Effect of gabapentin on hyperemesis gravidarum: a double-blind, randomized controlled trial

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BACKGROUND: Hyperemesis gravidarum is a disabling disease of nausea, vomiting, and undernutrition in early pregnancy for which there are no effective outpatient therapies. Poor weight gain in hyperemesis gravidarum is associated with several adverse fetal outcomes including preterm delivery, low birthweight, small for gestational age, low 5-minute Apgar scores, and neurodevelopmental delay. Gabapentin is most commonly used clinically for treating neuropathic pain but also substantially reduces chemotherapy-induced and postoperative nausea and vomiting. Pregnancy registry data have shown maternal first-trimester gabapentin monotherapy to be associated with a 1.2% rate of major congenital malformations among 659 infants, which compares favorably with the 1.6% to 2.2% major congenital malformation rate in the general population. Open-label gabapentin treatment in hyperemesis gravidarum was associated with reduced nausea and vomiting and improved oral nutrition.

OBJECTIVE: This study aimed to determine whether gabapentin is more effective than standard-of-care therapy for treating hyperemesis gravidarum.

STUDY DESIGN: A double-blind, randomized, multicenter trial was conducted among patients with medically refractory hyperemesis gravidarum requiring intravenous hydration. Patients were randomized (1:1) to either oral gabapentin (1800—2400 mg/d) or an active comparator of either oral ondansetron (24—32 mg/d) or oral metoclopramide (45—60 mg/d) for 7 days. Differences in Motherisk—pregnancy-unique quantification of nausea and emesis total scores between treatment groups averaged over days 5 to 7, using intention-to-treat principle employing a linear mixed-effects model adjusted for baseline Motherisk—pregnancy-unique quantification of nausea and emesis scores, which served as the primary endpoint. Secondary outcomes included Motherisk—pregnancy-unique quantification of nausea and emesis nausea and vomit and retch subscores, oral nutrition, global satisfaction of treatment, relief, desire to continue therapy, Nausea and Vomiting of Pregnancy Quality of Life, and Hyperemesis Gravidarum Pregnancy Termination Consideration. Adjustments for multiple comparisons were made employing the false discovery rate.

RESULTS: A total of 31 patients with hyperemesis gravidarum were enrolled from October 2014 to May 2019. Among the 21 patients providing primary outcome data (12 assigned to gabapentin and 9 to the active comparator arm), 18 were enrolled as outpatients and all 21 were outpatients from days 5 to 7. The study groups' baseline characteristics were well matched. Gabapentin treatment provided a 52% greater reduction in days 5 to 7 baseline adjusted Motherisk—pregnancy-unique quantification of nausea and emesis total scores than treatment with active comparator (95% confidence interval, 16—88; P=.01). Most secondary outcomes also favored gabapentin over active comparator treatment including 46% and 49% decreases in baseline adjusted Motherisk—pregnancy-unique quantification of nausea and emesis nausea (95% confidence interval, 19—72; P=.005) and vomit and retch subscores (95% confidence interval, 21—77; P=.005), respectively; a 96% increase in baseline adjusted oral nutrition scores (95% confidence interval, 27—165; P=.01); and a 254% difference in global satisfaction of treatment (95% confidence interval, 48—459; P=.03). Relief (P=.06) and desire to continue therapy (P=.06) both showed trends favoring gabapentin treatment but Nausea and Vomiting of Pregnancy Quality of Life (P=.68) and Hyperemesis Gravidarum Pregnancy Termination Consideration (P=.58) did not. Adverse events were roughly equivalent between the groups. There were no serious adverse events.

CONCLUSION: In this small trial, gabapentin was more effective than standard-of-care therapy for reducing nausea and vomiting and increasing oral nutrition and global satisfaction in outpatients with hyperemesis gravidarum. These data build on previous findings in other patient populations supporting gabapentin as a novel antinausea and antiemetic therapy and support further research on gabapentin for this challenging complication of pregnancy.

