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Original Article

Antiemetics to Control Vomiting in Children: A Double-Blind Placebo-Controlled Trial

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Abstract

Aim: The goal of this investigation was to prospectively compare the efficacy of ondansetron, metoclopramide and a placebo in children presenting to the emergency department with acute vomiting. ***Materials and Methods:*** In this randomised double-blind trial, the participants, who were younger than 18 years of age, were randomly assigned to receive treatment with (a) 0.15 mg/kg intravenous ondansetron, (b) 0.2 mg/kg intravenous metoclopramide in 100 mL normal saline, and (c) 100 mL normal saline as a placebo. The primary outcome was measured as recurrence of vomiting after 60 minutes subsequent to antiemetic therapy. ***Results:*** A total of 234 patients were randomised into the three treatment groups with (a) ondansetron (n=77), (b) metoclopramide (n=79) and (c) placebo (n=78). The median age was 68.27±39.97 months, and 49.1% were male. The results showed the occurrence of vomiting within the first 60 minutes was significantly different in the three groups (p=0.001), but there was no difference between the ondansetron and metoclopramide groups (p=0.557). The 30th, 120th, and the 240th minute results were statistically significant among the treatment groups (p=0.002, p=0.000, p=0.000 respectively), but there were no difference between ondansetron and metoclopramide (p=0.357, p=0.188, p=0.126, respectively). Extrapyramidal symptoms were found in 1 patient in the metoclopramide group (1.3%). There was no difference among the 3 treatment groups in terms of vomiting during the 24-hour follow-up (p=0.200). ***Conclusion:*** Intravenous single-dose slow infusion of antiemetics is effective in controlling vomiting compared to placebo.

Key words Antiemetics; Emergency Medicine; Paediatrics; Vomiting

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Introduction

Vomiting is a non-specific sign of a number of childhood diseases, and it constitutes a significant portion of emergency paediatric cases. The most common cause of vomiting in older infants and children is infectious gastroenteritis, many non-gastro-intestinal infections may generate vomiting as a symptom, as well. Stimulation of either the vomiting centre, a central "control centre" in the medulla near the respiratory centre, or the chemoreceptor trigger zone (CTZ) in the area postrema on the floor of the fourth ventricle can generate

vomiting. Afferent impulses from other areas of the brain, such as the vestibular system, the amygdala (as with emotion or fear), or from certain organs outside the GI tract can stimulate vomiting in a similar mechanism. In children with dehydration from gastro-enteritis, oral rehydration is recommended as the first line therapy by the American Academy of Paediatrics.[1] Parenteral therapy is considered to be useful in reducing vomiting symptoms in cases in which oral rehydration fluids are not adequate to correct the dehydration.

In the guidelines recorded before 2008, antiemetic therapy was not recommended, particularly as first-line treatments for children with gastroenteritis; nevertheless, it has been emphasized in subsequent guidelines that antiemetic treatment is effective in selected cases.[2-4] Despite all these suggestions, it has been noted that 79.2% of emergency physicians and only 52.2% of paediatricians in the United States prefer to use antiemetic agents in order to control vomiting and their side-effect.[5]

Antiemetics such as prochlorperazine, ondansetron and metoclopramide are recommended in the paediatric oncology guideline for the control of paediatric vomiting cases.[6] Studies on ondansetron and metoclopramide have mostly been performed for the control of post-operative vomiting and on hospitalised oncological patients receiving chemotherapy, but studies on single intravenous (IV) dose for rapid and effective vomiting control in the emergency department are limited. Although prochlorperazine and metoclopramide have been compared in a limited number of emergency department studies, they have not been found to be superior to normal saline infusion; however, the number of cases studied has been small.[7] In a limited number of studies, symptom control for patients during follow-ups in the emergency department was taken into consideration; the rates of post-discharge vomiting and re-admissions due to resistant vomiting were not specified.

Ondansetron, a selective serotonin antagonist, is the most commonly used antiemetic agent for the control of paediatric vomiting due to its effects on the central and peripheral nervous system. Placebo-controlled randomised trials have shown that ondansetron reduces the rate of hospitalisation, especially in the control of vomiting secondary to gastroenteritis, and it decreases the need for IV fluids and the frequency of vomiting.[8] However, there are controversies related to the use of ondansetron in many other studies[9] besides the high cost of the drug.

