Time-series Analysis of Ondansetron Use in Pediatric Gastroenteritis

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ABSTRACT

Objective: Emergency department use of ondansetron in children with gastroenteritis is increasing; however, its effect on clinical outcomes is unknown. We aimed to determine whether increasing ondansetron usage is associated with improved outcomes in children with gastroenteritis.

Methods: A retrospective cohort study was conducted at The Hospital for Sick Children, Toronto, Canada. Eligible children included those younger than 18 years old with gastroenteritis who presented to an emergency department between 2003 and 2008. There were 22,125 potentially eligible visits; 20% were selected at random for chart review. The primary outcome measure, the intravenous rehydration rate, was evaluated using an interrupted time-series analysis with segmented logistic regression. Secondary outcomes included emergency department revisits, hospitalization, and length of stay.

Results: A total of 3508 patient visits were included in the final analysis. During the study period, there was a significant reduction in intravenous rehydration usage (27%–13%; $P < 0.001$) and an increase in ondansetron administration (1%–18%; $P < 0.001$). Time-series analysis demonstrated a level break ($P = 0.03$) following the introduction of ondansetron. The mean length of stay for children declined from 8.6 ± 3.4 to 5.9 ± 2.8 hours, $P = 0.03$. During the week following the index visit, there was a reduction in return visits (18%–13%; $P = 0.008$) and need for intravenous rehydration (7%–4%; $P = 0.02$).

Conclusions: Ondansetron use has increased significantly and is associated with reductions in the use of intravenous rehydration, emergency department revisits, and length of stay. The selective use of ondansetron is associated with improved clinical outcomes.

Key Words: gastroenteritis, infusions, intravenous, ondansetron

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Acute gastroenteritis accounts for >1.5 million outpatient visits annually in the United States and 13% of all of the hospitalizations among young children (1,2). Despite clinical trial evidence that ondansetron use reduces the frequency of vomiting, intravenous rehydration, and hospitalization (3–8), guidelines recommend against the pharmacologic treatment of vomiting (1), citing a variety of reasons including safety concerns, adverse effects, and a shift away from appropriate fluid, electrolyte, and nutritional therapy (1,9,10).

These concerns have not dissuaded physicians from prescribing antiemetics. In 2005, in the United States, 23% of outpatients younger than 20 years old received a prescription for an antiemetic (11), most commonly promethazine, which now has a black-box warning against its use in children younger than 2 years old (12). More recently, American pediatric emergency medicine physicians have indicated that ondansetron has become their agent of choice (13).

Because ondansetron has entered into widespread use (14), we sought to evaluate how its usage correlated with clinical outcomes. We hypothesized that increasing ondansetron usage would result in a corresponding decrease in the administration of intravenous rehydration, shorter length of stay, and reduced hospitalization and emergency department (ED) revisit rates.

METHODS

Study Setting and Design

The Hospital for Sick Children is a tertiary care referral hospital in downtown Toronto. The ED treats approximately 60,000 children annually. The ondansetron oral disintegrating tablet became ward stock in July 2005. The administration of a single oral dose of ondansetron to children with evidence of dehydration and ongoing vomiting in the ED is recommended in our institution's clinical practice guideline. The recommended dose provided is within the previously evaluated dose range of 0.13 to 0.26 mg/kg (4,15). This retrospective report includes data from a consecutive series of children younger than 18 years old who presented to the ED between July 1, 2003 and June 30, 2008 with acute gastroenteritis.

Study Population

Potentially eligible children were identified by searching the ED database for relevant *International Classification of Diseases (ICD) -9-Clinical Modification (CM)* (2003–2007) and -10 (2007–2008) codes (003.0, 007, 007.9, 008.5, 008.6, 008.69, 008.8, 009.3, 276.51, 787.0, 787.01, 787.03, 787.91). Acute gastroenteritis was defined by the presence of either vomiting or diarrhea for <14 days (9) and the absence of an alternative diagnosis (eg, inflammatory bowel disease exacerbation). Twenty percent of visits identified as potentially eligible were selected at random for chart review. All of

the visits associated with a visit by the same child during the preceding 7-day period had the earlier visit coded as the index visit.