Key words: clinical trial, maternal-fetal medicine, metoclopramide, nausea, nutrition, obstetrics, ondansetron, pregnancy, vomiting

Introduction

Hyperemesis gravidarum (HG) is a disabling disease of severe nausea, vomiting, and undernutrition in early pregnancy leading to dehydration and/or weight loss. HG is the second leading cause of hospitalization during pregnancy.[1] The typical nausea and vomiting of pregnancy (NVP) affects about 80% of patients, is effectively treated with several different pharmacotherapies, and resolves in 91% of patients by 20 weeks' gestation.[2,3] In contrast, HG affects approximately 0.3% to 2% of pregnancies, persists throughout the duration of pregnancy in 22% of patients, and is associated with higher maternal morbidities, such as venous thromboembolism, and fetal morbidities, such as neurodevelopmental delay.[4–7] Several reviews of HG randomized controlled trials (RCTs) have concluded that there is insufficient evidence to support the use of any pharmacotherapy for reducing HG symptoms, although ondansetron, promethazine, and metoclopramide are frequently used in clinical practice.[8–12] Hospital admission and intravenous (IV) hydration provide temporary symptom relief for most patients with HG[13,14]; however, approximately 35% will require

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AJOG MFM at a Glance

Why was this study conducted?

This study was conducted to determine whether gabapentin was more effective than standard-of-care therapy for treating hyperemesis gravidarum in the outpatient setting.

Key findings

Gabapentin was more effective than standard-of-care therapy for reducing nausea and vomiting in outpatients with hyperemesis gravidarum and for increasing oral nutrition and global satisfaction of treatment. Gabapentin therapy was well tolerated.

What does this add to what is known?

Gabapentin is the first therapy shown to reduce nausea and vomiting and improve oral nutrition in outpatients with hyperemesis gravidarum. If these findings can be replicated, gabapentin therapy may improve the prognoses of hyperemesis gravidarum patients and their infants.

readmission owing to symptom recurrence once in the outpatient setting.[15] This lack of effective HG outpatient treatment likely contributed to survey results showing that 15% of patients with HG reported terminating at least 1 pregnancy primarily owing to feelings of "no hope for relief" and being "unable to care for self or family."[4] If an outpatient medical therapy was effective in reducing HG symptoms, this therapy could potentially improve the prognoses for both patients with HG and their infants.

In 2003, gabapentin was first reported to improve medically refractory, chemotherapy-induced nausea in an open-label trial among 9 patients with breast cancer.[16] Subsequently, several RCTs showed gabapentin therapy to be effective for postoperative and chemotherapy-induced nausea and vomiting.[17–24] Based on encouraging pilot data associating open-label gabapentin therapy with reduced HG symptoms and improved oral nutrition,[25] we performed an RCT comparing the effectiveness of gabapentin with an active comparator for treating HG. We focused on enrolling outpatients with HG to better address this unmet therapeutic need.

Materials and Methods

Trial design

A double-blind, parallel-group, RCT was performed with patient enrollment from October 2014 to May 2019 at 3 university medical centers. The study was registered with ClinicalTrials.gov (NCT02163434), and each university's institutional review board (IRB) approved the study before patient enrollment. All patients provided written informed consent.

Patients with NVP were screened for eligibility in participating emergency departments, outpatient clinics (obstetrics and gastroenterology), and antepartum inpatient wards. Eligible patients who provided a written informed consent were randomly assigned to either oral gabapentin or an active comparator therapy (1:1) for 14 days by an independent data monitoring center using an online system with randomization sequences concealed to all clinical personnel. The biostatistician and the research pharmacists at each site were the only unblinded study personnel, ensuring that the correct study drug was dispensed after patient randomization and treatment allocation was concealed from patients and clinical personnel. The active comparator was ondansetron before July 1, 2015, and metoclopramide after July 1, 2015. This change was deemed necessary owing to the public release of 2 separate studies associating ondansetron use in pregnancy with increased rates of congenital cardiac malformations and the publication of an opinion article expressing concern about ondansetron use in pregnancy.[12,26,27] Previous studies showed no treatment benefit for ondansetron, metoclopramide, or promethazine in head-to-head HG trials[28–30]; however, metoclopramide had the most extensive data supporting its safety for use in NVP and, thus, was selected to replace ondansetron.[31]

