS in children.

Aim of the study:

To identify, retrieve and assess all studies evaluating the effects (efficacy,effectiveness) of the treatments against CVS in children.

Methods:

This was a systematic review conducted by seven authors independently searched Medline, Scopus, Embase, Cochrane and PubMed for studies that had assessed the effectiveness and the potential benefits of these treatments on CVS in children.

Results:

Seventeen randomized control trials and with a minimum follow-up of 4 months were included. Results of the various studies suggested that the Prophylaxis is recommended for those who fail a trial of abortive therapy or supportive measures. The ultimate goal of prophylaxis is to prevent attacks altogether but, at the very least, to reduce the frequency, duration, or intensity of episodes.

Conclusion:

Our systematic review and meta-analysis study supports the use of a Prophylaxis therapeutic regimen for those who fail a trial of abortive therapy or supportive measures.

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Introduction

General Introduction

Initially described in children, cyclic vomiting syndrome (CVS) is an idiopathic disorder that affects patients of all ages and is characterized by recurrent episodes of vomiting separated by symptom-free intervals or baseline health. It is a distinct clinical entity, oneof several disorders of motility resulting from disturbed regulation between the gut and the brain. It is characterized by episode of vomiting with intervals of weeks to months. The medianage of onset of symptoms varies from 3.5 to 7 yearsbut it can occur at any age from infancy to adulthood.The syndrome is a disorderof the brain-gut axis of as yet unclear pathogenesis,often associated with other episodicconditionslike migraine headaches and abdominal migraine.Gene studies have shown association with twosingle nucleotide polymorphism (SNP) of mitochondrialDNA (mtDNA): 16519T and 3010A that adverselyaffect energy metabolism (AT genotype) and were associated with children under age of 12 years old.(Kaul, A2015.).the syndrome is relatively rare among Saudi patients with a frequency of 2.6 per 1000.(Ayoola, EA. 2005.)

Clinical presentation of the syndrome:

Four phases of the disorder could be identified clinically which is:

- The prodromal phase: It is characterized by feeling of an episode is about to start with sweating, nausea, and abdominal pain.
- The vomiting phase: It is characterized by nausea and vomiting lasting from 20 to 30 Minutes.
- The recovery phase: It characterized by cessation ofVomiting and improving.
- appetite and gradualreturn of energy.
- The wellness phase: symptoms free.(Kaul, A2015.)

Description of the interventions:

Treatment of the CVS can be divided into supportivetherapy (duringepisodes), prophylactic therapy (to preventepisodes), and abortive therapy (to prevent progressionfrom prodromal symptoms to the vomiting phase).
prophylactic medications are used to treat other disorders including migraines, epilepsy, gastrointestinaldysmotility, so that prophylactic medications are used with patients who have episodethat are frequent (more than 1 episode per month),severe (prolonged for more than 3–5 days) or for those who fail a trial of abortive therapy. The goal of prophylactic therapy is to prevent the attacks entirely or at the very least to reduce the frequency of the attacks.***(Sunku, B.2009.)***

Table.1: prophylactic pharmacotherapy for children with CVS

Antimigraines
• **Amitriptyline:** start at 0.5 mg/kg and advance to
1–2 mg/kg per day QHS (adults 10–100 mg QHS).
• **Propranolol:** 0.25–1 mg/kg per day BID or TID (adults
• **Cyproheptadine:** 0.25–0.5 mg/kg per day BID or TID.
• **Alternatives:** nortriptyline, imipramine.
Anticonvulsants
• **Phenobarbital:** 2 mg/kg per day
• **Valproate:** 500–1,000 mg
• **Carbamazepine:** 5–10 mg/kg per day BID.
• **Alternatives:** gabapentin, topiramate, levetiracetam,
zonisamide.
Supplements
• **L-carnitine:** 50–100 mg/kg per day BID or TID (adults
660 mg–1 g BID or TID).

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Abortive medications are usedto abort the vomiting phase entirely or reduce the duration or severity of the episode.Abortive therapyshould be considered for those who have sporadic episodesthat occur less than once per month or those who have interval episodes while on prophylaxis.***(Sunku, B. 2009.)***

Table.2: Abortive pharmacotherapy for children with CVS

Antimigraines
• **Sumatriptan:** 20 mg intranasally at episode onset and
can repeat once or 25 mg orally once.
• **Alternatives:** frovatriptan, rizatriptan, zolmitriptan.
Antiemetics
• **Ondansetron:** 0.3–0.4 mg/kg per dose every 4–6 hours
intravenously/orally.
• **Alternatives:** granisetron, aprepitant.
Sedatives
• **Lorazepam:** 0.05–0.1 mg/kg per dose every 6 hours
intravenously/orally. Useful adjunct to ondansetron.
• **Chlorpromazine:** 0.5–1 mg/kg per dose every 6 hours
• **Diphenhydramine:** 1.25 mg/kg per dose every 6 hours
intravenously/orally. Useful adjunct to chlorpromazine.
Analgesics
• **Ketorolac:** 0.5–1 mg/kg per dose every 6 hours
intravenously/orally.