Metoclopramide, a dopamine and serotonin antagonist, controls vomiting by affecting the chemoreceptor trigger zone in the central nervous system. Many adverse effects have been reported when using metoclopramide as an antiemetic, the most common being extrapyramidal symptoms is dystonia.[10] Defined extrapyramidal symptoms have been noted in the case-control series; but randomised double-blind placebo controlled studies on the safety of antiemetics are limited. It was demonstrated that these side effects occurred most frequently during rapid infusions of less than 15 minutes and in cases of chronic use. The frequency of extrapyramidal symptoms with single doses and slow infusions in the emergency department were not clearly defined. Studies on the control of vomiting and the frequency of re-admissions to the hospital after discharge are predominantly related to the oral use of antiemetics. The meta-analysis of these studies showed that oral antiemetics were superior to placebos, but many of the studies were found to be limited since they included high-risk bias criteria.[11]

AIM: The goal of this investigation was to prospectively compare the efficacy of ondansetron, metoclopramide and a placebo in children presenting to the emergency department with acute vomiting.

Methods

Study Design

A randomised, double-blind, placebo-controlled prospective study was carried out on paediatric patients presenting with the complaint of vomiting to the emergency department of Derince Training and Research Hospital, Kocaeli, Turkey between 01.01.2016 and 01.06.2016. Ethics committee approval of the study was provided by Kocaeli University, Faculty of Medicine, Kocaeli, Turkey (Number: 13/23, protocol: KOU KAEK 2014/180). The study was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki and the current guideline on effective clinical procedures. All patients were informed about the study before inclusion, and the consents of both patients and their relatives were obtained.

Participants

The study included patients of 1-18 years of age, who had presented to the Paediatric Emergency Department of the Derince Training and Research Hospital with the complaint of vomiting without the presence of blood and bile at least 3 times in the preceding 24 hours. At the time of admission, the patients were questioned about their history of drug use, drug allergy status and antiemetic use within the last 24 hours. The study excluded patients those weighing

less than 8 kg, those with a history of allergic reactions to any group of antiemetics, those who had taken oral antiemetic drugs within 24 hours before admission, who were suffering from severe dehydration or an underlying disease which would affect the assessment of volume (such as renal failure or known hypoalbuminaemia), those with a history of extrapyramidal side effects due to the use of any kind of drugs, and those with a history of previous abdominal surgery and with a complaint of vomiting after trauma and those with suffering from gastrointestinal haemorrhage (haematemesis, melena).

Randomisation

The participants were divided into 3 groups according to the type of treatment by a computer generated randomisation. All groups were equally distributed. The patients were to assigned respective groups as ondansetron group 1, metoclopramide group 2 and placebo group 3, according to the type of treatment. The types of treatment were numbered in closed envelopes according to the order of application. The randomisation codes were kept secret until all data were completed.

Procedures

Study Protocol

The patients included in the study were evaluated at the time of admission by a senior resident having at least 2 years' of experience. Their clinical features including those in the preceding 24 hours were recorded. Five etiologic sub-groups such as infection of the upper respiratory tract, the thorax, the abdominal or the genitourinary tract and other causes identified. Haemogram, blood urea, creatinine, sodium, potassium and c-reactive peptide levels were routinely requested from all patients at the time of admission. Complete urinalysis and stool analysis were determined as additional tests according to the patients' histories and physical examinations.

All of the patients were transferred to the standard short-stay units, and a different researcher who was not involved in the diagnosis and treatment processes, was informed and was given information only about the weight of the patients for determination of the drug dose. The researcher opened the closed envelopes according to the order of randomisation, and the treatment was administered according to the number in the envelope. The patients marked with the number 1 in their envelopes were injected with 0.15 mg/kg IV ondansetron (Zofran 10 mg/mL vial, Polifarma) in 100 cc normal saline; the patients marked with the number 2 were given 0.2 mg IV metoclopramide (Methpamid 1 g/ 2 mL, Onfarma) in 100 cc normal saline, the patients in group 3 were given 100 cc normal saline IV infusion for 30 minutes. All patients in the three groups were infused with 20 cc/kg/h normal saline after the loading treatment. All drugs and fluids given in the treatment were prepared at standard room temperature. No information about the treatment was given to the physician taking care of the patients, the health practitioners and the relatives of the patients.

