Metoclopramide Versus Ondansetron for the Treatment of Vomiting in Children With Acute Gastroenteritis

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ABSTRACT

Objective: To compare the efficacy and safety of ondansetron versus less expensive metoclopramide in the treatment of children with persistent vomiting with acute gastroenteritis.

Materials and Methods: A double-blind trial including consecutive consented patients ages 1 to 14 years was conducted in an urban infirmary setting from June 2008 through December 2008. Children were randomized to receive a single dose of intravenous ondansetron or metoclopramide. The primary efficacy outcome was the proportion of patients with cessation of vomiting shortly after completion of the study medication infusion in each group. Observed adverse effects and diarrhea frequency during admission and in follow-up were recorded to assess safety.

Results: One hundred sixty-seven previously healthy children (median age 3 years) diagnosed as having acute gastroenteritis with persistent vomiting completed treatment and observation. Cessation of vomiting was achieved in 68/84 patients (81%) of the ondansetron and 60/83 (72%) of the metoclopramide groups, $P = 0.14$. Mean time to complete cessation of vomiting was 39 minutes (SD 111) for ondansetron, and 61 minutes (SD 110) for metoclopramide, $P = 0.2$. The mean length of infirmary stay was 550 minutes (SD 427) for ondansetron and 575 minutes (SD 449) for metoclopramide, $P = 0.71$. Revisit rate, readmissions rate, and frequency of diarrhea after discharge were similar in the 2 treatment groups. No adverse reaction or other safety concerns were identified.

Conclusions: In the sample size tested, intravenous metoclopramide therapy did not differ from ondansetron in the treatment of persistent vomiting for children with gastroenteritis admitted for intravenous fluid hydration.

Key Words: gastroenteritis, metoclopramide, ondansetron, vomiting

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Acute gastroenteritis is among the most common gastrointestinal tract diseases in young children. In the United States 30 million children develop acute gastroenteritis annually, and 220,000 patients younger than 5 years old require hospitalization for the disease every year (1–3). In Qatar in 2008, 40,000 patients were presented to the Pediatric Emergency Center for acute gastroenteritis, 10% of whom required admission to the emergency short-stay unit.

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The American Academy of Pediatrics recommends oral rehydration solution as the first-line treatment in uncomplicated cases (1). Intravenous fluids may be required if vomiting persists or enough oral fluids cannot be tolerated to replace the ongoing losses. Although many patients demonstrate reduction in nausea and vomiting symptoms after initiation of parenteral fluids, others will continue to vomit and need a longer stay in the hospital (4–6).

Because vomiting is distressing and unpleasant for both children and their parents, antiemetics are used commonly. In a national survey in the United States, 79.2% of emergency physicians and 52.2% of pediatricians would prescribe antiemetics to treat vomiting in children with gastroenteritis (7). A similar survey in Italy revealed that 71% of hospital pediatricians and 96% of family physicians would prescribe antiemetics for the same group (8).

Metoclopramide is a dopamine and serotonin antagonist that works in the nervous system chemoreceptor trigger zone and promotes intestinal motility (9). It has been evaluated for the treatment of vomiting in children with acute simple gastroenteritis in 2 randomized trials, with conflicting results. One study showed that metoclopramide suppository is more effective than placebo at reducing nausea and vomiting, and the second found that intravenous metoclopramide did not significantly reduce vomiting when compared with placebo (10,11). Extrapyramidal reactions including dystonia, akathisia, and oculogyric crises are common adverse effects in children, reported in as high as 25% (12,13). In spite of the above, metoclopramide is still considered one of the preferred antiemetic treatments for children with gastroenteritis in some of the developed countries (8,14). In Qatar in 2008, more than 35% of children presented to the main pediatric emergency center with gastroenteritis and received metoclopramide.