Study Protocol

Data were extracted by 3 data abstractors who were blinded to the study's hypothesis. Medical records were reviewed from our Electronic Patient Chart system using a set of precise operational definitions for the key variables and uniform procedures for missing, conflicting, or ambiguous data. A standardized data collection instrument was used to record demographics, history and physical examination findings, intravenous fluid and medication administration, laboratory investigations, disposition, adverse events, and revisit data. Weekly meetings occurred during the data abstraction period to resolve disputes and review coding rules. A subset of randomly selected charts (10%) was independently abstracted by one of the investigators (M.R.) to evaluate inter-observer agreement.

Key Outcome Measures

Our primary outcome was the correlation over time between the proportion of children administered ondansetron and the proportion of children who received intravenous rehydration. Secondary outcomes included the correlation between ondansetron administration and the need for ED revisits, hospitalization, and length of stay.

Definitions

Medical history was considered as a 3-level categorical variable: none, mild systemic disease, and severe systemic disease (ie, likely would affect treatments administered). The Canadian Triage Acuity Scale score, a clinical variable, is assigned by the triage nurse and measures the acuity of the child's illness (16). Recorded temperatures were adjusted for location of measurement (17). Children with an adjusted temperature $\geq$38.0°C were considered to have a fever (17). General appearance was classified for all of the children by the data abstractor as well (''well appearing,'' ''no apparent distress,'' ''alert,'' ''normal mental status,'' ''interactive,'' ''smiling'') or unwell (''sick,'' ''toxic,'' ''shocky,'' ''decreased mental status,'' ''lethargic,'' ''unresponsive,'' ''irritable,'' ''fussy,'' ''inconsolable,'' ''not looking well,'' ''poor or decreased perfusion,'' ''decreased pulses'') (18). Descriptors that did not meet the above definitions were labeled ''unclear.''

Data Analysis

All of the variables were analyzed based on their group assignment, which was determined by the timing of the ED visit, with groups running from July 1 to June 30 for each of the 5 time periods (2003–2008). Frequency counts and percentages are given for discrete variables, means with standard deviations are provided for continuous variables. The χ^2 test was used for discrete variables, with Fisher exact test used when appropriate. Continuous variables were compared between time periods using analysis of variance. We assessed interobserver agreement for 6 outcome variables (intravenous fluid administration, ondansetron administration, hospitalization, return visit within 7 days, return visit requiring intravenous rehydration, return visit requiring hospitalization) with the κ statistic.

A regression analysis of an interrupted time-series dataset was conducted using segmented logistic regression, which divides a time series into pre- and postintervention segments (19). Such analyses allow an assessment of how much an intervention affected outcomes immediately and over time (19). Because our data revealed that ondansetron usage gradually increased during the period July 2005 to June 2006, we chose this interval as the intersection between segments (ie, the intervention). A regression model has 2 key parameters: a level and a slope. The difference between the 2 segments can be quantified by testing the change in these parameters. A change in level indicates an absolute change between the last measurement of the number of intravenous insertions in the preintervention segment and the first measurement of the postintervention segment; a change in slope indicates a change in the rate of intravenous insertions within each segment.

Because events closer together in time tend to be more similar than events further apart (autocorrelation) (20), the model residuals may not be independent (21) and may result in biased standard deviations, which can affect tests of significance (22). We evaluated and detected the presence of autocorrelation using the Durbin-Watson statistic. Autocorrelation was then corrected for by including a term in the regression model. Similarly, seasonal autocorrelation (annual trends) was evaluated and incorporated into the model.

