TOPICAL CAPSAICIN FOR THE TREATMENT OF CANNABIS HYPEREMESIS SYNDROME PRESENTING IN A 44-YEAR OLD MALE

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ABSTRACT

Cannabis hyperemesis syndrome (CHS) is a disorder that develops secondary to chronic cannabis use. In Canada, recent estimates suggest that over one sixth of households report using cannabis, and numbers have risen in the past year since cannabis legalization. CHS is characterized by intractable nausea and vomiting in the context of a benign hospital workup and history of long-term frequent cannabis consumption. Patients with CHS often undergo extensive, resource demanding investigations that yield no significant results. Topical capsaicin as abortive treatment in the emergency department has shown promising results in previous case reports. Here we provide a case report of a 44-year old male presenting to a rural emergency department with CHS and who was given abortive treatment with topical capsaicin. A literature review is presented on the pathophysiology of CHS and underlying mechanism of action of topical capsaicin treatment.

INTRODUCTION

Cannabis hyperemesis syndrome (CHS) is a clinical diagnosis characterized by intractable nausea and vomiting recurring in cyclic episodes and in the context of high-dose, long-term and frequent cannabis use. In Canada a 2019 household survey estimated that 17.5% of households[1] reported using cannabis in the last year, of which 44.6% indicated daily use [1]. This number is an increase from 14% in 2018[1] [1]. With cannabis legalization in 2018 [1] and increasing social acceptance for open cannabis use, it is possible that cannabis associated hospital visits will increase concurrently.

Historically, CHS has been underdiagnosed and often diagnosis is made only after extensive and expensive laboratory, imaging and surgical investigations that yield benign results [2, 3]. In the United States, one study found that patients diagnosed with CHS incur hospital costs significantly greater than patients diagnosed with non-CHS gastroparesis [3]. Classical anti-emetic treatments seem to have limited effect on relieving the symptoms of CHS, but in recent years, there have been case reports demonstrating novel methods, like topical capsaicin, for symptom management in CHS patients. The objective of this report is to present a case of CHS that presented to a rural Canadian emergency department and review present literature on the diagnosis of CHS, treatment recommendations and the physiological mechanism of topical capsaicin treatment.

CASE PRESENTATION

A 44-year old male presented to the emergency department a total of five times over the course of two weeks with severe nausea, and intractable vomiting and retching. At each visit the patient described the same symptoms. Symptom onset usually began in the early morning without any prior precipitating event. A feeling of discomfort and nausea localized to the epigastric region closely preceded recurrent episodes of vomiting. Emesis was bilious and non-bloody and occurred on average three times per hour in a given episode. As a consequence of the severity of the symptoms the patient explained that he was unable to eat normally because he could not "keep anything down". At home the patient had tried to alleviate his symptoms with dimenhydrinate but experienced no relief. The patient denied any history of travel, or recent contacts newly returned travellers or with

[1] Data derived from the Canadian Tobacco Use Monitoring Survey (CTUMS) and Canadian Tobacco, Alcohol and Drugs Survey (CTADS) from Statistics Canada. Data excludes households in the territories, full-time residents of institutions, the homeless and persons speaking languages other than English or French [1].

sick individuals. His bowel movements were normal but did have a "greenish" discoloration. He reports no recent coryza.

The patient had been experiencing similar episodes of nausea and repeated vomiting "for months" but the severity of discomfort and frequency of vomiting would be less. Episodes would generally begin in the morning and last no longer than two days. The patient's symptoms could be alleviated by completely submerging himself up to his neck in a hot bath at the hottest temperature he could tolerate.

On physical examination at the patient's fifth visit, the patient was diaphoretic but alert, oriented and hemodynamically stable. Vitals were: temperature 36.4^{O}C, blood pressure 163/92 mmHg, heart rate 72 bpm, respiratory rate 20 bpm. Blood oxygen saturation was 97% on room air. Abdomen was non-distended with normal bowel sounds and no visible masses. On palpation the abdomen was soft and non-tender with no palpable masses. No guarding or rigidity were present; however, the patient did complain of diffuse lower abdominal discomfort. There was no tenderness along either the costovertebral angle or suprapubic region. Laboratory studies were benign, showing only a slight elevation in serum glucose (6.4 mmol/L); CBC, electrolyte and liver function tests returned within normal ranges. Radiographs were negative for bowel obstruction and showed normal abdomen. CT scanning of the head and abdomen were normal. Gastroscopy resulted in a diagnosis of GERD without presence of Barrett's Esophagus, however, it is important to note that his history and physical exam were inconsistent with a final diagnosis of GERD as an explanation for the his symptoms of intractable and recurring, phasic vomiting.

