Intravenous Haloperidol Versus Ondansetron for Cannabis Hyperemesis Syndrome (HaVOC): A Randomized, Controlled Trial

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Study objective: Little is known about the cause or optimal treatment of hyperemesis in habitual cannabis users. Anecdotal evidence supports the use of haloperidol over traditional antiemetics for this newly recognized disorder. We compare haloperidol with ondansetron for cannabis hyperemesis syndrome.

Methods: We randomized cannabis users with active emesis to either haloperidol (with a nested randomization to either 0.05 or 0.1 mg/kg) or ondansetron 8 mg intravenously in a triple-blind fashion. The primary outcome was the reduction from baseline in abdominal pain and nausea (each measured on a 10-cm visual analog scale) at 2 hours after treatment. Although the trial allowed for crossover, the primary analysis used only the first treatment period because few subjects crossed over.

Results: We enrolled 33 subjects, of whom 30 (16 men, aged 29 years [SD 11 years] using 1.5 g/day [SD 0.9 g/day] since age 19 years [SD 2 years]) received at least 1 treatment (haloperidol 13, ondansetron 17). Haloperidol at either dose was superior to ondansetron (difference 2.3 cm [95% confidence interval 0.6 to 4.0 cm]; P=.01), with similar improvements in both pain and nausea, as well as less use of rescue antiemetics (31% versus 59%; difference −28% [95% confidence interval −61% to 13%]) and shorter time to emergency department (ED) departure (3.1 hours [SD 1.7] versus 5.6 hours [SD 4.5]; difference 2.5 hours [95% confidence interval 0.1 to 5.0 hours]; P=.03). There were 2 return visits for acute dystonia, both in the higher-dose haloperidol group.

Conclusion: In this clinical trial, haloperidol was superior to ondansetron for the acute treatment of cannabis-associated hyperemesis. The efficacy of haloperidol over ondansetron provides insight into the pathophysiology of this now common diagnosis in many EDs. [Ann Emerg Med. 2020;■:1-7.]

Please see page XX for the Editor's Capsule Summary of this article.

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INTRODUCTION

With more liberal attitudes toward and increasing recreational consumption of cannabis, a new disorder consisting of severe cycles of protracted vomiting has been recognized in habitual cannabis users.[1-3] First reported in a case series in 2004, the precise cause remains speculative.[2,4,5] The diagnosis is largely of exclusion, but hallmarks include its resistance to traditional antiemetics such as ondansetron and the need for prolonged abstinence as cure.[2,4-8]

Anecdotal evidence has emerged in favor of haloperidol, droperidol, benzodiazepines, and topical capsaicin as effective emergency therapies.[2,7-10] To better understand the underlying pathophysiology and given the limitations of conventional treatment, we undertook a clinical trial to test whether haloperidol was more effective than ondansetron in reducing abdominal pain and nausea in emergency patients with cannabis (or cannabinoid) hyperemesis syndrome.

MATERIALS AND METHODS

Study Design, Setting, and Selection of Participants

We designed a randomized, triple-blind crossover trial with up to 3 treatment periods per subject. Subjects were recruited from 2 academic emergency departments (EDs) (combined annual census 110,000 visits) in Ontario, Canada. The study was approved by the institutional research ethics board and registered.

From June 2017 to June 2019, research personnel approached consecutive eligible adults (≥18 years) in the

Editor's Capsule Summary

What is already known on this topic

Little is known about the optimal treatment of hyperemesis in habitual cannabis users. Anecdotal evidence supports the use of haloperidol over traditional antiemetics.

What question this study addressed

Is haloperidol superior to ondansetron for treatment of cannabis hyperemesis syndrome?

What this study adds to our knowledge

In this 33-patient randomized trial, haloperidol at a dose of either 0.05 or 0.1 mg/kg was superior to ondansetron 8 mg in reducing nausea and pain as measured by visual analog scale.

How this is relevant to clinical practice

This study suggests that haloperidol is superior to ondansetron for cannabis-induced hyperemesis.