All patients were followed for at least 240 minutes in the emergency room. Oral rehydration fluids, which were prepared beforehand, were given to the patients after 30 minutes, 1 hour, 2 hours and 4 hours. Vomiting episodes were recorded after each administration of the oral rehydration fluids. The patients in whom adverse effects such as extrapyramidal symptoms, allergies and pruritus were observed during the follow-ups were excluded from treatment by break-up of the randomisation, and the drug group in which the adverse effects were observed was recorded.

The patients who did not complain of vomiting and who had no evidence of dehydration within 4 hours were discharged from the hospital after the follow-up. Patients in whom persistent vomiting after 4 hours of follow-up continued received only normal saline infusion. No additional medical treatment was given in either study group. Unstable patients still complaining of vomiting and having dehydration findings were transferred to the paediatric department. After the evaluation, the patients were classified according to the discharge status, hospitalisation in the paediatric department and transfer to the intensive care unit. Oral antiemetic treatment was not prescribed for the patients after the discharge.

The researchers called the patients after 24 hours using their contact information in order to inquire about possible adverse effects and continuation of vomiting after discharge, and the patients were questioned about the re-admission to any emergency department due to vomiting, side effects and continuation of the existing complaints. The patients who could not be contacted through their phone numbers after 24 hours were excluded from the study.

Outcome

Primary Outcome: Recurrence of vomiting after 60 minutes subsequent to antiemetic therapy.

Secondary Outcome: Recurrence of vomiting after 30th, 120th, and 240th minutes, adverse effects, length of stay in

the emergency department, proportion of patients in all study group discharged within 4 hours, hospitalisation rates, re-admissions rates after 24 hours.

Sample Size

Sample size calculation was carried out the G power program with an assumption of α: 0.,05 and β: 0.80 and an effect size of 0.20 was used. The requisite sample size was calculated as 269.[12]

Statistical Analysis

Statistical analyses were carried out using the SPSS software version 21. The conformity of the variables with the normal distribution was examined using visual histograms, probability diagrams and analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk tests). Descriptive analyses were performed using the mean and standard deviations for normally distributed variables, and median and interquartile ranges for non-normal distributed variables. The One-way analysis of variance (ANOVA) or the Kruskal-Wallis analysis was utilised according to the compliance with the normal distribution for the comparison of demographic data among the treatment groups. While the effects of the different treatments on the patients' vomiting frequency, the two-way ANOVA and ANCOVA tests were performed in terms of the effects of sex and age. Repeated measurement analysis of variance was used for evaluation of the effects of the different treatments on the changes observed in patients' vomiting incidence over time. The analyses were not intention-to-treat analyses and only patients with outcome data available were analysed for each outcome. The Greenhouse-Geisser correction was used in cases when the assumption of sphericity could not be achieved. The total type-1 error level was determined as 5% for statistical significance.

Results

During the study period, 342 patients complaining of vomiting more than 3 times in the last 24 hours had presented to the emergency department. Of these patients, 27 were not included in the study because they did not qualify for inclusion, and 45 patients were also excluded since they did not give their consent to participate in the research. A total of 270 patients were included in the study and randomised into treatment groups (Figure 1). After treatment randomisations, 2 patients, who developed adverse reactions (allergic reaction in 1 patient in the ondansetron group, extrapyramidal reaction in 1 patient in the metoclopramide group), 22 patients, who could not be reached at the 24th hour on the contact number (9 patients in the ondansetron, 6 patients in the metoclopramide, 7 patients in the placebo groups), and 14 patients who withdrew from the study due to the individual factors such as long follow-up time (3 patients in ondansetron, 4 patients in metoclopramide, 7 patients in placebo group), were excluded from study. Finally, patients participating in the study were divided into groups to receive IV ondansetron (n=77), IV metoclopramide (n=79) and IV placebo (n=78) according to treatment groups.