The patient's medical history includes a diagnosis of asthma, osteoarthritis, anxiety and previous in-patient treatment for cocaine addiction. When queried the patient admitted to a having a history of chronic migraines; he described a traumatic head injury around the age of 3-years old that was followed by recurrent migraines throughout his childhood. Current at home medication was exclusively salbutamol sulphate (Ventolin®). There is no history of tobacco or frequent alcohol use; however, the patient explained that he has been smoking cannabis daily for "many years", which he uses to regulate his feelings of anxiety. His family history is significant for anxiety among all first-degree relatives and for depression in his mother. His sister also experienced chronic migraines throughout childhood that has continued into her adulthood. The patient's social history is significant for previous periods of incarceration and recurring periods of drug addiction (Percocet, cocaine, crystal meth); however, he has been abstinent from harmful drug use since 2014. As a consequence of his previous history, he is hesitant to use psychoactive medication for long durations to treat his anxiety and instead states that he manages his psychological symptoms with cannabis.

Hospital Management

The initial diagnosis was gastritis, however, during repeated hospital visits over a two-week period, the patient's symptoms proved resistant to treatment with omeprazole, amitriptyline, metoclopramide, clonazepam and ondansetron. During the fifth hospital admission, the patient was rehydrated with intravenous saline, treated with intravenous diazepam (10 mg) and haloperidol (2.5-5.0 mg), and a 'hot pepper' sauce rubbed across his stomach and promptly removed. This treatment regimen proved effective to abort the patient's nausea and vomiting. A clinical diagnosis of cannabis hyperemesis syndrome was made. The patient was discharged in stable condition with a

prescription for diazepam (5-10 mg taken as needed every 6-8 hours) and counselled to reduce his cannabis use and follow-up with his family physician. At the family clinic follow-up appointment one week later, the patient stated that over the course of previous two-weeks he had lost approximately 10kg but since his last hospital admission he had not since experienced another episode of nausea and vomiting and was once again able to eat normally.

LITERATURE REVIEW

Methods

A literature search of English language journal articles was carried out between July 25, 2019 and August 2, 2019. The databases interrogated included Pubmed and the Cochrane Library. A keyword and MeSH term search in PubMed was conducted to extract articles describing cannabis hyperemesis syndrome induced by chronic cannabis use and treatment with capsaicin specifically in adult populations. A keyword search among titles and abstracts was completed in the Cochrane Library database for review articles describing cannabis hyperemesis syndrome or cyclic vomiting syndrome associated with cannabis use. The precise search term interrogation strategy used for each database is detailed in Table 1. No filters were applied to the database search.

After applying the below search strategy, article titles and abstracts were screened to include articles published only in English and to exclude duplicate publications or articles discussing pediatric presentations. The remaining articles were then read in full to ensure that the included articles were those only describing cannabis-use related cases and those discussing the application of topical capsaicin for symptom management.

Table 1. Electronic database search strategies

Database	Search Strategy
PubMed	((("cannab* hyperemesis syndrome"[Title/Abstract]) OR ("cyclic vomiting syndrome"[Title/Abstract]) OR ("Cyclic Vomiting Syndrome-Plus"[MeSH Terms])) AND ("capsaicin"))
Cochrane Library	(cannab* hyperemesis syndrome in Title Abstract Keyword) OR (cyclic vomiting syndrome in Title Abstract Keyword)

Results

A total of 13 publications were reviewed after database interrogation and screening for study relevancy. Publication dates ranged from 2017 to 2019. Figure 1 describes the number of publications that were discovered during the initial database interrogation and the number that were excluded. The publications reviewed included: two case reports, one case series (13 patients), one expert panel publication, one cohort study and eight review papers. Table 2 lists the references determined from the systematic database search.