ED, confirmed by the treating physician to have a working diagnosis of hyperemesis caused by cannabis. To be eligible, subjects had to report greater than or equal to 3 episodes of emesis in a cyclic pattern separated by greater than 1 month during the preceding 2 years, and near-daily to daily use of cannabis by inhalation for greater than or equal to 6 months.[5] Individuals using opioids daily, allergic to or intolerant of either study drug, deemed unreliable for follow-up, or unlikely to return for crossover were excluded.

To qualify for study drug treatment on any given visit, patients were required to present with greater than 2 hours of ongoing, witnessed emesis or retching, to not be pregnant, and to not have received an antiemetic, anticholinergic, or antipsychotic agent intravenously (other than up to 100 mg dimenhydrinate) in the previous 24 hours. Subjects provided written consent to be randomly allocated to treatment for hyperemesis on the index visit (if the visit qualified; explained later), as well as up to 2 subsequent qualifying emergency visits.

Interventions

Subjects were weighed, had routine blood analysis, had urinalysis, had an ECG, and were asked to rate their baseline nausea and abdominal pain on 2 separate 10-cm visual analog scales (VASs) (anchors: 0=none, 10=worst possible).[11] They were then randomized to receive either ondansetron (8 mg) or haloperidol (at a nested random dose of 0.05 or 0.1 mg/kg) intravenously.

The primary aim of this 3-period crossover study was to compare ondansetron with haloperidol regardless of dose. We anticipated that many subjects might not return for all 3 treatment periods, and so designed the study to maximize the number who received both ondansetron and at least 1 dose of haloperidol. The randomization scheme was therefore constructed to ensure that subjects would receive ondansetron on either the first or second treatment (1:1 allocation), receive either high- or low-dose haloperidol on the other visit (also 1:1), and consequently receive the other haloperidol dose on the third visit (ie, 4 possible sequences: HOh, hOH, OHh, and OhH, where "H" and "h" represent the two dose levels of haloperidol and "O" the fixed dose of ondansetron). The randomization scheme was computer generated in blocks of 4 stratified by site, and the next assigned treatment for every active subject was maintained at each study site in sealed, opaque envelopes.

Using a standardized, preprinted order sheet, subjects were given 1 L of Ringer's solution intravenously over 30 minutes while baseline screening and preparation of the allocated study drug took place. A second nurse not otherwise involved in the patient's care and instructed to conceal the allocation opened the envelope, prepared and administered the assigned study drug intravenously during 10 minutes (beginning at t=0), and charted "HaVOC study drug administered" in the medical record. While receiving intravenous crystalloid at 250 mL/hour and sips of oral rehydration solution as needed, patients again scored their nausea and abdominal pain 60 and then 120 minutes after start of treatment, using a parallel 10-cm VAS with prior score(s) visible. At 120 minutes after treatment, the treating physician identified discharge readiness or, failing that, provided further intravenous fluid orders, ordered any rescue antiemetics (prochlorperazine or metoclopramide recommended), and eventually recorded to the nearest minute the time the patient was deemed discharge ready. Subjects were asked to complete and return abdominal pain and nausea VAS scores at 24 and 48 hours by mail in postage-paid preprinted envelopes or by e-mail.

A 7-day washout between treatment periods was mandated. Subjects, all physicians, nurses (other than the one), pharmacists, research personnel, and the investigators, including the biostatistician, were blinded to treatment allocation until the end of the trial.

Outcome Measures

The primary outcome measure was the average of the changes in abdominal pain and nausea scores at 2 hours versus baseline. Secondary efficacy outcome measures were