Ondansetron, a selective serotonin antagonist that works centrally and peripherally in the nervous system (9), was investigated for the treatment of vomiting in children with acute simple gastroenteritis and proved efficient in decreasing the need for hospital admission, decreasing the need for intravenous fluid use, vomiting cessation, and improving oral rehydration acceptance, as compared with placebo in randomized controlled trials (10,15–20). Mild self-limited diarrhea is the only reported common adverse effect based on the previous studies (10,17,18,21). Unavailability and relatively high cost of ondansetron are considered the main disadvantages of its use.

We reasoned that intravenous ondansetron may be more effective and safer when compared with metoclopramide in the treatment of vomiting in simple gastroenteritis in young children, alleviating symptoms and preventing longer hospitalization.

The 2008 guidelines from European societies stated that antiemetics should not be routinely used, but may be of value for selected children and should be evaluated in randomized controlled trials performed in this specific population (22). Therefore, we compared metoclopramide with ondansetron for efficacy in acute simple gastroenteritis with persistent vomiting.

MATERIALS AND METHODS

Study Design

We conducted a single-center, double-blind, randomized controlled clinical trial to compare the efficacy of a single dose of either intravenous ondansetron or metoclopramide in the treatment of persistent vomiting in acute simple gastroenteritis in patients admitted to the pediatric emergency infirmary short-stay unit.

Setting and Participants

The study was conducted between June 2008 and December 2008 in the short-stay unit of the Pediatric Emergency Center of Hamad General Hospital, the only pediatric emergency facility in Qatar. The center serves an average of 200,000 patients annually and manages 42 beds in an infirmary short-stay unit. Patients admitted to the unit are assessed at least every 6 hours by a pediatrician to determine readiness for discharge. The length of stay in the unit for gastroenteritis is generally 8 to 72 hours.

Children ages 1 to 14 years presenting to the unit for the treatment of acute simple gastroenteritis with persistent vomiting, who met defined criteria for mild-to-moderate dehydration (23), failed oral rehydration trial in the center, and were admitted to the short-stay unit for intravenous hydration, were eligible for the study. Acute simple gastroenteritis required having vomited with at least 1 episode of diarrhea. Persistent vomiting was defined as more than 3 episodes of vomiting within 24 hours of presentation. Hydration status on enrollment and through admission was determined by 1 of the 6 pediatric board–certified physicians covering the gastrointestinal bay of the unit, based on the predefined criteria (23).

Patients were excluded from the study if they had 1 or more of the following characteristics: suspected surgical abdomen, previous abdominal surgery, bile-stained vomitus during the illness before enrollment, history of diagnosed seizure disorder, inborn error of metabolism, renal or hepatic diseases, diagnosis of severe dehydration with or without shock, hypo- or hypernatremic dehydration, antiemetic treatment within 48 hours before presentation, or a history of hypersensitivity to 1 of the study medications.

Written informed consent, sought from 1 of the parents or legal guardians for eligible patients as soon as the patient was admitted to the unit, was obtained for all of the participating patients. The study was approved by the hospital institutional review board.