The median age of the patients was 68.27±39.97 months, and 49.1% of the patients were male (n=115). The focus of infection, laboratory results and the demographic data of the patients have been presented in Table 1. The demographic data, focus of infection and laboratory results obtained at the time of application were similar in all treatment groups. At the baseline laboratory findings, there was no patient in either group with elevated urea, elevated creatinine, hypoatraemia or hypernatraemia. The baseline C-reactive peptide levels were elevated in 38 patients (49.3%) in the ondansetron, in 46 patients (58.2%) in the metoclopramide, and in 30 patients (38.4%) in the placebo groups. Although not statistically significant, the average CRP in the placebo group appeared to be much lower than the treatment groups and this may confound the results (p=0.39). The vomiting conditions of the treatment groups depending on the duration have been summarised in Table 2.

Vomiting persisted in 13 patients (16.9%) in the ondansetron group, in 13 patients (16.5%) in the metoclopramide group, and in 31 patients (39.7%) in the placebo group after 60 minutes, and the difference among the treatment groups was statistically significant (p=0.001). This difference resulted from the placebo group, and there was no significant difference between the ondansetron and the metoclopramide groups (p=0.557). Vomiting was still observed in 11 patients (14.3%) in the ondansetron group, in 14 patients (17.7%) in the metoclopramide group and in 28 patients (35.9%) in the placebo group at the 30th minute. The continuation of vomiting at the 30th minute was statistically significant among the treatment groups (p=0.002). This difference was observed to have resulted from the placebo group subsequent to the binary cross-analysis carried out between each of the groups. At the 30th minute, there was no significant difference between the ondansetron and metoclopramide groups (p=0.357). There was a significant difference after 120 minutes and 240

minutes when measurements were made (p=0.000, p=0.000, respectively). No significant difference was found between the metoclopramide and the ondansetron groups in these periods (p=0.188, p=0.126, respectively).

The average emergency follow-up time for the patients was 250.26±26.1 minutes in the ondansetron group, 270.51±54.89 minutes in the metoclopramide group and 287.18±62.15 minutes in the placebo group. There was a significant difference among the three groups (p=0.000). The difference resulted from the placebo group in the post-hoc analysis, and there was no significant difference between the metoclopramide and the ondansetron groups (p=0.039).

When the current status of the patients was examined, 2 patients in the ondansetron group (2.6%), 6 patients in the metoclopramide group (7.6%) and 7 patients in the placebo group (9%) had been hospitalised, and 97.4% of the patients in ondansetron, 92.4% of patients in metoclopramide group, and 91% of patients in placebo group had been discharged after the follow-up period. Although hospitalisation cases were less commonly observed in the ondansetron group, the difference was not significant (p=0.234).

In terms of treatment complications, an allergic reaction was detected in 1 patient (1.3%) in the ondansetron group, and extrapyramidal symptoms were found in 1 patient in the metoclopramide group (1.3%). The symptoms of the patient determined to have extrapyramidal symptoms had regressed through treatment. Adverse effects were not observed in the placebo group. There was no significant difference among the groups in terms of adverse effects (p=0.405).

There was no significant difference among the 3 treatment groups in terms of vomiting in the 24-hour follow-up (p=0.200). When the re-admission cases due to resistant vomiting after discharge were analysed, 11 patients (14.6%) in the ondansetron group, 14 patients (19.1%) in the metoclopramide group and 12 patients (16.9%) in the placebo group had been re-admitted to the hospital due to recurrent vomiting. There were no statistically significant differences in the demographic characteristics such as age and sex at re-admitted to hospital group (p=0.835, p=0.135, respectively). It was observed that antiemetic agents were not superior to placebo (p=0.835).