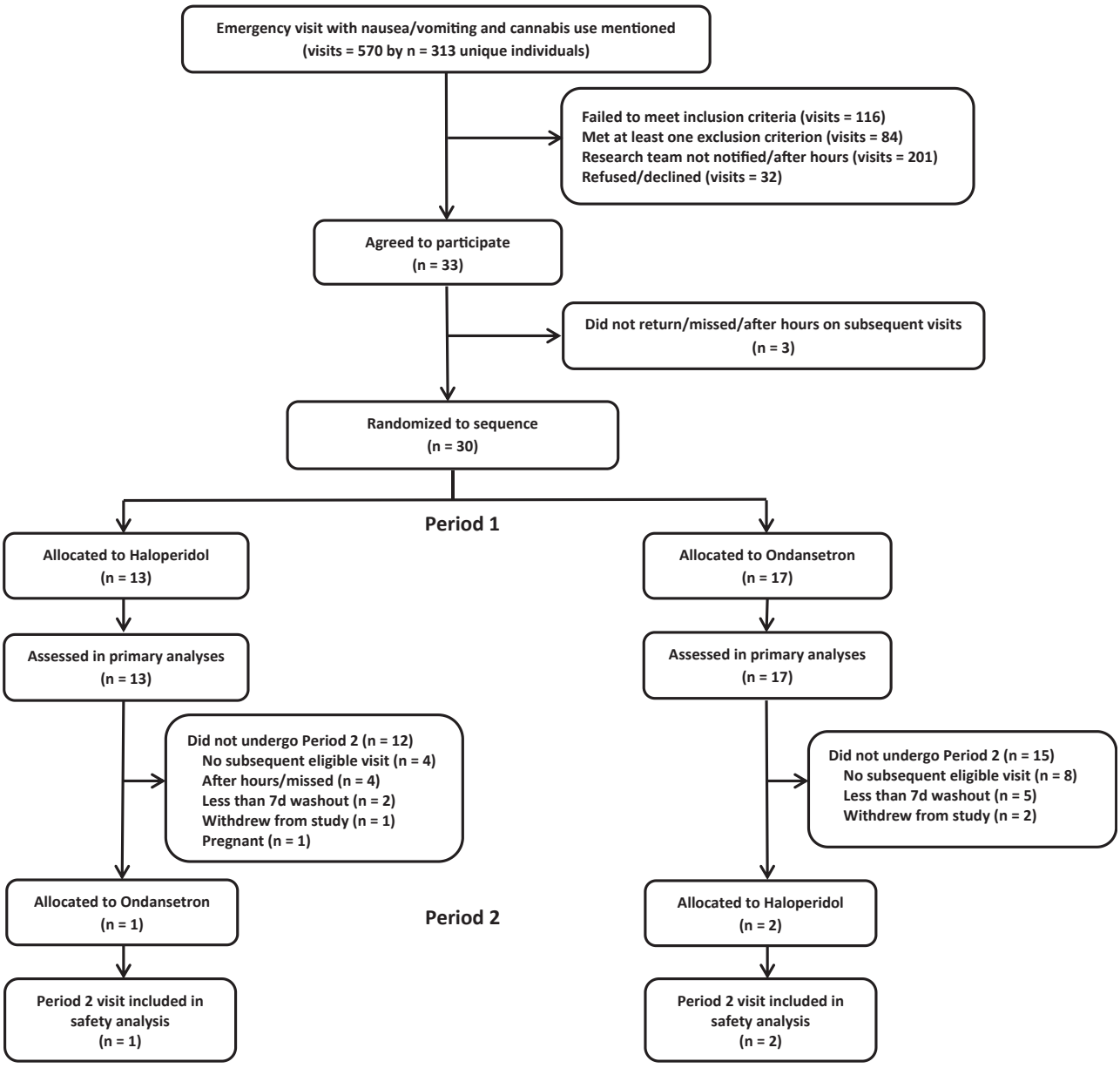

Figure 1. Study flow diagram.

changes in either abdominal pain or nausea score over time, treatment success (ie, both abdominal pain and nausea <2 cm at ≥ 2 hours), being discharge ready at 2 hours, use of rescue antiemetics before discharge, time to discharge readiness, length of stay greater than 12 hours, and unscheduled return visits within 7 days. Secondary safety outcomes were any adverse effects potentially related to the study drug, with acute dystonia or moderate to severe akathisia being prespecified.

Primary Data Analysis

Because less than 25% of subjects crossed over (ie, were treated more than once), the original protocol called for using ANOVA restricted to the first period alone for the primary efficacy analysis. All visits in which subjects received a study treatment, however, were included in the secondary safety analyses. An independent data and safety monitoring board (one biostatistician, one emergency physician, and one medical toxicologist) reviewed every serious adverse effect deemed potentially related to study drug. A blinded, unplanned interim analysis before extension of the trial to other enrollment centers led to a recommendation to halt the trial in accordance with a strong effect on the primary outcome in favor of one drug treatment. Complete details of the analysis plan, including sample size

Table. Baseline Characteristics and Outcomes by Study Drug.