Compounded gabapentin 300 mg, ondansetron 4 mg, or metoclopramide 7.5 mg (active pharmaceutical ingredients all purchased from PCCA, Houston, TX) identically appearing capsules were initiated at 1 capsule 2 times a day (bid) and titrated to 2 capsules 3 times a day (tid) for 7 days. For patients experiencing bothersome nausea or vomiting and no bothersome adverse events after day 7, the dosage could be increased to 2 capsules 4 times a day (qid). This equated to a maximum daily gabapentin, ondansetron, or metoclopramide dose of 2400 mg, 32 mg, or 60 mg, respectively. Patients who remained symptomatic and had 2 to 4+ ketonuria on provided home test kits were instructed to go to the local emergency department for IV hydration.

On May 25, 2016, the double-blind study phase was reduced from 14 days to 7 days and eligibility expanded to include patients with 2 to 4+ ketonuria (vs only 3–4+), owing to the lack of association between HG severity and degree of ketonuria.[32] In the outpatient setting, it seemed to the investigators that 14 days was too long of a time period for patients with HG, who were still highly symptomatic, to tolerate and was strongly contributing to high patient attrition. Study capsules were initiated at 1 capsule bid and titrated to 2 capsules tid by day 5. Patients experiencing bothersome nausea or vomiting and no bothersome adverse events could increase to 2 capsules qid for days 6 to 7. All protocol changes were approved by the National Institutes of Health and all IRBs before implementation.

After the double-blind study phase, patients were offered open-label gabapentin treatment, which was initiated according to the same titration schedule. As needed, ondansetron 8 mg qid, before July 1, 2015, or metoclopramide 10 mg

qid, after July 1, 2015, was also provided to patients during the open-label phase. Open-label gabapentin treatment was continued at the lowest effective dose for the duration of the pregnancy, if necessary, based on the patient's symptoms. The purpose of including the open-label phase was to improve patient enrollment and retention during the double-blind study phase.

Study site visits were made at the end of the double-blind phase and after 2 weeks of the open-label phase. All clinical research staff and patients remained blinded to treatment allocations until after the final patient completed the study, and all statistical analyses were completed on September 23, 2019.

Patients

Patients at the age of >18 years were eligible for enrollment if they had 2 to 4+ ketonuria, <3.4 mmol serum potassium, or >5% weight loss from their prepregnancy weight; failed therapy with at least 1 antiemetic agent; received at least 2 administrations of IV hydration separated by at least 1 week or daily vomiting for the previous 7 days and at least 1 administration of IV hydration; had a normal appearing, singleton pregnancy of <16 weeks' gestational age by fetal ultrasound; had a Motherisk—pregnancy-unique quantification of nausea and emesis (PUQE) score of ≥12 for the 24 hours before enrollment; did not receive or plan to receive a peripherally inserted central catheter line; did not decide to terminate the pregnancy; and agreed to discontinue all current prescription and over-the-counter antiemetic therapy.

Endpoints

The primary endpoint was change in Motherisk-PUQE total scores from baseline to days 5 to 7. The Motherisk-PUQE diary is a validated scale of NVP.[33] Baseline Motherisk-PUQE scores consisted of the 24-hour period before enrollment according to patients' recall. After enrollment, patients recorded Motherisk-PUQE data daily on a paper diary throughout the double-blind study phase and for the first 14 days of the open-label study phase.

Secondary outcomes included Motherisk-PUQE nausea and vomit and retch subscores and an investigator-developed daily oral nutrition score consisting of a score of 0 to 5 for each meal of breakfast, lunch, and dinner (0, nothing by mouth; 1, only a small amount of liquids; 2, a small amount of food [eg, crackers, bread]; 3, slightly more than a small amount of food; 4, a moderate amount of food intake; 5, normal or almost normal amount of food). Patients completed the Nausea and Vomiting of Pregnancy Quality of Life (NVPQOL) questionnaire[34] and the investigator-developed Hyperemesis Gravidarum Pregnancy Termination Consideration (HGPTC) questionnaire at baseline and at the end of the double-blind study phase (Supplemental Data). At the end of the double-blind phase and 2 weeks of the open-label phase, patients completed a global satisfaction of treatment question (ranging from 0 ["Dissatisfied"] to 4 ["Completely Satisfied"]), a relief question (ranging from 1 ["No Relief"] to 7 ["Complete Relief"]), and a no/yes (0/1) inquiry of whether they would choose to continue the study medication based on the benefits and side effects experienced.