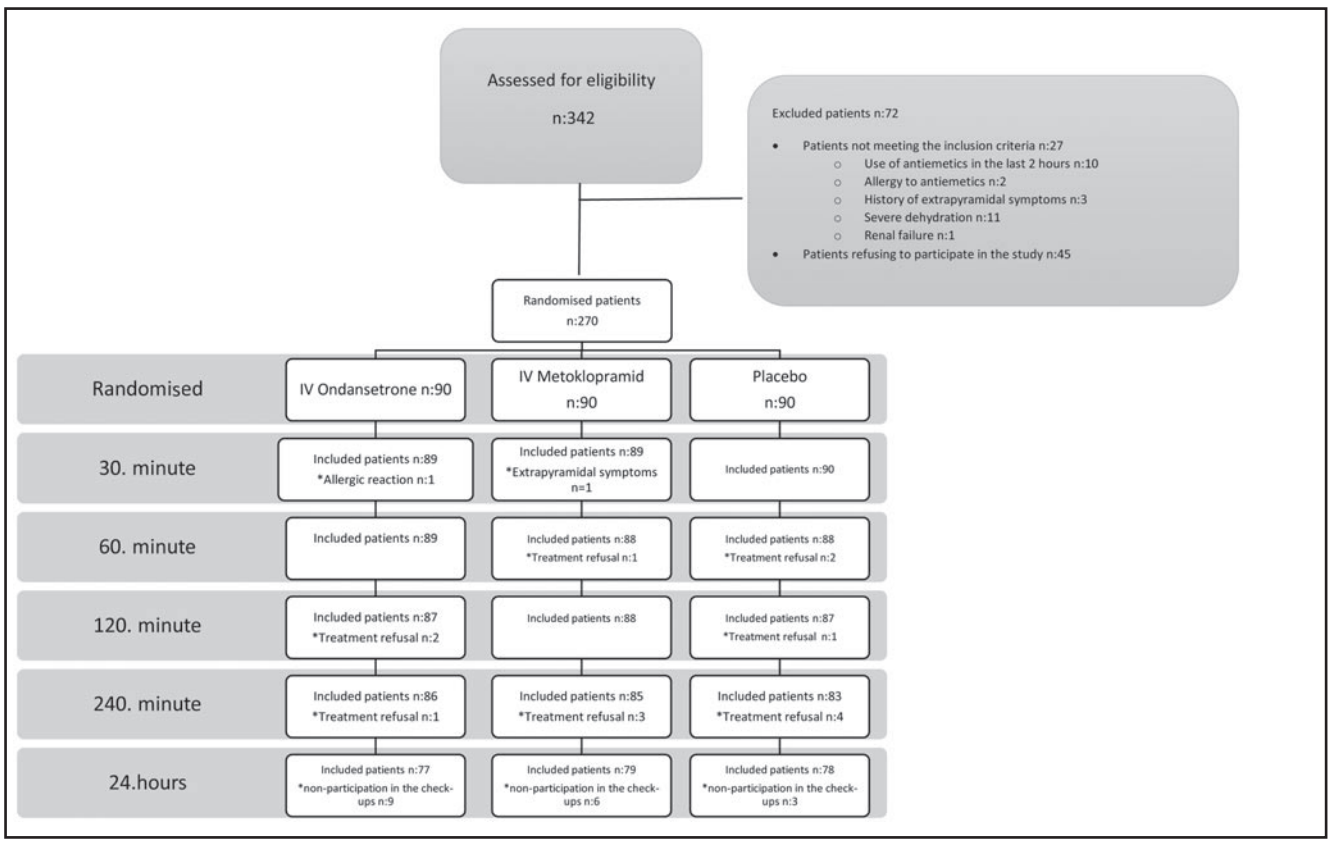

Figure 1 Consort diagram of enrolled patients.