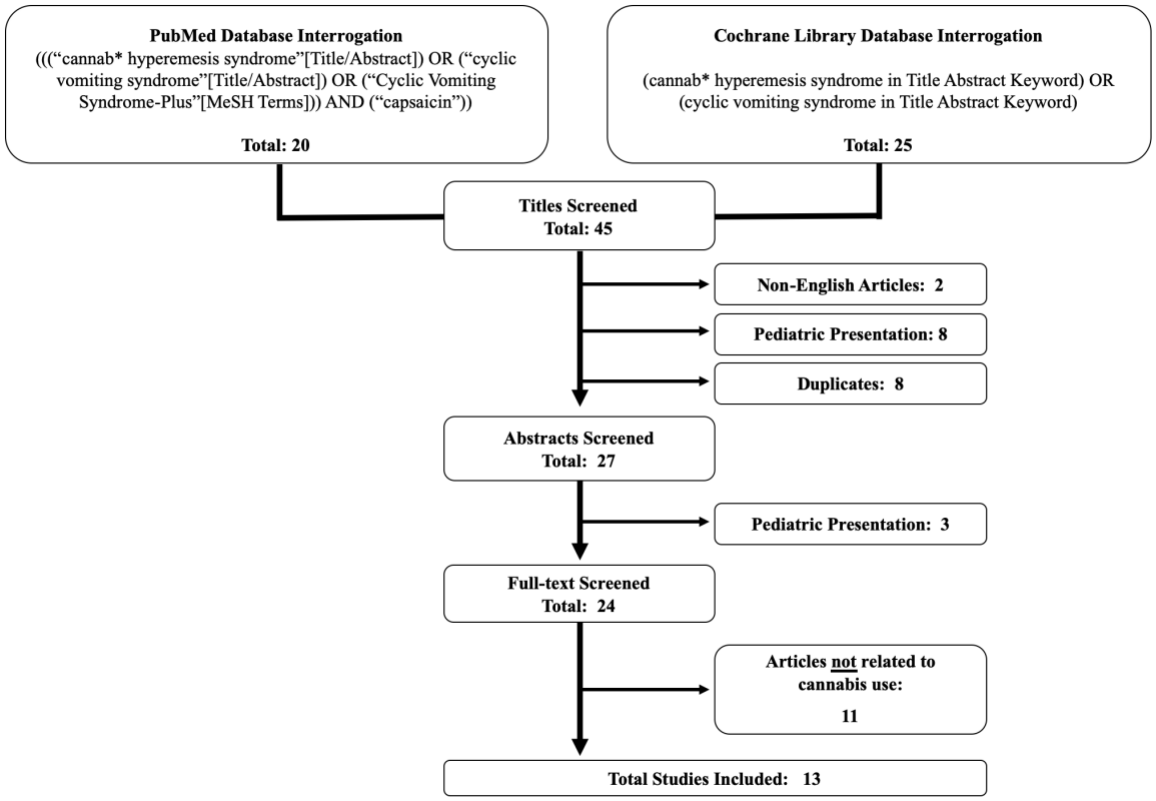

Figure 1. Flow diagram demonstrating the selection process for publications describing capsaicin use for cannabis hyperemesis syndrome in adults

Table 2. Publications extracted from the systematic literature search of PubMed and Cochrane Library discussing treatment of Cannabis Hyperemesis Syndrome with capsaicin.

			Ref.
Case Report			
Moon, Buckley, Mark	Successful Treatment of Cannabinoid Hyperemesis Syndrome with Topical Capsaicin	ACG Case Rep J, 5: e3; 2018	[13]
Sharma	Cannabis hyperemesis syndrome	BMJ Case Rep, 2018: 1-2; 2018	[4]
Case Series			
Dezieck, Hafez, Conicella, Blohm, O'Connor, Schwartz, Mullins	Resolution of cannabis hyperemesis syndrome with topical capsaicin in the emergency department: a case series	Clin Toxicol, 55(8): 908-913; 2017	[10]
Retrospective Cohort Study			
Sandhu, Alvarez, Akers, Smith, Heavener, Stephenson, Jaeger, Sears	Prevalence of Cannabinoid Hyperemesis Syndrome and Its Financial Burden on the Health Care Industry	Am J Gastroenterol, 112(435): S231-S232; 2017	[3]
Review			
Richards, Lapoint, Burillo-Putze	Cannabinoid hyperemesis syndrome: potential mechanisms for the benefit of capsaicin and hot water hydrotherapy in treatment	Clin Toxicol, 56(1): 15-24; 2018	[2]
Williams	Cannabinoids: Emerging Evidence in Use and Abuse	Emerg Med Pract, 20(8): 1-20; 2018	[6]
Khattar, Routsolias	Emergency Department Treatment of Cannabinoid Hyperemesis Syndrome: A Review	Am J Ther, 25(3): e357-e361; 2018	[5]
Waterson, Duncan, Macguire	Capsaicin topical in emergency department treatment of cannabinoid hyperemesis syndrome	Am J Emerg Med, 35(12): 1977-1978; 2017	[7]
Sorenson, DeSanto, Borgelt, Phillips, Monte	Cannabinoid Hyperemesis Syndrome – Diagnosis, Pathophysiology and Treatment – a Systematic Review	J Med Toxicol, 13(1): 71-87; 2017	[8]
Richards	Cannabinoid hyperemesis syndrome: pathophysiology and treatment in the emergency department	J Emerg Med, 54(3): 354-363; 2018	[11]
McConachie, Caputo, Wilhelm, Kale-Pradhan	Efficacy of capsaicin for the treatment of cannabinoid hyperemesis syndrome: A systematic review	Ann Pharmacother: 1-8; 2019	[15]
Richards, Gordon, Danielson, Moulin	Pharmacologic treatment of cannabinoid hyperemesis syndrome: A systematic review	Pharmacotherapy, 37(6): 725-734; 2017	[14]
Expert Panel			
Lapoint, Meyer, Yu, Koenig, Lev, Thihalolipavan, Staats, Kahn	Cannabinoid Hyperemesis Syndrome: Public Health Implications and a Novel Model Treatment Guideline	West J Emerg Med, 19(2): 380-386; 2018	[9]