The outcomes of interest in our time-series analysis were change in the level pre- and postintervention, change in the slope pre- and postintervention, and estimation of monthly average intervention effect considering the outcome (ie, intravenous rehydration rate) had the intervention (ie, increasing ondansetron usage) not occurred (23). This is estimated by comparing the intravenous insertion rate in the absence of ondansetron administration and the outcome with its use (Fig. 1).

All of the statistical tests were 2-sided and evaluated at the 5% level of significance. Statistical analysis was conducted with the use of SPSS (Windows version 16.0; SPSS Inc, Chicago, IL). The hospital's research ethics board approved the present study, and given the retrospective nature of the study, they waived the requirement for written informed consent.

RESULTS

During the 5-year study period, there were 22,125 potentially eligible visits identified. A total of 4064 charts of eligible children were reviewed representing 4425 patient visits. A total of 3508 visits were included in our final analysis (Fig. 2). Baseline features are reported by time period (Table 1) and ondansetron administration status (Table 2).

ED Interventions and Outcomes

During the 5-year study period, there was a significant reduction in the use of intravenous rehydration from 26% (312/1209) in the preintervention period to 14% (248/1735) in the postintervention period ($P < 0.001$). During the same time periods, ondansetron use rose from 1% (9/1209) to 18% (317/1735) (Fig. 3A). The reduction in intravenous rehydration between the first and the final year of the study was most notable in children 1 year old or older (99/390 (24%)–124/862 (14%); difference −11.0%; 95% confidence interval [CI] −16 to −6) compared with those <1 year old (27/149 (18%)–36/283 (13%); difference −5.4%; 95% CI −13 to 2). Similarly, a larger increase in ondansetron administration occurred among children 1 year old or older (0/390 (0%)–181/862 (21%); difference 21%; 95% CI 18–24) compared with those younger than 1 year old (0/149 (0%)–25/283 (9%); difference 9%; 95% CI 6–12).

Time-series analysis showed a statistically significant downward-level break (ie, a change in the number of absolute intravenous insertions between the pre- and postlevel intervention; $P = 0.03$) after ondansetron introduction. After adjustment, the

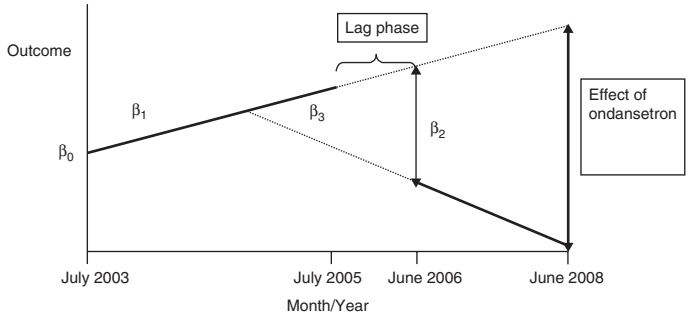

FIGURE 1. Graphical representation of time-series analysis.

intravenous insertion rate fell from 21.2 to 10.2 intravenous insertions per 100 gastroenteritis cases. The trend (ie, the change in intravenous insertions per month before and after the introduction of ondansetron) was not significant ($P = 0.59$). There was also evidence of first-degree autocorrelation ($P < 0.001$); thus, a regression parameter was inserted. There was no statistical significant evidence of seasonal autocorrelation.

During the study time period, the mean length of stay for children diagnosed as having acute gastroenteritis declined from 8.6 ± 3.4 in 2004 to 2005 to 5.9 ± 2.8 hours in 2007 to 2008, $P = 0.03$ (Fig. 3B). The reduction was similar among children 2 years old or younger (−2.83 hours) compared with those older than 2 years old (−2.47 hours). Among children diagnosed as having gastroenteritis there was a reduction in return visits (18% to 13%; $P = 0.008$; Fig. 3C). Among children diagnosed as having acute gastroenteritis at the initial visit, the proportion requiring an intravenous insertion at a subsequent visit declined (7%–4%; $P = 0.02$); there was no change in the need for hospitalization ($P = 0.32$). No adverse effects were documented that described any events construed to be related to ondansetron administration.

