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The Effect of Ondansetron on Decreasing the Hospitalization Rate in Children with Gastroenteritis and Recurrent Vomiting

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Abstract

Background: Diarrhea is one of the most common disorders in infancy and childhood and recurrent vomiting is a main reason for hospitalization for these patients. This study was to assess the effect of injective ondansetron on decreasing the hospitalization rate in children with diarrhea and recurrent vomiting.
Methods: In this clinical trial study, patients between six months and six years, with acute viral diarrhea and recurrent vomiting, were assessed for the possibility of being treated as outpatients, based on their response to ondansetron, compared to a control group who did not receive ondansetron. The sample size was 100 for each group. Cases for the ondansetron group were under observation for at least two hours in the emergency ward and were followed until 72 hours to find out if there was any need for them to return to the hospital due to vomiting. Otherwise, all cases in the control group were hospitalized. Data of both groups, including the rate and duration of hospitalization, was analyzed.
Results: Of the 100 individuals who received ondansetron (n = 91) 91% did not need to be hospitalized and 9 patients needed to be admitted in the next 72 hours, while (n = 100) 100% of control group were hospitalized (P value = 0.003). Vomiting in the control group continued in 35% of patients after 72 hours of admission. The duration of hospitalization for the patients of the control group was 2.94 $\pm$ 1.40 (mean $\pm$ SD) days.
Interpretation: Ondansetron can be considered as an effective agent to decrease the hospitalization rate in infants and children with diarrhea as well as vomiting. Injective forms of ondansetron seem to be more achieved than oral forms.

Keywords: Infant, Child, Diarrhea, Vomiting, Ondansetron, Hospitalization

1. Introduction

Diarrhea is one of the most common disorders in childhood. The world health organization (WHO) and UNICEF estimate that almost 2.5 billion episodes of diarrhea occur annually in children under 5 years of age in developing countries. The overall incidence of diarrhea is about 3.6 episodes per child a year and it is estimated to account for 13% of all childhood disability adjusted life years (DALYs) (1). Since recurrent vomiting is one of main reasons for admission of infants and children with gastroenteritis (GE) in hospitals, control of vomiting in these patients can decrease the rate of hospitalization and lead to oral rehydration therapy (ORT), which is the preferred method for rehydration of the patients and is also endorsed by WHO and other major health organizations (2). Rather than medical benefits of treatment of GE patients as outpatient cases at home, there are many socioeconomic advantages for the family and community, due to not admitting a child or infant into a hospital. Heavy costs of hospitalization, with the fact that a large number of people are not under insurance coverage in Iran, it is necessary to have a person accompanying the child/infant during their hospitalization period. However, this may lead to other problems such as when the parent or guardian is employed or has a problem caring for other children at home etc. Also, some problems related to health care systems, such as increased hospital occupancy, deficiencies in nurses and not enough hospital equipment are some of problems due to high rates of hospitalization for children and infants with diarrhea and vomiting. In addition, drugs-related adverse events predominate in academic pediatric centers, with children aged more than 1 year to 5 years (3). Freedman et al., in their conducted cost analysis study in USA and Canada, found out that routine administration of ondansetron to eligible children would annually save society 65.6 million US dollars and health care payers 61.1 million US dollars. In

Canada it would annually save society 1.72 million CDN dollars and the health care system 1.18 million CDN dollars (4).

Amongst several antiemetic agents, ondansetron is a highly potent and selective serotonin 5-HT3 receptor antagonist and has no worrisome adverse effects such as drowsiness, extra pyramidal reactions, hallucination, convulsion and neuroleptic malignant syndrome that may be seen in other antiemetic medications. When ondansetron is used for several clinical conditions related to vomiting there is a very low risk of adverse effects (5, 6). A large number of studies have been done and have shown different results of success and failure in which oral ondansetron was administered to assess the decrease rate of hospitalization in children with diarrhea and vomiting (7-9). This study was carried out to assess the effect of injective ondansetron on decreasing the hospitalization rate in children with gastroenteritis and recurrent vomiting.

2. Methods

2.1. Setting

Patients between the age of six months and six years were referred to Qods pediatrics academic hospital in Qazvin city (west of Tehran, I.R. Iran). This hospital is a state hospital under the supervision of Qazvin University of Medical Sciences and it is a referral hospital. Children with acute GE and recurrent vomiting were followed up for their response to injective ondansetron and the possibility of treating them as outpatient cases. Meanwhile, other cases in similar situations were selected as a control group who did not receive ondansetron. Consent letters were obtained from all parents prior to entering the study. This study was approved by the Qazvin ethic committee.

