COMPLEMENTARY EFFECT OF METOCLOPRAMIDE IN THE CONTROL OF
VOMITING DUE TO ACUTE VIRAL GASTROENTERITIS IN CHILDREN: A SINGLE-
BLIND RANDOMIZED CLINICAL TRIAL

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ABSTRACT: Acute gastroenteritis is associated with high mortality in childhood. A complication of the illness is dehydration, which should be well managed. This study aimed to analyze the effect of metoclopramide on the number of vomiting episodes in moderately dehydrated children with acute gastroenteritis. In this single-blinded clinical trial, 240 children of 1 to 7 years old with acute viral gastroenteritis were randomly classified into two groups of serum therapy (control) and metoclopramide (intervention). Children in the serum therapy group received dextrose 5% along with electrolytes management and those in the intervention group were treated with intravenous metoclopramide (0.1 mg/kg) and were subjected to serum therapy as well. The number of vomiting episodes was counted for 4 consecutive days. The obtained data were analyzed by the dispersion, t-student, and χ² tests. A total of 240 patients participated in the study with 120 patients in each of the control and intervention groups. The mean incidences of vomiting in the intervention group significantly differed with the control group during the days one to four (p-values were 0.21, 0.007, 0.002, and 0.001 for the first to the fourth days, respectively). Metoclopramide can be used to prevent vomiting in children with gastroenteritis. However, to achieve a decisive result, it is recommended to perform further research at other centers and compare it with other conventional antiemetics.

Clinical trial registration: This clinical trial was registered in the Iranian Registry of Clinical Trials (IRCT) with number IRCT201205159766N1

Keywords: Gastroenteritis, Vomiting, Dehydration, Metoclopramide, Child.

INTRODUCTION
Acute gastroenteritis is the inflammation of mucosal membranes of the alimentary tract, usually due to a viral infection commonly rotavirus and Norwalk virus (2, 3). Salmonella, Shigella, Campylobacter, and Escherichia coli are common causes of bacterial gastroenteritis (4, 5). Gastroenteritis is one of the most common causes of illness and mortality of children; such that 20-35 million episodes of gastroenteritis occur annually in 15.6 million children aging less than 5 years resulting in 2.1-3.7 million visits by physicians, 220,000 admissions, 924,000 days of hospitalization, and 300-400 deaths. In developing countries such as Iran, the mean annual number of gastroenteritis episodes in less than 5 years children is 5. This number is 1.3-2.3 per year in the United States (6-9). Clinical manifestations of acute gastroenteritis depend on the causing organism and the host defense and may include asymptomatic infection, vomiting, diarrhea, and abdominal cramps. Vomiting in patients is a
main cause of dehydration which is a dangerous condition in children, since their body has more water relative to their weights. Children are very sensitive to dehydration and thus it should be carefully managed (10-11). Vomiting can also result in electrolytes disturbance in children. Given the electrolytes levels in the stomach (60 mEq Na, 10 mEq K, and 90 mEq Cl), vomiting children should be treated by intravenous serum based on a specific protocol (12). Vomiting is mostly diagnosed and classified clinically. Mild dehydration (3-5% of body weight) has few clinical signs and symptoms. The child may be thirsty. Alert parents may notice reduced urine output. Heart rate is normal or there may be a weak tachycardia. Clinical findings are normal in physical examination. Moderate dehydration (5-10% of body weight) is associated with tachycardia without pulse weakness or hypotension, low or zero urine output, irritability or drowsiness, depressed fontanels and eyes, decreased tear, dryness of mucous membranes, mildly shrunk skin, delay in capillary filling (2 sec or more), and cold and pale skin. Symptoms of severe dehydration (10-15% of body weight) include tachycardia with weak pulse, zero urine output, very depressed fontanels and eyes, no tear, dried mucous membranes, shrunk skin, considerable delay in capillary filling (3 sec or more), and cold and mottled skin (13). Oral replacement therapy (ORT) is an effective, inexpensive, and simple method recommended by World Health Organization (WHO) for management of mild and moderate dehydration. However, intravenous fluid therapy and even admittance in intensive care unit is recommended for severe dehydration (14). Various studies showed that ORT reduces hospitalization and complication compared with intravenous fluid therapy (15, 16). However, fluid therapy is administrated intravenously when children with moderate dehydration cannot tolerate ORT due to severe vomiting or dilatation of stomach and intestine or when the parents cannot appropriately take care of the child (17, 18). Therefore, in addition to its direct role in dehydration, vomiting can inhibit correction of dehydration by ORT; thus children with repeated episodes of vomiting should be treated by intravenous fluid therapy. Administration of antiemetics is a controversial issue in the treatment of gastroenteritis-induced dehydration. Use of antiemetics has many advantages namely reduction in the unpleasant feeling of nausea and vomiting, prevention of further dehydration, earlier initiation of ORT, and thus reduction in treatment complications and hospitalization duration (6, 9). The exact mechanism of vomiting is not understood. As a well known antiemetic, metoclopramide acts through blocking of dopamine receptors and increasing of lower esophageal sphincter tonus and thus increasing of upper alimentary tract peristalsis and stomach emptying. It is used for prevention of nausea and vomiting caused by chemotherapy, surgery, pregnancy, and gastroenteritis (19, 20). The recommended dose in children is 0.1 mg/kg up to 10 mg; with this dose the adverse effects such as extrapyramidal symptoms, drowsiness, and tachycardia is minimal (21). Fedorowicz et al. systematically analyzed 7 clinical trials and studied the effectiveness and safety of antiemetics in children’s gastroenteritis. They reported no specific adverse effect for metoclopramide (22).