DISCUSSION

Clinical Presentation

Patients experiencing CHS typically present multiple times to emergency department complaining of vague diffuse abdominal pain and nausea with persistent vomiting [2, 4-10]. Their symptoms closely resemble the classic presentation of Cyclic Vomiting Syndrome, and patients are often misdiagnosed as such; however, patients with CHS will uniquely describe that they are able to relieve their symptoms with a hot bath or shower, and in addition, the physician will have a high degree of suspicion that the patient uses cannabis regularly [2, 5, 8, 11]. Symptoms present in recurring cycles that follow three phases. The prodromal phase can last months to years and is characterized by vague abdominal discomfort, nausea and anorexia that are most intense in the morning [2, 6]. The hyperemetic phase that follows may persist for 24-48 hours, but can continue as long as 7-10 days, during which time patients experience diffuse unremitting abdominal pain and intractable emesis [2, 6]. During the hyperemetic phase patients may discover that hot baths or showers can provide intermittent symptom relief [6]. Finally, the recovery phase is characterized by the patient returning to good health [2, 6]. The duration of this phase is dependent on the interval of time during which the patient avoids cannabis use [6]. A return to cannabis use induces the cycle to re-start. Patients may record a weight loss greater than five kilograms on average and often deny dysuria or abnormal bowel movements [2]. CHS is more common in males and patients under the age of 50 years and there is some data to support that patients with a childhood history of migraines are at greater risk for developing CHS as adults if they use cannabis chronically [2, 9, 12].

Diagnosis

In practice, CHS has historically been a diagnosis of exclusion. Hospital investigations for patients presenting with CHS are often extensive but unremarkable. Laboratory results may indicate ketonuria or electrolyte imbalances consistent with dehydration due to emesis, and mild leukocytosis; imaging results are consistently benign [5-7]. The diagnostic criteria for CHS relies on a strong clinical assessment. Box 1 states the major criteria determined from a literature review by Sorensen et al. (2016) of 211 case reports [8]. Point-of-Care tools (Dynamed Plus) endorse a diagnosis of CHS if the clinical presentation meets the Rome IV criteria for CHS [12]. The clinical differential for CHS should include cyclic vomiting syndrome, hyperemesis

Box 1. CHS diagnostic criteria from Literature Review and Point-of-Care Tools

Literature Review [8]

- Recurrent cyclic episodes of emesis with abdominal pain
- Long-term cannabis use ≥1/week
- Compulsive hot baths/showers producing symptom relief
- Resolution of symptoms with cannabis use cessation
- First cannabis use during adolescence
- Symptom onset within third decade of life

Point-of-Care [12]

Rome IV Criteria for CHS:

All of the following, present for most recent ≥3 months, with symptom onset ≥6 months prior to diagnosis:

- Episodic vomiting that resembles the same onset, frequency and duration as Cyclic Vomiting Syndrome
- Prolonged cannabis use
- Symptom relief with cannabis use cessation

Additional: pathologic prolonged hot baths/showers with effective short-term symptom relief

gravidarum, psychogenic vomiting, bulimia, Addison disease and chronic migraine headaches, all of which can be differentiated from CHS with a strong patient history and physical exam or simple laboratory test [6]. Careful assessment of the patient's neurological and mental state is important to differentiate cannabis intoxication from toxicity due to alcohol, other illicit drugs, or harmful use of prescription medications [6].