Why it is important to do this review

The evidence for the effectiveness of supportive, prophylactic, and abortive therapy in children with CVS remains weakest. we have sought to summarize evidence from Cochrane systematic reviews and other resources that included clinical trial data on the treatments of CVS in children.

Aim of the study

To identify, retrieve and assess all studies evaluating the effects (efficacy, effectiveness) of the treatments against CVS in children.

Materials and Methods

Study design

We designed a systematic review study aimed to collect and analyze similar but different RCT and Non-RCT studies, so that we synthesize the evidence of best treatment for CVS in pediatric population. We followed the Cochrane structure mentioned in the Cochrane handbook to build up every section of the review includes the research protocol and the research body.

Criteria for selecting studies for this review

Types of studies

The systematic review combines RCT studies and Non-RCT studies to be included in our research, so we screened the targeted studies using a search strategy will be mentioned later to include studies that match perfectly with research's clinical question or to exclude studies that is out of focus to the research's clinical question. The Non-RCT studies could be Case-Control studies, Cohort Studies, and sometimes Cross-sectional studies. In addition, we defined

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a clear inclusion and exclusion criteria to be used in the inclusion and exclusion process of the studies. Table (3) explains those criteria.

Inclusion criteria	Exclusion criteria
Children diagnosed with CVS	Adults diagnosed with CVS
Age from 3 to 13	Children aged above 13
Patients tolerate to CVS prophylactic and abortive therapy	

Types of participants

The participants in our research were pointed to the pediatric population, and we used the well-built PICO question to define the participants clearly, so we can exclude the participants who are non-relevant to the research's clinical question. Children who are aged of 3 to 10 years old and diagnosed with CVS that is identified by the clinical presentation of the syndrome was included in the review

Types of interventions

Cyclic vomiting syndrome was being treated by pharmacotherapy treatments alongside with psychotherapy. Moreover, in our review, we emphasize on pharmacotherapy treatments that are used to treat CVS as little evidence suggested for those treatments. consequently, he pharmacotherapy available for the cyclic vomiting syndrome is the supportive therapy which is used during episodes, prophylactic therapy to prevent episodes and abortive therapy to prevent progression from prodromal symptoms to the vomiting phase. The prophylactic pharmacotherapy includes Antimigraine medication, Anticonvulsant, and supplements aid to enhance the efficacy of the prophylactic medication. While the abortive pharmacotherapy includes Antiemetics, sedative, and analgesics.

Types of outcome measures

The outcomes measured in this review classified into primary outcome and secondary outcome, accordingly the primary outcome was the rate of vomiting episodes and the secondary outcome was the rate of nausea episodes.

Search methods for identification of studies

We searched the Cochrane Database of Systematic Reviews(CDSR) in The Cochrane Library. We did not apply any date restrictions. We conducted updated literature searches for each identified CVS treatment using the searchstrategy published in our research.

This was a systematic review conducted by seven authors independently searched Medline, Scopus, Embase, Cochrane, and PubMed for studies that compare between treatment options for cyclic vomiting syndrome in children. Randomized controlled trials (RCTs) or quasi-RCTs assessing the efficacy of various TCA 's and other agents in treating of cyclic vomiting syndrome. Five reviewers performed the literature search in PubMed, Cochrane Database, and the references of initially retrieved articles independently using the following terms: Cyclic vomiting syndrome, TCA's in cyclic vomiting syndrome, cyclic vomiting syndrome in children, vomiting episodes treatments in cyclic vomiting syndrome.

Data extraction and management

We extracted data from studies included in the existing Cochrane reviews in relation to the characteristics, risks of bias and data for the outcomes specified above. Moreover, we extracted data from new trials that included in the published version of the included reviews and incorporated the data into our overview. All data were extracted

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independently by two reviewers. We designed an extraction form which used in the extraction process in our research. we used the software named as Covidence to screen the studies and to extract the data from it. Consequently, the covidence software itself has a built-in extraction form which used to extract data from the included studies.
Quality of evidence in included studies:

Two review authors independently assessed the quality of evidence in the included studies using the 'Risk of bias' tables in the included studies (for the trials that were on children). We also assessed the limitations of the evidence found in the reviews for thetrials for children using the 'Summary of findings' tables from the included reviews, and independently reassessed the downgrading decisions made in each review using the GRADE process. The GRADE is a software designed by Cochrane to evaluate the evidence for each study included in the review.