Study Procedures

Patients were examined on presentation in the examination area of the center and those with acute gastroenteritis with mild-to-moderate dehydration and persistent vomiting were sent to the oral rehydration area of the center. Oral rehydration fluids were started at a rate of 5 mL every 5 minutes as per the rehydration policy of the unit. Patients who developed $\geq$3 episodes of vomiting or did not tolerate $\geq$20 mL of oral rehydration solution for a 1-hour period, were admitted to the short-stay unit for intravenous hydration and were potentially eligible for the study. Vomiting was defined as any episode of forceful expulsion of stomach content. Two episodes within less than 2 minutes were considered 1. Those with gastroenteritis including persistent vomiting were assessed for study eligibility within 2 hours of the initial physician assessment. The study was explained to eligible patients and families, and then informed signed written consent was sought. Patients for whom consent was obtained underwent intravenous line insertion and had venous blood sent for complete blood count, serum electrolytes, renal function, and serum HCO_3 level. Then a previously computer-generated list of random numbers was used by the enrolling physicians in consecutive order to identify a sealed envelope accessed and unsealed only by the preparing pharmacist who was blinded to patient assignment, containing 1 of 2 codes identifying 1 of 2 blind-study medication. Antiemetic dose was calculated by the preparing pharmacist based on the patient presenting body weight; ondansetron was given at 0.15 mg/kg, maximum dose of 4 mg, and metoclopramide at 0.3 mg/kg, maximum dose of 10 mg. Study medication was mixed in a sterile environment with normal saline to make up 50 mL of solution for intravenous administration. Prepared solution was infused for 10 minutes, and then intravenous fluids based on the level of dehydration were started right after completion of the study medication. Enrolled patients were kept nil per os for 1 hour after the completion of the study solution and last episode of vomiting; then oral rehydration fluids were started at 5 mL every 5 minutes for 2 hours and then increased as tolerated. If vomiting recurred, then nil per os was extended for another 30 minutes and then oral rehydration fluid was restarted the same way. Successful oral rehydration therapy was defined as tolerance of 100 mL of oral rehydration therapy, not interrupted or followed by a vomiting episode. Additional treatments (eg, antipyretics, antibiotics) were given at the discretion of the treating physician. Patients with suspected or observed extrapyramidal side effects were given diphenhydramine at 1 mg/kg, maximum dose of 50 mg for 5 minutes, and then observed until free of symptoms. Patients could be discharged when the treating physician determined the patient was well hydrated, was tolerating oral fluids well, had no significant fluid loss through stool, and was free of major medication adverse effects. Follow-up by study nurse by telephone was mandatory daily for 3 days after discharge, and the patient could return to the pediatric emergency center earlier if desired or needed.

Study Measurements and Outcomes

Vomiting and amount of oral fluids tolerated, as well as diarrhea episodes, were documented for each patient, with the exact time of the former 2 recorded all through admission. The primary outcome in this blinded study was the proportion of patients with cessation of vomiting right after completion of the study medication infusion in each group. Secondary outcomes were time to complete cessation of vomiting, time to successful oral therapy, length of hospital stay, reported adverse effects, diarrhea episodes during admission and daily follow-up, number of patients requiring readmission after discharge to the short-stay unit, and number revisiting the pediatric emergency center in the 3 days after discharge.

Statistical Analysis

To estimate the proportion of enrolled patients with cessation of vomiting after the start of intravenous fluid hydration only, 50 patients meeting the study inclusion criteria, admitted to the short-stay unit for intravenous hydration after failing the oral rehydration policy and receiving no antiemetic treatment, were observed before the beginning of the study. Twenty-four of the 50 observed cases (48%) stopped vomiting. We hypothesized that metoclopramide treatment would have a similar outcome to this observed group receiving no antiemetic (10), and based on the previous studies, ondansetron would provide an extra 20% improvement. With 80% power and 5% 2-sided alpha level, assuming a 50% vomiting cessation rate in the metoclopramide and 70% in the ondansetron

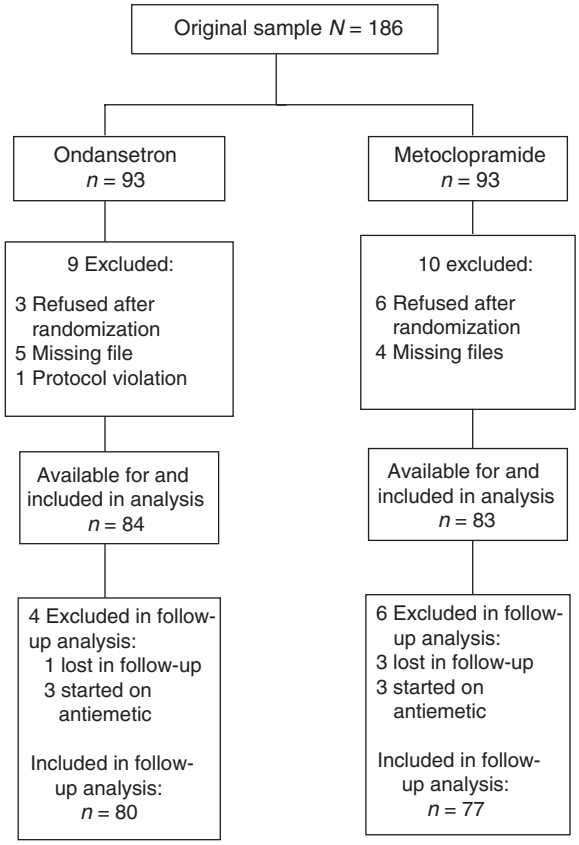

FIGURE 1. Study flowchart of enrolled patients.