Pathophysiology of CHS

The origin of central control for nausea and vomiting is localized to the chemoreceptor zone, known as the area postrema, of the medulla oblongata. In this region there are chemical receptors that are sensitive to a variety of noxious stimuli that, when activated, induce a signalling cascade to the central pattern generator and efferent branches of the vagus nerve [2, 5, 6, 10]. This ultimately shifts the balance between the parasympathetic and sympathetic nervous systems and induces nausea and emesis [2, 5, 6, 10]. One of the classes of signalling receptors known to function in this signalling pathway are the transient receptor potential vanilloid-1 (TRPV1) family [5-7, 13, 14]. They are a class of nonselective cation channels expressed in vagal sensory neurons of the gastrointestinal tract, in intrinsic enteric neurons of the myenteric plexus and in gastric epithelial cells [7, 13, 14]. They are also found centrally in high concentrations in the chemoreceptor region of the medulla oblongata, called the area postrema [13, 14]. TRPV1 signalling exerts anti-emetic downstream effects through substance P signalling, but when inactivated the ablation of TRPV1 signalling can have pro-emetic consequences [5, 6, 10, 14]. TRPV1 receptors are highly stimulated by extremes of heat (>43ºC), low pH (<6), low osmolarity, pain stimulation and the plant product capsaicin (8-methyl-N-vanillyl-6-nonenamide) [5, 6], and they are inactivated by the endocannabinoid system through dephosphorylation [6, 13].

There have been a number of mechanisms proposed to explain the development of CHS from chronic cannabis exposure [2, 7, 13, 14]. One theory in particular provides a relevant mechanistic explanation for the development of CHS and its response to abortive capsaicin treatment. Delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), the two most concentrated active components found in cannabis, mimic the activity of endocannabinoids and are able to dephosphorylate TRPV1 receptors [2]. Chronic exposure to THC and CBD, as in chronic cannabis use, interrupts normal TRPV1 anti-emetic effects leading to the promotion of nausea, gastroparesis and emesis [2, 6, 13].

Capsaicin Treatment

There is severely limited data on the efficacy of various treatments for CHS [14]. Patients are often first managed with anti-emetic treatment, proton pump inhibitors and intravenous rehydration, although, they typically find little relief from anti-emetic treatment [6, 12, 14]. Subsequent therapies that have been attempted include treatment with benzodiazepines or tricyclic anti-depressants used to manage cyclic vomiting syndrome associated with migraines [12, 14]. Notably, case reports in recent years have suggested that the combined topical application of capsaicin and intravenous antipsychotics (ie. haloperidol) have been effective emergency room treatment strategies to immediately abort intractable vomiting during the hyperemetic phase of CHS [4, 5, 7, 10, 12, 13, 15]. Topical capsaicin is applied in a 0.075% concentration to the back, abdomen and arms for a short incubation period, and avoiding mucosal surfaces to prevent skin burns [3-7, 10, 11, 13]. Data supporting the use of topical capsaicin for the treatment of CHS remains limited to case reports [4,

5, 7, 13] and case series [10] however, the underlying physiological effect of capsaicin is mechanistically a plausible explanation for its anti-emetic effect. Capsaicin is a potent stimulator of TRPV1 receptors that induces high-level receptor activity [5, 13, 14]. During the hyperemetic phase of CHS, acute stimulation of peripheral TRPV1 receptors by capsaicin leads to receptor activity sufficient to overcome receptor inactivation by THC and CBD and induce the anti-emetic effects of normal TRPV1 signalling [5, 13, 14].

Topical capsaicin treatment, however, is only symptomatic management; the intractable symptoms of CHS will return should the patient continue to use cannabis chronically. Moreover, the development of CHS is itself a symptom of a deeper underlying cannabis addiction. Thus, the cure for CHS is complete cannabis-use cessation, and long-term management follows the same multi-disciplinary approach as that for any other substance use addiction [6, 14].

CONCLUSION

As of yet there has been no empiric research assessing the efficacy and complications of topical capsaicin as abortive therapy for CHS, although case reports in the last two years have been promising. In a rural context, hospitals are not equipped to support extensive laboratory testing and sophisticated imaging investigations that CHS patients typically undergo. Extensive investigation requires transport to a larger facility at a distance away and results are routinely returned at least 24 hours later if not longer. This delays appropriate diagnosis and management and prolongs patient suffering. The diagnosis and differential for CHS can be determined with a strong history and physical exam, and alternate emergent or urgent conditions ruled out with basic laboratory and imaging methods. Topical capsaicin is a simple and largely benign abortive treatment for intractable nausea and vomiting in CHS patients and is an easily accessible therapy for rural emergency departments. Given the growing prevalence of recreational cannabis use in Canada, a strong awareness and understanding of CHS would reduce the number of extraneous, expensive and time delayed investigations, and promote faster patient diagnosis and appropriate management.

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