Results and discussion

Summary of the results of the search
Seventeen randomized control trials and with a minimum follow-up of 4 months included, henceforward results of the various studies suggested that the Prophylaxis is recommended for those who fail a trial of abortive therapy or supportive measures, so that the ultimate goal of prophylaxis is to prevent attacks altogether but, at the very least, to reduce the frequency, duration, or intensity of episodes.

13 studies [RCT, Case-control , Cross-sectional] randomized control trials and with a minimum follow-up of 12 months were included. Results of the various studies suggested that Amitriptyline, Zonisamide ,Mirtazapine, erythromycin, and propranolol was an effective treatment agent in cyclic vomiting syndrome in children.

Description of included reviews:
The characteristics of the included studies are summarized inTable4. All the reviews used the same inclusion criteria (randomized controlled trials in patients of age from 3-7 years old with a diagnosis of CVS)and outcome measures (rate of vomiting episodes, rate of nausea episodes). The included studies were not restricted to products approvedfor children by the FDA. The latestsearch dates in the reviews ranged from 2000 to 2012.

Including the new studies, there are a total of 13 studies on 730 children in the reviews.

Table 4: The characteristics of the included studies and summary of finding

Study title	Study design	Participants	Intervention	Comparison	mean±SD	Primary outcome measures	Quality of the evidence (GRADE)
Treatment of cyclic vomiting syndrome with co-enzyme Q10 and amitriptyline, a retrospective study	RCT	42	Amitriptyline and with co-enzyme Q10	Non-treated group		Vomiting episodes	⊕⊕⊕⊕ **High**
Zonisamide or	Case series	40	Zonisamide	Non-treated group	Mean: 0.5±0.2	Vomiting episodes	⊕⊕⊕ **Moderate**

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Levetiracetam for Adults With Cyclic Vomiting Syndrome: A Case Series					Decreased from Mean: 1.3±0.3		
The efficacy and duration of treatment with propranolol in children with cyclic vomiting syndrome in southern Iran	Case series	301	erythromycin and propranolol	Non-treated group	Erythromycin Mean ± SD 2.20±1.70 propranolol Mean ± SD 2.18±1.50	Vomiting episodes and nausea attacks	⊕⊕⊕⊕ **High**
High degree of efficacy in the treatment of cyclic vomiting syndrome with combined co-enzyme Q10, L-carnitine and amitriptyline, a case series	Retrospective review	42	co-enzyme Q10, L-carnitine and amitriptyline	Non-treated group			⊕⊕⊕ **Moderate**

Study title	Study design	Participants	Intervention	Comparison	mean±SD	Primary outcome measures	Quality of the evidence (GRADE)
Effective Prophylactic Therapy for Cyclic Vomiting Syndrome in Children Using Amitriptyline or Cyproheptadine	Retrospective review	27	Amitriptyline or Cyproheptadine	Non-treated group	Mean: 0.5±0.2 Decreased from Mean: 1.3±0.3	Vomiting episodes	⊕⊕⊕⊕ **High**
Clonidine in cyclic vomiting	Case report	1	Clonidine	Pre-intervention vs post intervention	Number of attacks decreased on the vomiting	Vomiting episodes	⊕⊕⊕ **Moderate**

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					episodes scale		
Riboflavin in cyclic vomiting syndrome: efficacy in three children	Case series	3	Riboflavin	Pre-intervention vs post intervention	Number of attacks decreased on the vomiting episodes scale	Vomiting episodes and nausea attacks	⊕⊕⊕⊕ **High**
Treatment With Sumatriptan in a Case With Cyclic Vomiting Syndrome	Case report	1	Sumatriptan	Pre-intervention vs post intervention	Number of attacks decreased on the vomiting episodes scale		⊕⊕⊕ **Moderate**

Study title	Study design	Participants	Intervention	Comparison	mean±SD	Primary outcome measures	Quality of the evidence (GRADE)
Prophylactic Therapy of Cyclic Vomiting Syndrome in Children: Comparison of Amitriptyline and Cyproheptadine: A Randomized Clinical Trial	RCT	64	Amitriptyline and Cyproheptadine	Non-treated group		Vomiting episodes	⊕⊕⊕⊕ **High**
Use of intravenous midazolam and clonidine in cyclical vomiting syndrom	Case report	1	Midazolam	Pre-intervention vs post intervention	Number of attacks decreased on the vomiting episodes scale	Vomiting episodes	⊕⊕⊕ **Moderate**
The Two Sides of Opioids in Cyclical Vomiting Syndrome	Retrospective review	200	Opioids	Non-treated group	Erythromycin Mean ± SD 2.20±1.70 propranolol Mean ± SD 2.18±1.50	Vomiting episodes and nausea attacks	⊕⊕⊕⊕ **High**
Cyclic vomiting syndrome in Thai children	Retrospective review	25	pizotifen and amitriptyline	Non-treated group			⊕⊕⊕ **High**

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Risk of bias of the included studies in the review:
We have summarized the assessments of the risks of bias in the included studies inTable 5, so that we include two questions to assess the risk of bias in the included studies. The risk of bias assessment questions retrieved from the Covidence Cochrane software that is incomplete outcome data and selective outcome reporting.