Owing to the protocol change on May 25, 2016, decreasing the double-blind study phase from 14 to 7 days, the Motherisk-PUQE and oral nutrition endpoints were also changed on that date to changes from baseline to the means of days 5 to 7 for all patients, including those enrolled before this protocol change, for data consistency. Questionnaire secondary endpoints were included in the double-blind study phase analyses whether they were assessed at day 14 (before May 25, 2016) or day 7 (after May 25, 2016) because these were assessed at the end of double-blind study phase. These protocol changes were locked on May 25, 2016.

Statistical analysis

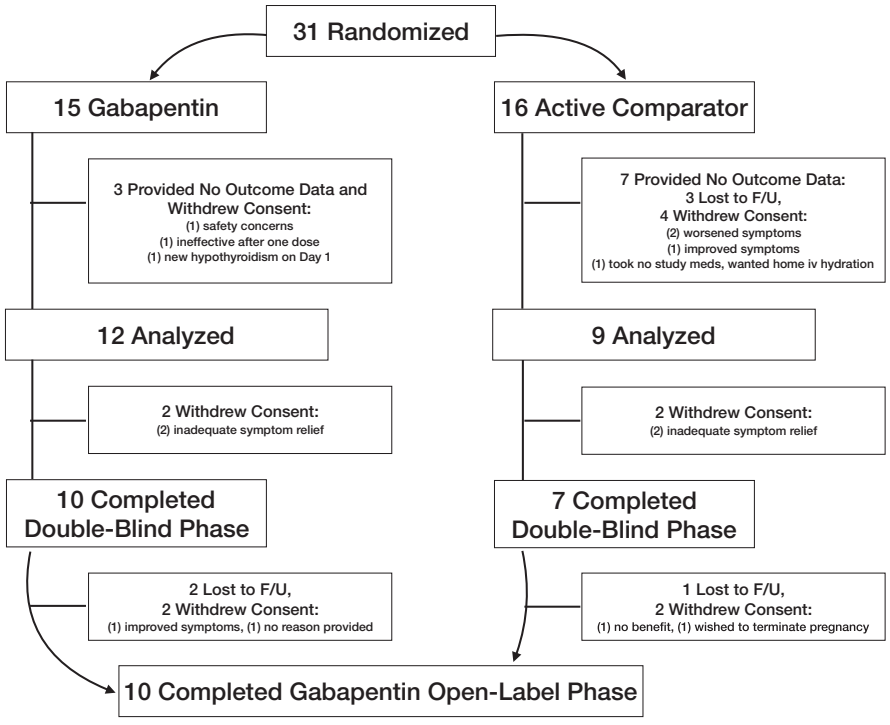
Based on the results from the gabapentin HG pilot study,[25] we anticipated a 4.4 point intergroup difference for the primary endpoint with a standard deviation of 6 and a 15% patient attrition rate. With these assumptions, we calculated that 40 subjects per group would be necessary to provide 85% power to detect a significant intergroup difference with a 2-sided type I error of 0.05. On May 25, 2016, the sample size calculation was modified to 60 using the same calculations but with the power reduced to 80%.

Baseline comparisons were completed using *t* tests or Fisher exact tests as appropriate to the data. Differences between the treatment groups in Motherisk-PUQE and oral nutrition score outcomes were averaged for days 5 to 7, adjusted for baseline scores, and evaluated based on the intention-to-treat principle by employing a linear mixed-effects model.[35] For other secondary outcomes with single time point assessments, intergroup analyses also used a linear mixed-effects model adjusting for baseline values as appropriate. Adjustments for multiple comparisons of all endpoints were made employing the false discovery rate.[36] In addition to point and 95% confidence interval estimates, we also assessed effect sizes for reprobated treatment effects (Cohen's d).[37] All analyses were carried out using SAS/STAT software version 9.4 of the SAS System (SAS Institute, Cary, NC) on a Windows 10 platform.