In the present study the impact of these two methods was investigated in preventing acute viral gastroenteritis-induced vomiting in children due to the following reasons: no study has been performed so far on the use of metoclopramide as an adjuvant in the treatment of dehydration in children; the common method of treatment of vomiting in dehydrated children is intravenous fluid therapy; and early initiation of oral replacement therapy benefits the patient and the treatment system.

MATERIALS AND METHODS

This study was a single-blinded clinical trial whose statistical population consisted of moderately dehydrated 1-7 year old patients with acute viral gastroenteritis admitted in the pediatric ward of AmirKabir Hospital of Arak City. The patients were selected based on inclusion and exclusion criteria and their informed consent. According to the Pocock principle and given that the study was a clinical trial, to obtain more accurate results, 240 children were randomly selected and assigned into two groups of serum therapy (control) and metoclopramide (intervention) (each 120 children) based on alternate admission. Inclusion criteria included children aged between 1 and 7 years, acute viral gastroenteritis, oral intolerance, isonatrencic moderate dehydration, no treatment before admission, no need for other treatments, and obtaining informed consent from patients’ parents or guardians for taking part in the trial. Exclusion criteria included mild and severe dehydration, hyponatremic and hypernatremic moderate dehydration, laboratory findings in favor of colitis and parasitic disease such as blood, white cells, or parasite in stool sample, evidence of acute abdomen and any emergency condition such as peritoneal irritation and hard and painful abdomen, gastroesophageal reflux history (given the difficulty of proving gastroesophageal reflux), patient relinquishment or patient self consent discharge before complete recovery. Viral gastroenteritis was diagnosed based on its clinical characteristics in which the child suffers from mild to moderate vomiting and then from...
occasional watery diarrhea. No blood and white cells were seen in the stool sample, otherwise the viral diagnosis would be ruled out. The study was carried out during fall and winter of 2008 when viral gastroenteritis was prevalent (23). At admission, the essential tests were performed according to clinical symptoms of the patients. They included Na and K concentrations, serum pH, and urinalysis to find out the type of dehydration. Children with moderate isonatremic dehydration (Na 135-145 mEq/L) were included in the study. Daily maintenance fluid was calculated for each child based on patient weight as follows:

- For the first 10 kg, 100 ml/kg
- For 11-20 kg, 1000 ml plus 50 ml/kg
- Over 20 kg, 1500 ml plus 20 ml/kg

The maximum fluid administered in 24 hours was 2400 ml. Then the fluid deficit was calculated according to the guidelines through multiplication of the weight to the degree of dehydration (5-10%) (12). All patients received 20 ml/kg normal saline over 20 minutes. Then the needed fluid for 24 hours was calculated by adding the maintenance and deficit volumes from which the given isotonic volume was subtracted. The remaining fluid deficit was compensated by dextrose 5% plus 20 mEq/L KCl. But if the patients had an ongoing loss due to vomiting or diarrhea, they received 1 ml dextrose 5% plus sodium bicarbonate (20 mEq/L) and KCl (20 mEq/L) for each ml of diarrhea, and 1 ml normal saline plus KCl (10 mEq/L) every 1-6 h (24) for each ml of vomiting. Besides serum therapy, the patients in the intervention group received metoclopramide with the recommended dose of 0.1 mg/kg (22, 25, 26) intravenously via serum (to better control the received dose). To reduce its side effects, the medicine was administered as needed (PRN) up to 2 times in 24 h and until 3 days after initiation of vomiting. Complications such as diarrhea and extrapyramidal symptoms were recorded in the patients’ questionnaires. The episodes of vomiting were recorded as well during four days.