2.2. Patients

Inclusion criteria: All individuals in both groups had evidence of viral GE, recurrent vomiting was the only indication of referring them to hospital and the time of their referral to the hospital was not more than 48 hours after the beginning of the symptoms.

Exclusion criteria: Other cases with other causes (bacterial GE, protozoan GE, etc.), vomiting secondary to other diseases and patients with symptoms prolonger than 48 hours were excluded. Considering a narrow duration of symptoms was for having similar situations in both groups.

The sample size was calculated through the following formula:

$$N = \frac{2\left(Z_1 - \frac{\alpha}{2} + Z_{1-\beta}\right)^2 \overline{P}\left(1 - \overline{P}\right)}{\left(P_1 - P_2\right)^2} \quad (1)$$

Considering $\overline{P} = \frac{(P_1+P_2)}{2}$, P1 = 0.7, P2 = 0.5, α = 0.05 and β = 0.2 that yielded N = 96 (10).

2.3. Study Design

This study is a randomized controlled clinical trial done for 200 patients with Gastroenteritis (GE) referred to the Qods hospital from Feb 2014 to Jan 2015. Patients recruited in this study randomly were assigned to two groups based on Balanced Block Randomization. We have 6 blocks (AABB-BBAA-ABAB-BABA-BAAB-ABBA) that will randomly be arranged. The control group received a routine plan (Metoclopramid) and the intervention group received ondansetron. They are followed through hospital reception documents and telephone calls until 72 hours after discharge. This follow up is to find out whether the patients have had any need to return to the hospital due to recurrence of vomiting. All included cases of both groups were treated with serums. The difference between the two groups was receiving a dose of 0.15 mg/Kg ondansetron through injection in study group. It should be noted that some patients receive ondansetron routinely based on their physician guidelines and others receive previous drug regimes such as metoclopramid, ORS or other treatments (registration ID in IRCT is IRCT2014090719077N1).

2.4. Primary Outcome

Our primary outcome was to find out whether the patients had any need to be returned to the hospital because of recurrence of vomiting. However, all cases that did not receive ondansetron were hospitalized as was routinely done for years. All data of both groups including the rate and duration of hospitalization were registered.

2.5. Statistical Analysis

We calculated the number and percentage of gender and needing to admit which was analyzed by χ^2 measure. The duration of hospitalization was analyzed by mean $\pm$ SD. The Mann-Whiteny program was used to compare the hospitalization rate, age and duration of gastroenteritis between two groups since the distribution of variables were not normal. Furthermore, the ,duration of hospitalization was analyzed by the Cox-Regression model. Statistical analysis was done by means of SPSS-version 19 and P less than 0.05 was considered significant.

3. Results

In our study, of the 200 participated individuals in two equal case and control groups, the mean age (year) was

3.69 ± 2.61 and 3.16 ± 1.52, respectively. There were no significant differences between them. Ninety percent of patients in the control group who were admitted were under 5 years old. However, 76 of the patients (76%) in the intervention group with ondansetron were fewer than 5. Only 6% were admitted after receiving this drug.

Gender distribution included 44 girls and 56 boys in the case group and 42 girls and 58 boys in the control group. That did not show any significance (Table 1).

In the ondansetron group of people who received the drug, 55% took only one dose and 45% needed the second dose without observing any drug side effects.

Out of 100 individuals who received ondansetron (n = 91), 91% of cases did not need to be hospitalized or get rest (n = 9) and 9 % needed to be admitted in the next 72 hours. All 100 cases of the control group were hospitalized (P = 0.003) (Figure 1).

Vomiting in the control group of people who did not receive ondansetron continued in 35 % after 72 hours of admission.

The duration of hospitalization for the patients of the control group was 2.94 ± 1.40 days, amongst which the durations compared with the case group (Table 2) from one to six days were 16, 27, 24, 19, 8 and 6 %, respectively (Figure 2).

The Cox-Regression model showed that the age and gender of patients did not have any significant effects on the survival analysis; however, the leading complaints such as fever, diarrhea and vomiting had the significant confounder effect on it (Table 3).

4. Interpretation

The results of this study showed that 91% of infants and children with diarrhea and vomiting who received ondansetron could be treated without hospitalization and as outpatients, while only 9% were hospitalized. On the other hand, the patients of the control group had a duration of 2.94 ± 1.40 days (range of one to six days) in the hospital and repeating vomiting occurred in 35% of them. This high percent of not hospitalized patients implies money, time saved for the family and a lower load of admitted patients for hospitals. These consequences are desirable in all aspects.