Interobserver Agreement

Interobserver agreement was assessed for 362 patients. Agreement for the outcome variables evaluated was good, with κ values ranging from 0.82 (95% CI 0.78–0.86) for return visits requiring intravenous rehydration to 0.97 for ondansetron administration (95% CI 0.96–0.97).

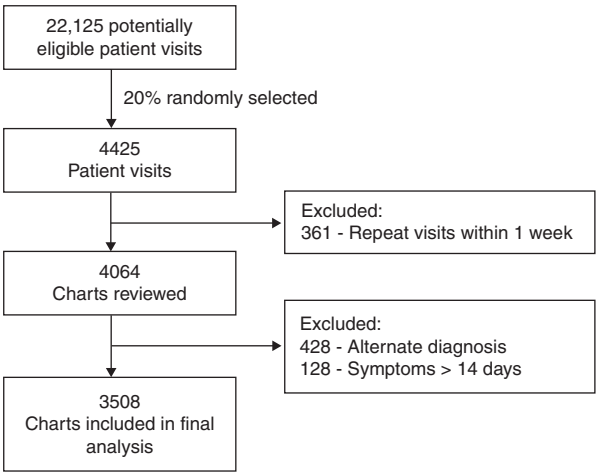

FIGURE 2. Summary of eligible patients and charts selected for review. Patients with repeat visits within 1 week had the initial visit included as the index visit, with the subsequent visit identified as a revisit.

DISCUSSION

We report an increase in the use of ondansetron in children with acute gastroenteritis, from 1% to 18%, during a 5-year period. This corresponded with a 46% relative decrease in the use of intravenous rehydration, from 26% to 14%, with evidence of a downward-level break following the introduction of ondansetron. This reduction occurred in conjunction with a reduction in length of stay, ED revisits, and revisits requiring intravenous rehydration.

Randomized clinical trials and a meta-analysis have demonstrated that ondansetron administration can reduce the need for intravenous rehydration (3,6,8,13). The estimated absolute risk reduction in these clinical trials ranged from 15% (8) to 33% (6), with corresponding relative risk reductions of 55% (4) to 68% (8). Thus, the finding of a 14% absolute and 52% relative risk reduction following the introduction of ondansetron in our ED is in keeping with previous reports. These benefits, although slightly lower than those achieved in clinical trials, demonstrate that ondansetron can effectively be incorporated to result in improved outcomes in children with acute gastroenteritis.

Guidelines that have not supported the routine use of ondansetron cite concerns about a possible increase in the number of diarrheal stools (9,10). Although the reported increases have been statistically significant (4,8), they have not usually been clinically significant, with clinical outcomes such as length of stay and return visits favoring ondansetron administration. In our ED, all of the relevant secondary outcomes demonstrated improvement over time, thereby further enhancing the likelihood that a beneficial effect is directly derived from ondansetron administration. Although a formal cost-effectiveness analysis was not conducted, recent publications have demonstrated that the appropriate use of ondansetron has the potential to result in an annual savings of >$65 million in the United States (24).

Additional concerns have focused on the possibility that the use of a pharmacologic agent would shift the focus away from appropriate fluid, electrolyte, and nutritional therapy; that ondansetron use will result in adverse events; and that it may not be cost-effective (1). A shift in focus logically would either result in an increase in intravenous rehydration at the index visit or inadequate oral rehydration following discharge resulting in an increase in future health care provider visits; however, we found a reduction in intravenous rehydration and revisit rates. Although we do not have data related to revisits at other institutions, we have reported that because our institution has the only pediatric ED in the region, few caregivers bring their children elsewhere for care following an initial visit to our ED (25). Sturm et al (14), using logistic