groups, the sample size calculated for each group was 90 patients completing treatment and observation. Descriptive statistics (mean, standard deviation, and frequency) with percentages were calculated for relevant variables. χ^2 tests and unpaired *t* tests were applied to assess the significant differences between the 2 groups. SPSS 14.0 statistical packages (SPSS Inc, Chicago, IL) were used for data entry and analysis.

RESULTS

One hundred eighty-six otherwise previously healthy children diagnosed as having acute gastroenteritis, median age 3.0 years (range 1–13.2 years), were enrolled in the study (Fig. 1). Nineteen children were excluded from the primary outcome analysis: 9 with missing files, 9 electively removed by their parents soon after enrollment, and 1 inadvertently received a dose of unblinded intravenous ondansetron 4 hours after the study medication. Of the 167 children remaining, 84 were randomized to receive ondansetron and 83 were to receive metoclopramide. In follow-up, 4 patients were lost, 1 in the ondansetron group and 3 in the metoclopramide group, and 6 were started on oral or rectal antiemetic, 3 in each arm. Subjects' baseline characteristics (Table 1) were similar in the 2 treatment arms before enrollment.

Efficacy

Cessation of vomiting after enrollment was achieved in 68 patients (81%) in the ondansetron group and 60 (72%) in the metoclopramide group ($P = 0.14$). Mean time to complete cessation of vomiting was 39 minutes (SD 111) for the ondansetron group and 61 minutes (SD 110) for the metoclopramide group ($P = 0.2$). Successful oral therapy could have begun sooner in the ondansetron group at a mean of 256 minutes (SD 192), as compared with the metoclopramide group, at 307 minutes (SD 172), but the difference was not statistically significant ($P = 0.08$; difference −50, 95% confidence interval for the difference, −106 to 5). The mean length of infirmary stay was 550 minutes (SD 427) for the ondansetron group and 575 minutes (SD 449) for the metoclopramide group ($P = 0.71$). Because our data were not normally distributed, an unpaired *t* test was performed for nonequal variances to check for the difference in the mean time to cessation of vomiting, mean time to successful oral therapy, and mean length of stay for the 2 groups.

The number of diarrhea episodes after admission to the short-stay unit was similar for both groups: 1.7 (SD 2.2) for the ondansetron group, and 1.3 (SD 2.5) for the metoclopramide group ($P = 0.28$) (Table 2).

Follow-up

The rate of revisits to the pediatric emergency center in the 3 days after discharge was similar in the 2 treatment groups:

TABLE 1. Baseline characteristics of enrolled patients

Characteristics	Ondansetron (n = 84)	Metoclopramide (n = 83)	*P*
Age, y, mean ± SD	4.2 ± 3.2	4.34 ± 3.1	0.86
Male/female	46/38	39/44	0.32
Time in department before enrolment, min*	61.6 ± 99	51.3 ± 87	0.48
Duration of symptoms before enrollment, d*	1.5 ± 1.08	1.6 ± 1.11	0.70
Vomiting episodes within 24 h before emergency visit*	5.6 ± 2.9	5.3 ± 1.9	0.54
Diarrhea episodes within 24 h before emergency visit*	4.7 ± 3.7	4.1 ± 3.2	0.21
Dehydration severity			
Mild, no. (%)	39 (46.5)	35 (42)	0.53
Moderate, no. (%)	45 (53.5)	48 (58)	
Serum HCO_3 level, mmol/L, on admission*	20.6 ± 3.5	20.4 ± 4.1	0.71
Patients with serum HCO_3 <15 mmol/L, no. (%)	8 (9.5)	11 (13.3)	0.45
Antibiotic treatment on admission, no. (%)	3 (3.5)	2 (2.5)	0.93
Antipyretic treatment on admission, no. (%)	42 (50)	43 (52)	0.98

SD = standard deviation.
* Mean ± SD.