Characteristics, Mean (SD)	Haloperidol (n=13)	Ondansetron (n=17)	Difference (95% CI)
Baseline characteristics immediately before study drug administration			
Age, y	29.3 (13.2)	28.1 (9.4)	1.2 (−7.2 to 9.6)
Sex, men, No. (%)	7 (54)	9 (53)	1 (−38 to 39)
Mass, kg	73.4 (19.6)	64.8 (15.5)	8.5 (−4.6 to 21.6)
Daily cannabis use, g	1.5 (0.8)	1.4 (1.0)	0.1 (−0.9 to 1.1)
Age at first use, y	17.4 (3.0)	21.0 (1.4)	−3.6 (−9.6 to 2.4)
Most recent use, days	1.5 (0.7)	2.6 (2.7)	−1.1 (−5.4 to 3.2)
Current episode duration, days	2.1 (3.4)	2.9 (2.1)	−0.9 (−2.9 to 1.2)
Pulse rate, beats/min	73 (19)	81 (22)	−9 (−24 to 7)
Blood pressure, mm Hg	136/82 (21/17)	133/78 (17/19)	3/4 (−11/−10 to 17/17)
QTc interval, ms*	423 (35)	434 (32)	−11 (−39 to 17)
WBC, $\times 10^9$/L	13.2 (4.1)	13.9 (2.9)	−0.7 (−3.3 to 1.9)
Total carbon dioxide, mmol/L	20.8 (3.2)	22.5 (4.4)	−1.8 (−4.7 to 1.2)
Anion gap, mmol/L	13.6 (4.2)	13.5 (2.3)	0.1 (−2.3 to 2.5)
β-Hydroxybutyrate, mmol/L	1.1 (1.3)	0.9 (0.7)	0.2 (−0.6 to 1.0)
Urine, No. (%)†			
Ketones ≥8 mM	8 (80)	9 (90)	−10 (−49 to 30)
THC by immunoassay	11 (100)	14 (100)	0 (−28 to 23)
Opiates	0	1 (7)	−7 (−34 to 23)
Amphetamines	3 (27)	0	27 (−5 to 61)
ED arrival to study drug administration, h	2.5 (1.4)	2.2 (0.8)	0.3 (−0.6 to 1.1)
Baseline nausea, cm	6.8 (2.5)	7.0 (3.1)	−0.2 (−2.4 to 1.9)
Baseline abdominal pain, cm	5.9 (2.7)	5.2 (3.2)	0.7 (−1.6 to 2.9)
Efficacy outcomes			
Change from baseline			
Nausea at 2 h, cm‡	−5.0 (2.7)	−2.4 (2.4)	−2.5 (−4.4 to −0.6)
Nausea at 48 h, cm‡	−5.8 (1.2)	−6.0 (3.5)	0.2 (−2.0 to 2.3)
Abdominal pain at 2 h, cm‡	−4.3 (3.0)	−2.1 (2.8)	−2.2 (−4.4 to 0)
Abdominal pain at 48 h, cm‡	−3.0 (2.5)	−2.5 (2.9)	−0.5 (−2.6 to 1.7)
Combined at 2 h, cm§	−4.6 (2.5)	−2.3 (2.4)	−2.3 (−4.2 to −0.5)
Combined at 48 h, cm‡	−4.4 (1.8)	−4.3 (2.9)	−0.2 (−2.1 to 1.8)
Treatment success, No. (%)‡	7 (54)	5 (29)	24 (−16 to 59)
Rescue medication, No. (%)			
Antiemetic‡	4 (31)	10 (59)	−28 (−61 to 13)
IV haloperidol or ondansetron‡	1 (8)	4 (24)	−16 (−44 to 18)
Benzodiazepine‖	1 (8)	7 (41)	−33 (−62 to 4)
Opioid‖	0	1 (6)	−6 (−29 to 21)
Any‡	4 (31)	13 (76)	−46 (−74 to −4)
Advanced imaging, No. (%)‖	0	1 (6)	−6 (−29 to 21)
Interval from study drug to departure, h‡	3.1 (1.7)	5.6 (4.5)	−2.5 (−5.0 to −0.1)
ED total length of stay, h‖	5.5 (2.1)	7.8 (4.3)	−2.3 (−4.9 to 0.4)
ED length of stay >12 h, No. (%)‡	0	2 (12)	−12 (−36 to 16)
Admitting service consulted, No. (%)‡	0	1 (6)	−6 (−29 to 21)
Return to ED <7 days, No. (%)‡	4 (31)	6 (35)	−5 (−40 to 34)

THC, Tetrahydrocannabinol; *IV*, intravenous.