TABLE 1. Baseline demographic characteristics by year

	2003–2004 (n = 539)	2004–2005 (n = 670)	2005–2006 (n = 564)	2006–2007 (n = 590)	2007–2008 (n = 1145)	Total	*P*
Age, y (mean ± SD)	3.2 ± 3.4	3.2 ± 3.2	3.3 ± 3.5	3.3 ± 3.4	3.6 ± 3.8	3.4 ± 3.5	0.11
Weight, kg (mean ± SD)	15.5 ± 11.3	15.8 ± 11.0	16.3 ± 12.4	16.0 ± 11.8	17.0 ± 13.0	16.3 ± 12.1	0.11
Sex, male (%)	54.9	52.4	57.1	57.6	56.2	55.6	0.34
Triage time, hh:mm (mean ± SD)	14:37 ± 06:25	13:42 ± 06:35	14:20 ± 06:29	13:54 ± 06:29	13:58 ± 06:31	14:04 ± 06:31	0.11
CTAS (mean ± SD)	3.5 ± 0.59	3.4 ± 0.58	3.4 ± 0.58	3.4 ± 0.60	3.2 ± 0.65	3.4 ± 0.62	<0.001
Significant MH, %	9.3	11.3	9.2	9.8	11.4	10.4	0.48
Fever, %	37.7	39.5	40.3	36.4	39.0	38.7	0.67
Fever, days (mean ± SD)	0.65 ± 1.53	0.67 ± 1.49	0.73 ± 1.87	0.78 ± 1.96	0.83 ± 1.91	0.75 ± 1.78	0.24
Diarrhea, episodes (mean ± SD)	4.80 ± 3.60	4.95 ± 4.15	4.82 ± 3.73	4.60 ± 3.76	4.38 ± 3.27	4.71 ± 3.72	0.20
Diarrhea, days (mean ± SD)	2.86 ± 2.67	2.83 ± 2.77	3.16 ± 3.07	3.01 ± 3.06	3.03 ± 2.83	2.98 ± 2.88	0.44
Vomiting, episodes (mean ± SD)	4.91 ± 4.61	5.27 ± 4.86	4.87 ± 4.43	5.35 ± 4.55	5.11 ± 4.79	5.12 ± 4.69	0.58
Vomiting, days (mean ± SD)	2.12 ± 2.05	2.05 ± 1.85	2.03 ± 2.00	1.98 ± 1.78	2.18 ± 219	2.09 ± 2.02	0.48
Hematochezia, %	2.8	3.6	5.9	3.8	3.5	3.8	0.08
Hematemesis, %	2.0	0.9	0.9	0.7	1.5	1.2	0.19
Temperature, °C (mean ± SD)	37.4 ± 1.00	37.6 ± 0.95	37.9 ± 0.97	37.8 ± 0.88	37.8 ± 0.89	37.7 ± 0.94	<0.001
Heart rate, beats/minute (mean ± SD)	123.4 ± 20.6	123.9 ± 22.0	123.5 ± 20.4	120.1 ± 20.6	119.3 ± 21.3	121.6 ± 21.2	<0.001
Respiratory rate, breaths/min (mean ± SD)	26.7 ± 7.4	26.9 ± 7.9	26.6 ± 8.2	26.5 ± 8.3	26.0 ± 7.4	26.4 ± 7.8	0.16
BP systolic (mean ± SD)	96.3 ± 11.4	98.6 ± 12.0	98.4 ± 11.8	97.6 ± 14.5	98.4 ± 12.0	98.0 ± 12.4	0.39
BP diastolic (mean ± SD)	58.2 ± 10.1	60.7 ± 10.1	60.2 ± 9.1	59.9 ± 7.7	59.4 ± 10.1	59.7 ± 9.6	0.45

BP = blood pressure; CTAS = Canadian Triage Acuity Scale; hh:mm = military time in hours:minutes; MH = medical history; SD = standard deviation.

regression, found that ondansetron administration, although associated with a reduction in admissions (odds ratio 0.47; 95% CI 0.42–0.53), was also associated with increased revisits (odds ratio 1.74; 95% CI 1.27–1.65). These contrasting findings likely reflect the different study methodologies using and the challenge in controlling for all of the factors that may influence outcomes in the design used by Sturm et al (14). Although the present study cannot determine the frequency of adverse events following ondansetron administration, and there are reports in the literature (26), overall, ondansetron has been shown to be remarkably safe, with few severe adverse events reported and a favorable safety profile (27).