Results

From October 2014 to May 2019, 31 patients with HG were enrolled and randomized. Enrollment was closed before enrolling the planned 60 patients owing to cessation of funding. Notably, 10 patients (3 assigned to gabapentin and 7 to the active comparator arm) failed to provide any postrandomization data and were excluded from the efficacy analyses, according to the predefined analysis plan (Figure 1). Among the 21 patients providing primary outcome data (12 assigned to gabapentin and 9 to the active comparator arm, 4 of whom received ondansetron and 5 metoclopramide), 18 were enrolled as outpatients and all 21 were outpatients on days 5 to 7. Treatment group baseline characteristics were well matched (Table 1). Moreover, 4 of these 21 patients, 2 from each treatment arm, withdrew during the double-blind phase

FIGURE 1
Patient flow



F/U, follow-up.

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all because of inadequate symptom relief (Figure 1).

Gabapentin treatment provided significantly greater reductions in days 5 to 7 baseline adjusted Motherisk-PUQE total scores (−6.87 points; P=.01; Cohen's d=1.25) (Table 2; Figure 2). Secondary outcomes of Motherisk-PUQE nausea and vomit and retch subscores, oral nutrition (Figure 3), and global satisfaction of treatment all significantly favored gabapentin treatment whereas relief and desire to continue therapy both showed trends favoring gabapentin treatment (Table 2). Notably, 5 patients in each group received IV hydration during the double-blind study phase. Open-label gabapentin treatment observations are presented in the Supplemental Data.

Adverse events

Notably, 4 of the 15 patients receiving gabapentin (27%) and 3 of the 16 patients receiving the active comparator treatment (19%) reported adverse events of rapid heart rate, hot flashes, fatigue, and dizziness with fatigue and nausea (respectively for gabapentin) and headache with dizziness, diarrhea, and abdominal pain (respectively for the active comparator). None of these adverse events contributed to patient withdrawal except for the patient receiving gabapentin experiencing dizziness with fatigue and nausea owing to nausea. During the open-label gabapentin treatment phase, 1 patient reported mild dizziness, confusion, and forgetfulness that did not necessitate any change in gabapentin dosing. There were no serious adverse events throughout the study. Pregnancy and fetal outcomes were available for 9 patients (5 receiving gabapentin and 4 receiving active comparator during the double-blind study phase). One patient from each group delivered prematurely at 36 and 35 weeks' gestation, respectively, whereas the other 7 patients delivered at term. All infant weights at delivery were appropriate for gestational age. No infant congenital defects were reported by the patients or documented in hospital or pediatrician records.

Structured Discussion/ Comment

Principal findings

This RCT showed oral gabapentin to be more effective than standard-of-care HG outpatient therapy for reducing nausea and vomiting and increasing oral nutrition and global satisfaction and to provide large treatment effect sizes for all of these endpoints (ie, a Cohen's d of ≥0.8) (Table 2).[37] The treatment effect sizes and improved global satisfaction support gabapentin's benefits to be clinically meaningful to patients. The outcomes of relief and desire to continue therapy, but not NVPQOL and HGPTC, trended to favor gabapentin treatment (Table 2). Factors that may have contributed to the lack of therapeutic benefit favoring 1 therapy on the NVPQOL and HGPTC scales include inadequate power, insensitivity of these scales to capture therapeutic benefits for a 7-day period, and lack of HGPTC scale validity. Gabapentin therapy was well tolerated using our titration schedule with a comparable rate of adverse events with standard-of-care therapy. The adverse events of tachycardia and hot flashes were unlikely caused by gabapentin therapy because gabapentin has not previously been reported to have cardiovascular effects and is known to effectively reduce hot flashes in postmenopausal women.[38,39]

Results

No outpatient therapies have been shown to improve HG symptoms before this report.[8–11] The American College of Obstetricians and Gynecologists 2018 practice bulletin provided level B support for the use of methylprednisolone in patients with severe and refractory NVP "as a last-resort" owing to its increased "risk profile"[8] for congenital oral cleft.[40] Recently, the use of transdermal clonidine for 5 days was shown to provide significant improvements in Motherisk-PUQE and visual analog scale