The "Difference" column tabulates the unadjusted difference comparing haloperidol with ondansetron, with exact 95% CIs for binomial proportions. Combined=average of abdominal pain and nausea 10-cm VAS measurements. Rescue medications include intravenous and oral antiemetics, analgesics, and sedatives administered in the ED after study drug administration but before discharge.

*QTc=corrected QT interval on 12-lead ECG.

†Urinalysis for ketones not conducted in 3 haloperidol and 7 ondansetron subjects, and urine drug immunoassay not conducted in 2 haloperidol and 3 ondansetron subjects; percentages shown exclude missing values.

§Prespecified primary outcome.

‡Prespecified secondary outcomes.

‖Post hoc outcomes.

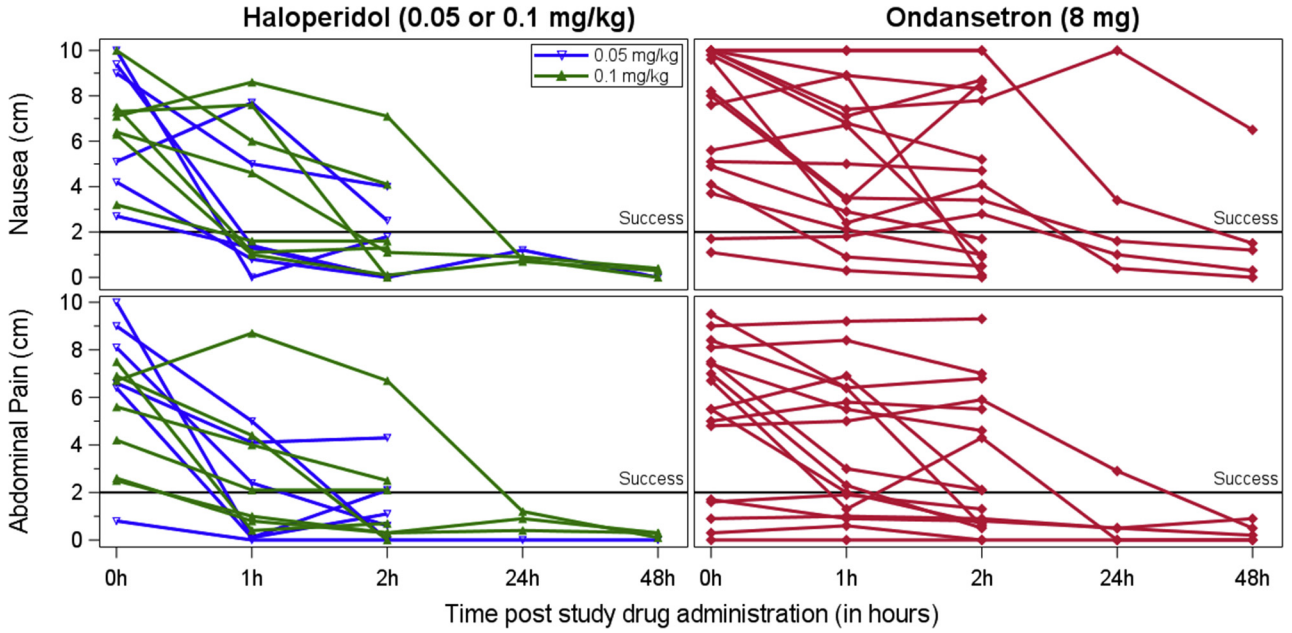

Figure 2. Improvement in nausea and abdominal pain after study drug administration. Nausea (upper row of charts) and abdominal pain (lower row) as recorded by each subject on 10-cm VAS over time are shown at baseline (t=0) and after study drug administration. The 2 dose levels of haloperidol (in blue and green, triangles) are combined in the left column and compared with ondansetron (in red, diamonds) on the right column of charts. The prespecified threshold of VAS score less than 2 cm to denote treatment "success" is shown.

calculation, are given in Appendix E1, available online at http://www.annemergmed.com.