Most of the similar studies have shown the same results as ours, although a few differences in results could be found. Golshekan et al. compared two groups of oral ondansetron and placebo in children with diarrhea and vomiting and found that 27% had persistent vomiting and 13.6% were hospitalized in their 48 hour follow up (11). The results of a similar study by Roslund et al. showed that 21.6% needed intravenous serum therapy after receiving oral ondansetron (12), which both showed higher rates of admission than ours. In a study on 1 to 14 year-old children,done by Al-Ansari et al., it was found that after a single dose of ondansetron, cessation of vomiting was achieved in 81% of cases (13), which shows a lower rate of vomiting cessation than ours. Das et al., through their review study, concluded that oral and IV ondansetron significantly reduced the incidence of hospitalization by 64% (RR: 0.36, 95% CI: 0.18, 0.72) and 79% (RR: 0.21, 95% CI: 0.05, 0.94) respectively (14). This difference in the rout of ondansetron administration is the reason of gaining a higher result in our study when comparing similar studies in which the oral form of ondansetron was used. Other similar studies by Setayesh et al. (8), Tabbah (15), Freedman et al. (14, 16), DeCamp et al. (17), Gavagan et al. (18) and Mullarkey et al. (19) all showed that ondansetron therapy decreases the risk of persistent vomiting, the use of intravenous fluid and hospital admissions in children with vomiting due to gastroenteritis and/or its cost-effectiveness. In another study, results showed after drug administration, 30 (81.1%) patients in the ondansetron group did not experience vomiting as compared to 9 (24.3%) patients of the placebo group (P < 0.01) (20). In addition, children who received ondansetron were less likely to vomit not only during the first 8 hour follow-up in the emergency department [relative risk (RR): 0.33, 95% CI: 0.19 - 0.56,] but also during the next 24 hour follow-up (RR: 0.15, 95% CI: 0.07 - 0.33) (21).

Despite these studies in agreement with administration of ondansetron and its effectiveness, some other studies point to its effect on prolongation of diarrhea duration due to fluid and toxin retention. The UK guideline determined that ondansetron prolongs the QT interval in a dose-dependent manner; therefore, it should be avoided in people with congenital long QT syndrome. Doctors should pay more attention to some patients such as those with electrolyte abnormalities, congestive heart failure, bradyarrhythmias and so on (22). Another study declared that although ondansetron is a widely accepted treatment for GE in children, a broader spectrum of primary diagnoses such as non GE, otitis media, diabetes and pneumonia for which ondansetron is being used should be considered (23).

4.1. Limitation and Strength

The limitation of this study was the absence of the prolonged follow-up of the patients in the ondansetron group to find out the probable effect of the drug on the duration of diarrhea. This was not included in our study targets. Suggestions for future studies consist of assessment of ondansetron effects on severity and duration of diarrhea, especially with regards to its etiology and cost-effectiveness

Table 1. Demographic Variables in Two Groups of Study (Intervention with Ondansetron and Control Group)

Group	Age, Mean ± SD	Duration of Gastroenteritis, Mean ± SD	Duration of Hospitalized, Mean ± SD	Gender		Chief Complaint	
				Female, No. (%)	Male, No. (%)	Recurrent Vomiting, No. (%)	Fever, No. (%)[a]
Control, N = 100	3.16 ± 1.52	1.34 ± 0.48	2.94 ± 1.41	42 (42)	58 (58)	80 (80)	20 (20)
Case, N = 100	3.69 ± 2.61	1.07 ± 0.26	0.11 ± 0.37	44 (44)	56 (56)	75 (75)	25 (25)
	Z = -0.207	Z = -4.717	Z = -12.592	$X^2 = 0.082$		$X^2 = 0.717$	
P value	0.836	< 0.001	< 0.001	0.775		0.397	

[a] Diarrhea and vomiting.