TABLE 1
Baseline characteristics

	Gabapentin (n=12)	Active comparator (n=9)
Characteristic, mean (SD)		
Age, y	26.2 (5.9)	26.3 (3.9)
Gestational age, wk	8.8 (2.0)	9.9 (2.6)
Duration of nausea, wk	3.9 (2.7)	5.2 (2.5)
Duration of vomiting, wk	3.7 (2.6)	4.4 (2.2)
Ketonuria grade, 1−4+	3.0 (0.7)	2.8 (1.3)
Weight loss from prepregnancy, %	4.5 (6.4)	5.8 (2.9)
>5% weight loss from prepregnancy, % of patients	67	50
Number of times received intravenous hydration this pregnancy	3.0 (1.5)	2.3 (1.2)
Number of different antiemetics tried this pregnancy	2.6 (1.4)	3.0 (1.2)
Motherisk-PUQE, total score	18.8 (4.3)	17.0 (6.5)
Motherisk-PUQE, nausea subscore	4.5 (0.8)	4.3 (1.0)
Motherisk-PUQE, vomit/retch subscore	4.9 (1.6)	5.1 (1.0)
Oral nutrition score	2.3 (3.7)	2.6 (2.5)
NVPQOL score	175.1 (25.4)	192.3 (20.4)
HGPTC score	2.0 (0.9)	3.6 (1.4)
Number reporting severe nausea and vomiting in a previous pregnancy/number with a previous pregnancy	3/9	5/8
Demographics, n (%)		
Non-Hispanic white	2 (16.7)	2 (22.2)
Non-Hispanic black	10 (83.3)	6 (66.7)
Hispanic white	0 (0)	1 (11.1)

Differences between gabapentin and active comparator groups were assessed using a *t* test with or without Satterthwaite correction or Fisher exact test, as appropriate. The only baseline intergroup comparison showing a significant difference with $P \leq 0.05$ was the HGPTC score.

HGPTC, Hyperemesis Gravidarum Pregnancy Termination Consideration; *NVPQOL*, Nausea and Vomiting of Pregnancy Quality of Life; *PUQE*, pregnancy-unique quantification of nausea and emesis; *SD*, standard deviation.

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scores in a single-site, double-blind, randomized controlled, cross-over design trial among 12 inpatients with HG but did significantly decrease patients' systolic blood pressure.[41] It remains to be determined whether transdermal clonidine can provide similar benefits for HG in the outpatient setting and whether it can improve oral nutrition.

Clinical and research implications

Pregnancy registry data have reported 8 major congenital malformations (MCMs) among 659 infants (1.2%) exposed to first-trimester maternal gabapentin monotherapy,[42,43] which compares favorably with the 1.6% to 2.2% MCM rate in the general population.[44,45] Approximately 500 first-trimester exposures are needed to provide 80% power to detect a 2-fold increase in MCMs.[46] Maternal gabapentin use has also been associated with roughly equivalent rates of premature birth, birthweight after correction for gestational age, and maternal hypertension/eclampsia as those reported in the general population.[42] These data support gabapentin's relative safety for use in pregnancy; however, a larger number of exposures may reveal increased risks of less common MCMs or other adverse outcomes. Therefore, patients with NVP or HG who are prescribed gabapentin therapy should be encouraged to register in a pregnancy registry, such as the North American Antiepileptic Drug Pregnancy Registry, to increase the power to detect any potential risks associated with first-trimester maternal use.

A safe and effective outpatient HG therapy may reduce not only HG-induced maternal psychosocial distress and the associated 15% rate of fetal mortality[4] but also other HG-associated adverse fetal outcomes including low birthweight, small for gestational age,

TABLE 2
Primary and secondary outcomes (raw data)