The most significant potential limitation to our data is that other changes may have occurred during the study period; however, during the 5-year time period, there were no major changes at our institution (eg, ED layout, nursing or physician staffing, protocols, pathways, guidelines), nor were there major advances in the management of acute gastroenteritis aside from evidence supporting the use of ondansetron. Furthermore, in a similar cohort of children (tertiary care Canadian pediatric ED) during the same period (2004–2007), only a 2.6% absolute reduction in the rate of intravenous rehydration was reported (28). This occurred despite the implementation of a formal oral rehydration clinical pathway.

TABLE 2. Characteristics of children stratified according to ondansetron administration

	Ondansetron (n = 374)	No ondansetron (n = 3134)	*P*
Sex, male (%)	50.8	56.2	0.05
Significant medical history, yes (%)	12.6	10.2	0.15
Age, y (mean ± SD)	4.1 ± 3.6	3.3 ± 3.5	<0.001
Weight, kg (mean ± SD)	17.9 ± 11.1	16.1 ± 12.2	0.004
Weight for age *z* score (mean ± SD)*	−0.015 ± 1.26	0.049 ± 1.27	0.36
Weight for age percentile (mean ± SD)*	49.5 ± 32.7	51.6 ± 32.1	0.24
Triage time, hh:mm (mean ± SD)	12:48 ± 7:23	14:13 ± 6:23	<0.001
CTAS (mean ± SD)	3.1 ± 0.6	3.4 ± 0.6	<0.001
Heart rate, beats/min (mean ± SD)	122.1 ± 19.3	121.6 ± 21.4	0.62
Respiratory rate, breaths/min (mean ± SD)	25.3 ± 5.9	26.6 ± 8.0	0.002
Temperature, °C (mean ± SD)	37.8 ± 0.9	37.7 ± 1.0	0.23
Vomiting, days (mean ± SD)	1.8 ± 1.6	2.2 ± 2.1	0.001
Frequency of vomiting past 24 h (mean ± SD)	8.0 ± 5.9	4.6 ± 4.3	<0.001
Days of diarrhea (mean ± SD)	2.0 ± 1.8	3.1 ± 2.9	<0.001
Frequency of diarrhea past 24 h (mean ± SD)	4.0 ± 3.6	4.8 ± 3.7	0.01

CTAS = Canadian Triage Acuity Scale; hh:mm = military time in hours:minutes; SD = standard deviation.

* The weight-for-age *z* score is a method used to estimate malnutrition in a population. In the context of the present study, because we had no accurate method of estimating dehydration given that the samples likely have similar weight for age *z* scores when well, it was used as a proxy measure for degree of dehydration. More negative *z* scores and lower percentiles reflect greater degrees of dehydration.