Table 1 Baseline characteristics of enrolled patients

	Ondansetron	Metoclopramide	Placebo	P
Demographic				
Age (Months, Mean, CI)	65.57 [(57.09)-(74.06)]	67,67 [(58.68)-(76.66)]	71,56 [(61.99)-(81.13)]	0.64
Sex (male, %)	35 (48,5%)	44 (55.7%)	36 (46.2%)	0.36
Vomiting frequency (n, CI)	5.96 [(5.34)-(6.59)]	6.35 [(5.81)-(6.9)]	6,31 [(5.71)-(6.9)]	0.59
Vital sign				
Temperature(°C) (Median)	36.54	36.68	36.9	0.3
Fever (n, %)	11 (14.6%)	14 (19.1%)	12 (16.9%)	0.51
Infection				
URT (n, %)	20 (26%)	24 (30.4%)	19 (24.4%)	
LRT (n, %)	5 (6.5%)	5 (6.3%)	6 (7.7%)	
Abdominal (n, %)	32 (41,6%)	35 (44.3%)	33 (42.3%)	0.76
Genitourinary (n, %)	10 (13%)	3 (3.8%)	7 (9%)	
Other (n, %)	10 (13%)	12 (15.2%)	13 (16.7%)	
Laboratuary				
Haemoglobin (g/dl) (CI %)	12.58 [(12.33]-(12.83)]	12.49 [(12.24)-(12.73)]	12.79 [(12.53)-(13.04)]	0.23
WBC (10^3/µgL) (CI %)	13411.69 [(12139.25)-(14684.12)]	12579.11 [(11458.08)-(13700.15)]	15700 [(9900.16)-(21496.84)]	0.43
Platelet (10^3/µgL) (CI %)	286493.5 [(267531.96)-(305455.56)]	272278.49 [(253442.39)-(291114.57)]	294465.56 [(274631.64)-(314299.49)]	0.26
Urea (mg/dl) (CI %)	28.22 [(26.56)-(29.88)]	30.42 [(28.26)-(32.58)]	27.95 [(26.28)-(29.62)]	0.12
Creatinin (mg/dl) (CI %)	0.52 [(0.5)-(0.54)]	0.54 [(0.51)-(0.56)]	0.5 [(0.48)-(0.52)]	0.49
Sodium (mEq/l) (CI %)	137.22 [(136.71)-(137)]	137.04 [(136.45)-(137.62)]	135.41 [(132.26)-(138.57)]	0.33
Potasium (mEq/l) (CI %)	4.19 [(4.11)-(4.26)]	4.15 [(4.04)-(4.26)]	4.27 [(4.19)-(4.36)]	0.18
C-reactive protein (mg/l) (CI %)	12.65 [(6.26)-(19.04)]	12.1 [(7.68)-(16.51)]	9.56 [(4.84)-(14.29)]	0.39

CI: Confidence Interval, n: Number; URT: Upper Respiratuary Track, LRT: Lover Respirautary Track; WBC: White Blood Cells

Table 2 Primary and secondary outcomes for total and by treatment arm

		Ondansetron	Metoclopramide	Placebo	P
30 minutes	Vomiting (+) n,%	11 (14.3%)	14 (17.7%)	28 (35.9%)	0.002
60 minutes	Vomiting (+) n,%	13 (16.9%)	13(16.5%)	31(39.7%)	0.001
120 minutes	Vomiting (+) n,%	8 (10.4%)	14 (17.7%)	29 (37.2%)	0.000
240 minutes	Vomiting (+) n,%	5 (6.5%)	11 (13.9%)	23 (29.5%)	0.000
24 hours	Vomiting (+) n,%	17 (22.1%)	18 (22.8%)	26 (33.3%)	0.200
Length of stay	Minute (±SD)	250.26 (±26.1)	270.51 (±54.89)	287.18 (±62.15)	0.000
Discharged	n, %	75 (97.4%)	73 (92.4%)	71 (91%)	0.236
Hospitalisation	n, %	2 (2.6%)	6 (7.6%)	7 (8.9%)	0.234
Readmission	n, %	11 (14.6%)	14 (19.1%)	12 (16,9%)	0.835

n=number

Discussion

In a randomised, double-blind, placebo-controlled study, it was observed that ondansetron and metoclopramide were more effective than the placebo at the 60-minute vomiting control, and that neither of the two antiemetic agents were superior to each other at the target measurement and other measurement times. In our study, it was seen that there was no significant difference between antiemetic agents and placebo in terms of side effect profiles, and the rate of extrapyramidal symptoms related to metoclopramide after slow infusion was found to be 1.3%. Antiemetics were not superior to the placebo in terms of vomiting control after discharge and reducing the rate of re-admission.