Mean (SE)	Gabapentin (n=12)	Active comparator (n=9)	Difference (95% CI)	Cohen's d	*P* value[a]
Primary outcome					
Motherisk-PUQE, total score, baseline adjusted average for days 5–7	6.35 (2.44)	13.22 (2.39)	−6.87 (−11.61 to −2.14)	1.25	.01
Secondary outcomes					
Motherisk-PUQE, nausea subscore, baseline adjusted average for days 5–7	2.01 (0.45)	3.69 (0.45)	−1.69 (−2.67 to −0.70)	1.87	.005
Motherisk-PUQE, vomit/retch subscore, baseline adjusted average for days 5–7	2.97 (0.77)	5.80 (0.89)	−2.83 (−4.47 to −1.20)	2.15	.005
Oral nutrition score, baseline adjusted average for days 5–7	7.86 (1.23)	4.01 (1.34)	3.85 (1.10–6.61)	1.22	.01
Global satisfaction of treatment score (range, 0–4)	2.22 (1.56)	0.63 (0.74)	1.60 (0.30–2.89)	1.31	.03
Relief score (range, 1–7)	4.56 (2.40)	2.50 (1.31)	2.06 (0.02–4.10)	1.07	.06
Desire to continue therapy score (0=no, 1=yes)	0.67 (0.50)	0.14 (0.38)	0.52 (0.04–1.01)	.50	.06
NVPQOL score, follow-up adjusted for baseline	128.31 (19.11)	148.58 (15.16)	−10.39 (−62.79 to 42.14)		.68
HGPTC score, follow-up adjusted for baseline	2.44 (0.48)	2.02 (0.41)	0.42 (−0.93 to 1.77)		.58

Difference=gabapentin−active comparator values.

CI, confidence interval; *HGPTC*, Hyperemesis Gravidarum Pregnancy Termination Consideration; *NVPQOL*, Nausea and Vomiting of Pregnancy Quality of Life; *PUQE*, pregnancy-unique quantification of nausea and emesis; *SE*, standard error.

[a] Corrected for multiple comparisons using the false discovery rate.[36]

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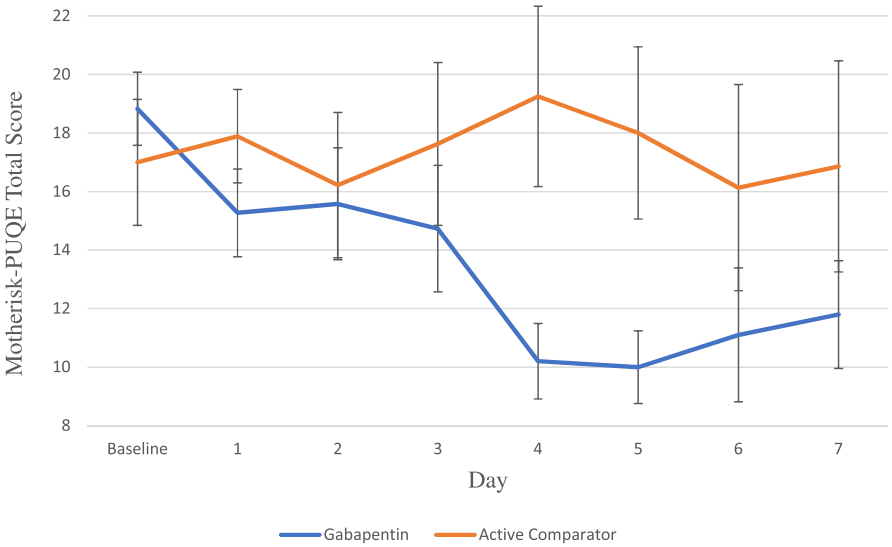
FIGURE 2
Motherisk-PUQE total scores by treatment



Mean daily Motherisk-PUQE total scores with standard error bars. A value of 6 denotes no nausea or emesis.

PUQE, pregnancy-unique quantification of nausea and emesis.