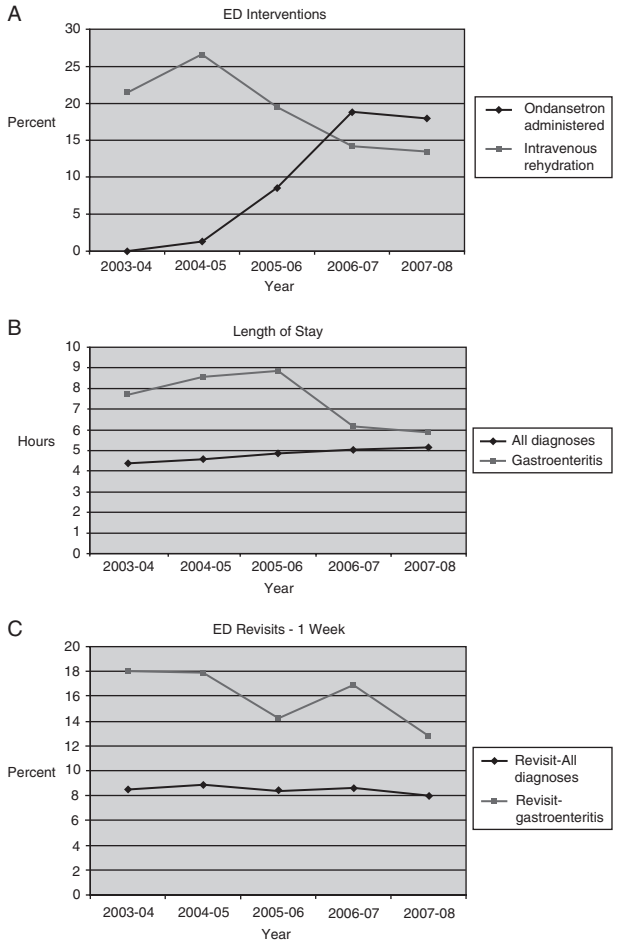

FIGURE 3. Changes in outcomes during the 5-year period. A, Changes in gastroenteritis interventions over time. Increasing use of ondansetron during the 5-year period is associated with a concomitant decrease in the use of intravenous rehydration in children with acute gastroenteritis. B, Length of stay. The length of stay for children with acute gastroenteritis is depicted in relation to the length of stay for all of the children evaluated in the emergency department (ED) during the identical time interval. C, ED revisits. The proportion of children with acute gastroenteritis who experienced an ED repeat visit within 1 week of the index visit is depicted in relation to the proportion of children with all of the other diagnoses who experienced a revisit.

Moreover, ondansetron use at this institution remained low even in the final year of the study (3.5% in 2007).

Rotavirus vaccination status theoretically may be a confounding variable in our model; however, it is not covered at present by provincial health plans. In winter 2009, only 2% of caregivers reported that their child had received the rotavirus vaccine (S.B.F., unpublished data, 2010). Thus, rotavirus vaccine is unlikely to explain the change in outcomes that we reported and the use of an interrupted time-series model is justified to conduct our analysis.

Although a case-control design is an alternative method of assessing the clinical effect of ondansetron administration, the potential effect of bias was believed to outweigh the potential advantages of this design. Our concern focused on sources of bias, particularly in the identification of controls with similar baseline likelihoods of experiencing the outcomes of interest (29). Given that the outcome of intravenous rehydration is subjective and heavily influenced by patient (ie, clinical, physiological, social), physician (ie, inter- and intraphysician), and environmental (ie, time of day, ED volume, and wait times) factors, we could not satisfactorily match cases with controls. By the very nature of the decision to administer ondansetron, such patients have a priori been identified at high risk for needing intravenous rehydration.

An additional limitation was the switch from *ICD-9* to *ICD-10* coding during the final year of our study. Studies of the comparability between revisions have found that for some diagnoses, there are substantial changes because of the coding (30). Thus, we saw a significant increase in the frequency of the coding of diagnoses that corresponded to our diagnostic list when our institution switched to *ICD-10* coding. It is possible that in the earlier years, potentially eligible subjects were not included in the analysis, whereas in the final year, some ineligible children were actually included. Our data indicate, however, that the subjects included in our dataset had similar baseline characteristics over time (Table 1).

In conclusion, this analysis provides evidence from a large cohort at a single institution that the use of ondansetron is associated with clinically significant reductions in the use of intravenous rehydration, length of stay, and need for revisits. The present study highlights that in addition to evidence of efficacy, there exists evidence of effectiveness regarding the administration of ondansetron to children with gastroenteritis. The incorporation of ondansetron into the treatment of pediatric gastroenteritis appears to result in improved clinical outcomes.

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