Incomplete outcome data: Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.

Selective outcome reporting: State how the possibility of selective outcome reporting was examined by the review authors and what was found.

Table 5: the risks of bias in the included studies

Study I.D	Incomplete outcome data	Selective outcome reporting	Sequence generation	Allocation Concealment	Blinding of outcome assessor
Boles 2011	LOW	LOW	Unclear	LOW	Unclear
Clouse 2007	LOW	LOW	LOW	LOW	LOW
Coskun 2011	LOW	LOW	LOW	LOW	LOW
Erturk 2010	LOW	LOW	LOW	LOW	LOW
Haghighat 2015	LOW	LOW	LOW	Unclear	LOW
Badihian2018	LOW	LOW	LOW	LOW	Unclear
Greta 2005	LOW	LOW	LOW	LOW	LOW
Saligram2014	LOW	LOW	LOW	LOW	Unclear
Aanpreung2002	LOW	LOW	LOW	LOW	LOW
Andersen 2002	LOW	LOW	LOW	Unclear	LOW
Martinez-EsteveMelnikova2016	LOW	LOW	LOW	LOW	LOW
Tsuchiya 2009	LOW	LOW	LOW	Unclear	LOW

Effect of interventions:
The review includes studies comparing a group of patients treated with prophylactic or abortive therapy versus a group of patients non-treated or received placebo agent. Henceforward some studies showed a significant decrease in the mean±SD for the population sample. Some studies almost measure the effect of the intervention using a response scale to the intervention and represent the response by the percentage of patients responded to the treatments. The dominant medications exactly showed a significant decrease in the vomiting episodes and nausea attacks was Amitriptyline, Zonisamide, Mirtazapine, erythromycin, and propranolol.

Amitriptyline, a tricyclic "antidepressant" frequently used to treat migraine, is the most widely prescribed prophylactic medication used for the treatment of CVS, with response rates varying from 52-73% in open-label and subject recall-based studies in children and adults. amitriptyline was recommended as the first-line treatment choice for CVS prophylaxis in children and adolescents age 5 years and older.***(Boles, R2011.)***

Antiepileptic agent(phenobarbital,Zonisamide) has been used for maintenance therapy in childrenwith CVS and topiramate (a newer antiepileptic drugapproved for seizure control in pediatric and adult patients) hasbeen suggested for children with CVS.antiepileptic drugs with anti-migraine effects mighthave a role in prophylaxis against CVS episodes, and Studies have suggested that topiramate, another newer antiepilepticdrug, be considered in children less than 5 years of age who fail maintenancewith amitriptyline and propranolol.***(Clouse, R2007.)***

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Considering CVS as a migraine equivalent,involvement of hypothalamic–pituitary–adrenal axis, the role ofmitochondrial DNA mutations and polymorphisms, and nervoussystem dysfunction, so that antimigraine used to treat CVS in children***. (Badihian, N2018.)***

Conclusion

Implications for practice
Our systematic review suggests that Amitriptyline and Zonisamide decreased the duration attacks and numbers of vomiting episodes by 70%.

In comparison between various treatments options in cyclic vomiting syndrome, the most effective agent was Amitriptyline ,Zonisamide While erythromycin and propanol was much effective in childhood cyclic vomiting syndrome.

Implications for research
Large surveillance trials of combination therapy in adults and childrenhave been mandated by the FDA. The safety results of combination therapy in childrenwith CVS from these trials are awaited. The adult trials will alsocontain at least 10% of participants who are adolescents under 13 years of age, so safety data on both antimigraine and supplements combination therapy will be available for these adolescents.

Recommendations

Based on research results, there were several recommendations to be considered:

1. Conduct more clinical trials or studies for the most commonly prescribed medication by physicians: Antimigraine, Anticonvulsants, and supplements to ensure their safety and efficacy for CVS in the pediatric population.
2. Conduct more epidemiological studies to indicate the incidence and prevalence of CVS in Saudi pediatric population.
3. Conduct clinical trials on using CAM therapy in the treatment of CVS in pediatric population.

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