RESULTS

Of 62 eligible patients approached for consent, 33 agreed to participate; 30 received at least 1 treatment (17 patients ondansetron 8 mg; 7 haloperidol 0.1 mg/kg, and 6 haloperidol 0.05 mg/kg) and 3 crossed over on a subsequent visit (Figure 1). Subjects were aged 18 to 66 years, were evenly split in a male:female ratio, and reported consuming an average of 1.5 g (SD 0.9 g) of cannabis daily beginning at approximately aged 19 years (SD 2 years). All subjects had positive urine tetrahydrocannabinol results by immunoassay. Baseline characteristics were comparable between study arms (Table).

Haloperidol at either dose caused a much larger reduction than ondansetron in both abdominal pain and nausea within 2 hours of administration (Figure 2). After adjusting for baseline, the mean difference in the primary outcome between the ondansetron and pooled haloperidol groups was 2.3 cm (95% confidence interval [CI] 0.6 to 4.0 cm; P=.01) favoring haloperidol (Table; Figures E1 and E2, available online at http://www.annemergmed.com). The use of haloperidol also resulted in higher treatment success (54% versus 29%; difference 24% [95% CI –16% to 59%]), reduced use of rescue antiemetics (31% versus 59%; difference –28% [95% CI –61% to 13%]), benzodiazepines (8% versus 41%; difference –33% [95% CI –62% to 4%]), or any medication (31% versus 76%; difference –46% [95% CI –74% to –4%]), and a shorter time to discharge (3.1 hours [SD 1.7] versus 5.6 [SD 4.5] hours; difference 2.5 hours [95% CI 0.1–5.0 hours]; P=.03, Wilcoxon rank sum). Among the 13 patients first randomized to haloperidol, the improvement in the primary outcome was similar between dose levels (0.9 cm in favor of the lower dose; 95% CI –1.7 to 3.4 cm).

No patients were lost to follow-up to ascertain the primary outcome at 2 hours, but only 9 (4 haloperidol, 5 ondansetron) returned the 24- and 48-hour VAS scores despite reminders by telephone, text, and e-mail. The safety analysis combining both treatment periods (18 ondansetron, 15 haloperidol) identified 3 prespecified events (1 moderate akathisia and 2 return visits for acute dystonia) (Table E1, available online at http://www.annemergmed.com), all after the higher haloperidol dose of 0.1 mg/kg. All 3 subjects were treated without difficulty, discharged, and withdrawn from further study eligibility for crossover, given the compromised blind. There were a total of 4 return visits (2 for dystonia and 2 for ongoing nausea and vomiting) within the week after haloperidol compared with 6 return visits (all for ongoing nausea and vomiting) after ondansetron.

LIMITATIONS

Our trial did not achieve the prespecified enrollment target. Trial enrollment was inefficient in part because of the requirement for ongoing, witnessed emesis, the frequent administration of intravenous ondansetron as a standing medical order for all-cause emesis before physician assessment, the reliance on on-site research personnel to facilitate enrollment, and the belief by several physicians that their own preferred treatment approach (whether haloperidol or ondansetron first) was superior. Furthermore, approximately half the potentially eligible subjects approached for consent refused, often because of skepticism regarding the diagnosis as disclosed during the consent process. We were unable to persuade subjects to return the 24- and 48-hour follow-up data despite several strategies. These inefficiencies proved difficult to overcome during the trial and contributed to low enrollment, much lower crossover rate than expected, and limited insight into the persistence of the treatments studied. Nevertheless, the effect size was also much stronger than anticipated, resulting in the trial's being halted early for efficacy despite the small sample size and unpaired analysis. Although the subjects do represent a convenience sample, the narrow inclusion and exclusion criteria support generalization of the findings to similar patients. Ultimately, most subjects were enrolled by the study authors, mitigating concerns that the low enrollment might introduce undue bias arising from unknown patient factors. Finally, absent a better understanding of the underlying cause,[5] and given the heterogeneity of cannabis and its constituents, the findings of this study may not be stable over time, or in other settings.