TABLE 2. Early results of treatment

Characteristics	Ondansetron (n = 84)	Metoclopramide (n = 83)	P
Patients with cessation of vomiting after treatment, no. (%)	68 (81)	60 (72)	0.14
Patients who continued to vomit after treatment, no. (%)			0.44
1 vomiting episode	7 (8)	9 (11)	
2 vomiting episode	6 (7)	6 (7)	
≥3 vomiting episodes	3 (4)	8 (10)	
Time to complete cessation of vomiting, min*	39 ± 111	61 ± 110	0.2
Time to successful oral therapy, min*	256 ± 192	307 ± 172	0.08
Duration of hospital stay, min*	550 ± 427	575 ± 449	0.71
Patients stayed ≥24 h no. (%)	4 (4.7)	4 (4.8)	0.98
Diarrhea episodes during admission*	1.7 ± 2.2	1.3 ± 2.5	0.28

SD = standard deviation.
* Mean ± SD.

10 (12%) in the ondansetron group and 13 (16.2%) in the metoclopramide group ($P = 0.44$, χ^2 test). Short-stay readmission was needed for 4 (5%) of the ondansetron group and 5 (6%) of the metoclopramide group ($P = 0.68$, χ^2 test). The number of diarrhea episodes was comparable in the 3-day follow-up for both groups. On the first follow-up day, diarrhea continued in 51 patients (64%) in the ondansetron group and 43 (56%) in the metoclopramide group ($P = 0.6$). On the second day, 41 patients (51%) in the ondansetron group and 29 (38%) in the metoclopramide group had persistent diarrhea ($P = 0.12$). The third day follow-up revealed diarrhea symptoms in 24 patients (30%) in the ondansetron group and 20 (26%) in the metoclopramide group ($P = 0.7$).

Safety

There was no reported adverse effect in any of the study patients. No abnormal movement or any other neurological signs and/or symptoms were recorded. Diphenhydramine was not needed for any of the enrolled patients. No study patients required hospital admission during their study visit for gastroenteritis.

DISCUSSION

Although antiemetic use in gastroenteritis was not recommended in the initial guidelines, this position was revised in 2008, with the current guidelines stating that antiemetic use may be of value for selected children with severe vomiting (22).

In our study, the failure rate for intravenous metoclopramide was numerically higher compared with ondansetron, with no statistical significance in the study outcome measures. There is only 1 randomized trial comparing intravenous ondansetron and metoclopramide to placebo for the treatment of vomiting in children. That trial studied 12 subjects for each group and showed superiority of ondansetron to placebo in cessation of vomiting and decrease in the number of vomiting episodes, but no statistically significant difference was found between metoclopramide and placebo (10). The small sample size of the study may have affected the latter result.

Rehydration by nasogastric tube may have been an option in our study population, but because of the lack of its acceptance in our medical culture, it was not attempted. Even though we used an efficacious dose of metoclopramide, 0.3 mg/kg in our study, we reported no adverse effects, and the safety records for both treatment groups were similar. In addition, diarrhea frequency during admission and follow-up were no different.

Based on our study results and because of the wide availability and lower cost of metoclopramide, metoclopramide could be considered an attractive alternative to ondansetron for persistent vomiting in children with gastroenteritis, especially in poor countries.

Our study had limitations, primarily that it was a single-center trial; a multicenter trial would have further enhanced the validity of our results.

We conclude that in the sample size tested, intravenous metoclopramide appeared effective and may be considered a safe alternative to ondansetron for the treatment of persistent vomiting in children with gastroenteritis admitted for intravenous fluid hydration.

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