Although it has been stated in the guidelines of the American Academy of Pediatrics and NICE that there is no need for using antiemetics in eliminating the symptoms of vomiting after diarrhoea,[13-14] in the meta-analysis of the studies carried out in contrast to the above-mentioned guidelines,[15] antiemetics were found to be effective, and this contradiction has necessitated the emerging of new studies in the field. The current contradiction has limited the use of these agents in emergency departments. In a limited number of studies comparing antiemetics with placebo, Ansai et al demonstrated that ondansetron was not superior to metoclopramide (p=0.14) in controlling vomiting, but the efficacy of both groups against a placebo was not compared.[4] In the study carried out on paediatric patients receiving chemotherapy, it was stated that antiemetics were superior to placebo; however, the superiority of antiemetics among themselves was not examined, and it was emphasized that ondansetron was effective in patients receiving oral rehydration.[16] Contrary to all these studies, it was demonstrated in another study conducted on adult patients that antiemetics were not superior to placebo; nevertheless, the low number of patients constitutes the basic limitation of the study.[17] In our study, antiemetics were shown to be effective in controlling vomiting compared to placebo, and our results are important due to the limitations of other studies.

In the American Academy of Pediatrics guideline, the use of antiemetics for control of vomiting cases, especially those resulting from gastroenteritis, has been restricted due to the adverse-effect profiles; however, the safety and efficacy of antiemetic agents have been described in the compilation of 7 studies carried out on 1020 patients.[18] The use of metoclopramide in daily practice is particularly limited by clinicians due to the side effects of defined extrapyramidal symptoms related to metoclopramide. Extrapyramidal symptoms have been predominantly described in case-control series, and their frequency has been defined to be contradictory, because they are lower than 1% in certain studies[19] and 9% in some case-control series.[20] It has been shown that this extrapyramidal side effect is more frequently observed after a rapid infusion of less than 2 minutes, and that this adverse effect decreases in slow infusions. The reliability of these studies is limited, since they are not randomised and double-blinded. Our study is important, because it is randomised and double-blinded, and the adverse effect profile in the slow infusion is as low as 1.3% and not life-threatening. At the same time, priority is given to the cost-effective use of metoclopramide, since ondansetron costs $26 and it is difficult to access.

Limitations

The present study has several limitations. First, our study was conducted in a single centre with a relatively small sample size, which limits the generalisability of our findings. All patients also received an IV isotonic sodium chloride solution infusion after bolus first-line treatment, which may also have affected their vomiting. The presence of vomiting at the 30th minute after the initial treatment is likely to have been caused by 'IV drip'. For this reason, in our study, the presence of vomiting was determined as the primary outcome at 60 minutes rather than 30 minutes. Although vomiting was not significant at 30 minutes, the effectiveness of antiemetics in the early period was taken into account statistically. In our study, in order to keep the sample size high, different etiologies that cause vomiting were included in our study, so that our study group was heterogeneous. Despite the heterogeneous distribution of the patient groups, there was no statistically significant difference between the patient groups in terms of the source of infection. We also think that antiemetic agents will not cause any significant limitation, since they affect the same aetiology frequently with the same mechanism. There are patients who withdrew from treatment in each treatment group after the patient had been treated after randomisation and we could not reach 18 patients after they were discharged from hospital; therefore, the adverse-effect profiles of the patients and the presence of vomiting could not be defined, since they did not participate in the check-up sessions. The analyses were not intention-to-treat analyses and only patients with outcome data available had been analysed for each outcome.

Conclusion

IV single-dose slow infusion of antiemetics is effective in controlling vomiting compared to placebo, and they reduce the length of hospital stays, but there is no evidence that they are effective in reducing the hospitalisation rate or the readmission rate. Although the slow infusion of metoclopramide has been shown to reduce extrapyramidal symptoms compared to rapid infusion in a small proportion of patients, the clinician should be careful that metoclopramide may cause extrapyramidal side effects.

Declaration of Interest

The authors declare that there is no conflict of interest.

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