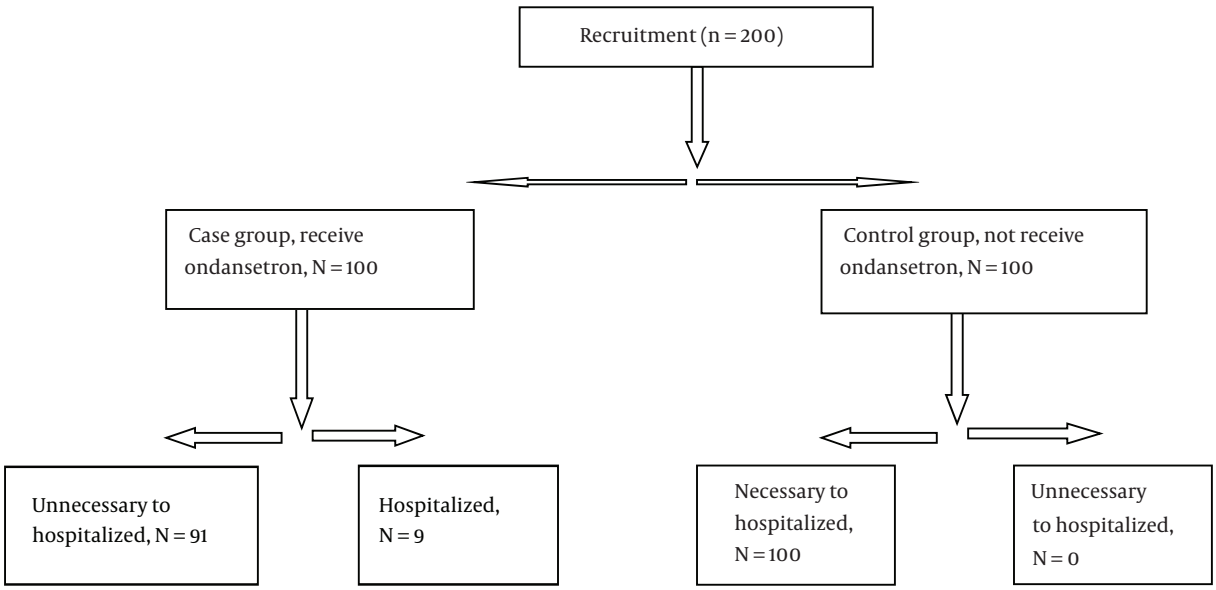

Figure 1. Profile of Participants in Two Groups of Study

of administration the drug, which can be different from one community to another.

4.2. Conclusion

The main conclusion of the current study is the emphasis on administrating ondansetron, which can lead to a decreased rate of hospitalization in infants and children with diarrhea and recurrent vomiting. Also, when comparing similar studies on using the oral form of the drug it showed that it had a better result when the injective form was used.

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Footnotes

Authors' Contribution: Design of study and preparation of article, Manoochehr Mahram; data collection, Maryam Darabi; analysis and interpretation of data, Sonia Oveisi.

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Table 2. Means and 95% Confidence Interval for Survival Time of Two Groups

Group	Mean				Log Rank (Mantel-Cox)	
	Estimate	Std. Error	95% Confidence Interval		Chi-Square	P Value
			Lower Bound	Upper Bound		
Control	2.940	0.141	2.664	3.216	22.579	0.001
Case	1.222	0.147	0.934	1.510		
Overall	2.798	0.137	2.529	3.067		

Table 3. β and SE of Chief Complaint Variable in the Equation of of Cox-Regression Model Based on Forward- LR.

Non- Equation	Score	Sig.	Equation		B	SE	Sig.	Exp (B)
Age	0.057	0.811	Step 1	Group	-1.443	0.378	< 0.001	0.236
Gender	0.479	0.489	Step 2	Chief complaint	-.573	0.249	0.021	0.564
Chief complaint	5.677	0.017		Group	-1.415	0.376	< 0.001	0.243
Group	17.201	< 0.001						

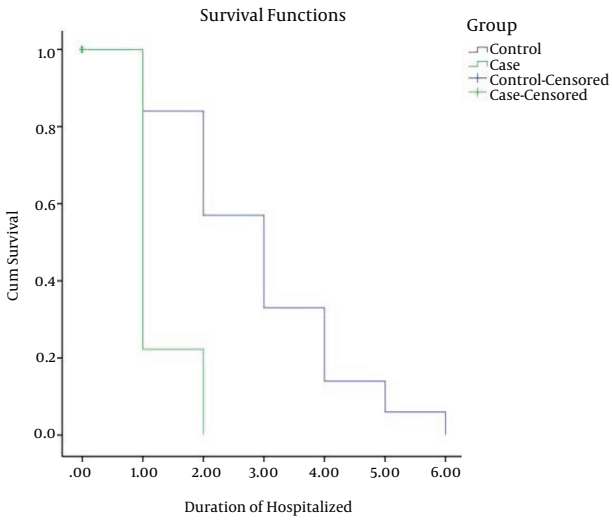

Figure 2. Plot of Survival Function in Two Groups Based on the Cox-Regression Model

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