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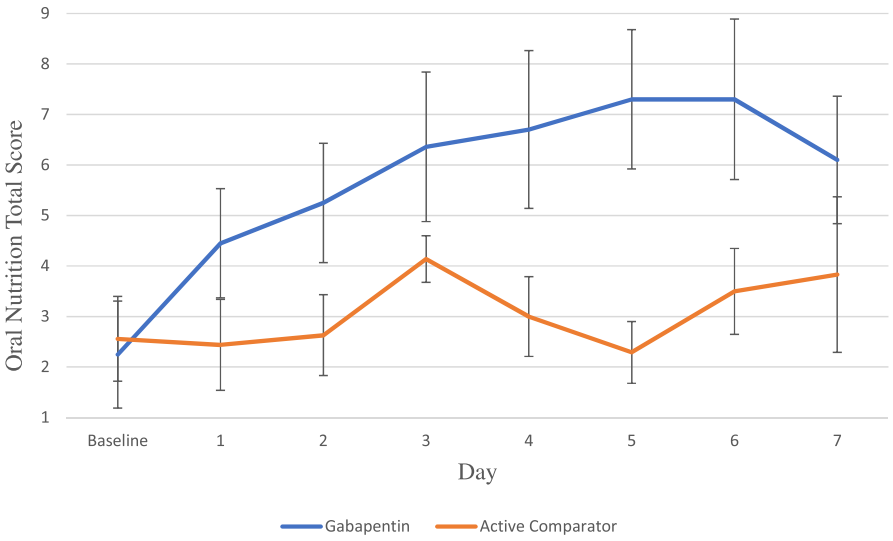
preterm delivery, low 5-minute Apgar scores, and neurodevelopmental delay.[5,6,47] Because poor maternal nutrition and weight gain are strongly associated with most HG-associated adverse maternal and fetal outcomes,[47] an HG therapy shown to improve oral nutrition, such as gabapentin (Table 2; Figure 3), may be particularly beneficial.

It has been theorized that gabapentin's mechanism of action in the treatment of all the aforementioned nausea and vomiting conditions, including HG, involves the mitigation of calcium currents in central nausea/vomiting centers (such as the area postrema of the medulla) by binding to alpha-2/delta subunits of voltage-gated calcium channels that have been up-regulated in this location in response to the relevant central nervous system stressor such as chemotherapy, anesthesia, or increased systemic factors[48] in early pregnancy.[24,25] In support, altered intracellular calcium homeostasis has been implicated in the

FIGURE 3
Oral nutrition total scores by treatment



Mean daily oral nutrition total scores with standard error bars. A value of 15 denotes normal oral nutrition.

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pathophysiology of HG based on family genetic studies.[49] Further research is needed to explore this hypothesis.

Strengths and limitations

The strengths of this study are its randomized, double-blind, parallel-group, multicenter design using a standard-of-care comparator in the outpatient setting. However, there were several weaknesses of this study. First, it is difficult to assess how the 2 major protocol changes may have affected the study results but both were felt to be necessary to preserve patient enrollment and retention. Despite these efforts, the number of patients enrolled was only 52% of the planned sample size (31 of 60). It seemed to the investigators that the main reason eligible patients declined to enroll was because of a reluctance to stop their current antiemetic therapy before randomization, although these data were not formally captured. Second, only 68% of enrolled patients provided outcome data (21 of 31). Such a high patient attrition rate in a small study has the potential to affect the study arms in unpredictable ways. For example, over twice as many patients assigned to the active comparator failed to provide outcome data as those assigned to gabapentin (Figure 1), which could have impaired the power of patient randomization and introduced bias. It is reassuring that the groups' baseline characteristics were well-matched and gabapentin provided significant and large magnitudes of benefit (a Cohen's d of $\geq$0.8) for the primary and several secondary endpoints (Table 2). Nevertheless, it would be beneficial for our findings to be confirmed in a larger RCT with a much lower patient attrition rate. To achieve this goal, a study design other than the parallel-group RCT may be necessary particularly when enrolling HG outpatients. Previous clinical trials enrolling patients with moderate to severe NVP have reported similar challenges with patient enrollment and/or compliance with study procedures as this study.[50,51] One of these studies was only able to enroll 56% of its planned inpatient sample size,[50] and the other study received complete questionnaire data from only 57% of enrolled patients.[51] It is unclear how much the condition of NVP contributes to these research challenges vs pregnancy, in general.[52] For example, in a survey of postpartum patients, only 12% stated that they would have enrolled in a RCT comparing vaginal with cesarean delivery.[53]

Conclusions

This small trial showed gabapentin to be more effective than standard-of-care therapy for reducing nausea and vomiting and improving oral nutrition and global satisfaction in HG outpatients and provided large treatment effect sizes across all of these endpoints. These results support further research on gabapentin for treating HG. ■

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