DISCUSSION

Although little is known about the underlying cause of this recurrent and distressing condition, an increasing body of case-based literature supports the use of haloperidol (or the closely related droperidol) for emergency treatment of cannabis hyperemesis syndrome.[5,7,8] This randomized controlled trial demonstrates the superiority of intravenous haloperidol over ondansetron, especially at a low, onetime dose of 0.05 mg/kg, for the common symptoms of nausea, vomiting, and abdominal pain. The average improvement in both nausea and abdominal pain exceeded the prespecified minimal clinically significant difference of 2 cm, a threshold widely used to represent a meaningful improvement in either symptom.[11] Subjects in the haloperidol arm also received fewer rescue medications, had shorter time to discharge from the ED, and had fewer return visits to the ED for ongoing symptoms compared with those in the ondansetron arm. Although the number of enrolled patients was small, the large improvement in measured outcomes suggests that haloperidol (or perhaps droperidol) should be considered the comparator agent in future trials and that ondansetron (especially at the far more common initial dose of 4 mg) should no longer be used as the first-line agent to abort emesis.

In addition to the clinical relevance, the marked difference in efficacy between these 2 very different antiemetic agents sheds some light on the underlying pathophysiology of this poorly understood condition. Disturbances of the foregut, including diurnal nausea and food aversion, are now recognized to be common adverse effects of regular cannabis use.[1,3,6] Ondansetron, a peripheral and central 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor antagonist, is believed to act primarily at the chemoreceptor trigger zone. Both ondansetron and cannabis derivatives have antiemetic properties and have received regulatory approval for patients with nausea and vomiting caused by chemotherapy. As such, one might expect ondansetron to be somewhat effective assuming some commonalities in mechanism of action, but this does not seem to be the case.[9] Ondansetron is also more effective in preventing nausea and vomiting, and less so when patients are actively vomiting. Additionally, the poor efficacy of ondansetron likely undermines patient confidence and contributes to the challenge of treating this disorder in the ED.

Haloperidol and other butyrophenones have long been recognized to have antiemetic properties in migraine, gastroparesis, and postanesthesia, perhaps because of their potent D_2-receptor inverse agonism or 5-HT$_{2A}$ antagonism.[2,7,10] Haloperidol also antagonizes σ, α-adrenergic, and other receptors. The efficacy of the lower dose suggests that the therapeutic effect is mediated through one of the drug's primary sites of action. Dopamine synthesis, turnover, and efflux have been shown to increase in response to Δ^9-tetrahydrocannabinol, and complex interactions exist between dopamine and cannabinoid-1 receptors.[2,8] In addition to being antiemetic, haloperidol is highly anxiolytic, and extreme anxiety and apprehensiveness during bouts of hyperemesis are characteristic of this disorder. We observed a significant improvement in abdominal pain (as well as nausea) in our subjects despite that haloperidol is not traditionally considered to have analgesic properties. We encourage future research to measure the domain of anxiety, in addition to vomiting and pain. Neither haloperidol nor ondansetron is known to interact with the vanilloid (TrpV1) receptor, the putative site of action of capsaicin also used for this disorder.[9]

In summary, we found intravenous haloperidol to be superior to ondansetron as first-line treatment in cannabis users who present to the ED with active and ongoing vomiting. Haloperidol rapidly reduces abdominal pain and nausea, reducing the need for rescue antiemetics, and allowing earlier discharge from the ED. A onetime, low dose of haloperidol is less likely to cause acute dystonia than higher doses and is therefore recommended. The distinct mechanism of action of haloperidol may provide insight into the underlying pathophysiology of this common adverse effect of habitual cannabis use.

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Author contributions: MLAS conceived the study. AJR, MLAS, and AGD designed the trial. AJR and MLAS supervised the conduct of the trial and data collection, and managed the data, including abstraction, entry, and quality control. All authors promoted recruitment of subjects. AGD provided statistical advice on the study design and analyzed the data, and all authors contributed to the interpretation of the results. AJR and MLAS drafted the article, and all authors contributed substantially to its revision. MLAS takes responsibility for the paper as a whole.

All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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