RESULT

A total of 240 patients participated in the study, out of which 120 were assigned to the intervention group and 120 to the control group. The patients consisted of 113 boys (47.1%) and 127 girls (52.9%). The numbers of boys in the intervention group and the control group were 48 (40%) and 65 (54.17%), respectively. The mean age of the participants was 35.88 ± 17.69 months. The mean ages of the patients in the intervention and control groups were 36.08 ± 18.10 and 35.68 ± 17.35 months, respectively. There was no significant difference between the two groups in terms of mean age (p = 0.861). The means of vomiting episodes at the first day in the intervention and control groups were 3.00 ± 1.50 and 3.52 ± 1.90, respectively; accordingly they had a significant difference (p= 0.021). The mean of vomiting episodes at the second day was 1.83 ± 1.67 in the intervention group and 2.41 ± 1.64 in the control group (p = 0.007); it was 1.30 ± 1.47 and 1.95 ± 1.67 in the intervention and control groups, respectively at the third day (p = 0.002), and 2.37 ± 1.51 and 1.70 ± 1.47, respectively at the fourth day (p < 0.001). The course of changes in the mean of vomiting episodes is shown in Figure 1.
Figure 1: The course of changes of the mean vomiting episodes during four consecutive days

The vomiting episodes of the children were compared in terms of gender and age groups and the results were summarized in Tables 1 and 2.

Table 1: Comparison of vomiting episodes during the days one to four in terms of gender in the two groups of intervention and control

<table>
<thead>
<tr>
<th>Group</th>
<th>Vomiting Episodes</th>
<th>First day</th>
<th>p-value</th>
<th>Second day</th>
<th>p-value</th>
<th>Third day</th>
<th>p-value</th>
<th>Fourth day</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boy</td>
<td>Intervention</td>
<td>3.12 ± 1.72</td>
<td>0.164</td>
<td>1.60 ± 1.71</td>
<td>0.04</td>
<td>1.18 ± 1.29</td>
<td>0.004</td>
<td>2.25 ± 1.56</td>
<td>0.089</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>3.61 ± 1.91</td>
<td></td>
<td>2.27 ± 1.69</td>
<td></td>
<td>2.00 ± 1.58</td>
<td></td>
<td>1.75 ± 1.48</td>
<td></td>
</tr>
<tr>
<td>Girl</td>
<td>Intervention</td>
<td>2.93 ± 1.35</td>
<td>0.090</td>
<td>1.98 ± 1.64</td>
<td>0.04</td>
<td>1.38 ± 1.58</td>
<td>0.080</td>
<td>2.45 ± 1.49</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>3.41 ± 1.89</td>
<td></td>
<td>2.58 ± 1.58</td>
<td></td>
<td>1.90 ± 1.78</td>
<td></td>
<td>1.65 ± 1.46</td>
<td></td>
</tr>
</tbody>
</table>

Results obtained from t-student test

Table 2: Comparison of vomiting episodes in the two groups of intervention and control separately for different age groups

<table>
<thead>
<tr>
<th>Age group</th>
<th>Vomiting Episodes</th>
<th>First day</th>
<th>p-value</th>
<th>Second day</th>
<th>p-value</th>
<th>Third day</th>
<th>p-value</th>
<th>Fourth day</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-24 month</td>
<td>Intervention</td>
<td>2.72 ± 1.26</td>
<td>0.046</td>
<td>1.82 ± 1.63</td>
<td>0.262</td>
<td>1.62 ± 1.65</td>
<td>0.710</td>
<td>2.07 ± 1.43</td>
<td>0.036</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>3.59 ± 2.42</td>
<td></td>
<td>2.22 ± 1.62</td>
<td></td>
<td>1.50 ± 1.40</td>
<td></td>
<td>1.40 ± 1.41</td>
<td></td>
</tr>
<tr>
<td>25-36 month</td>
<td>Intervention</td>
<td>3.41 ± 2.06</td>
<td>0.546</td>
<td>1.54 ± 1.50</td>
<td>0.065</td>
<td>0.91 ± 1.34</td>
<td>0.019</td>
<td>2.50 ± 1.38</td>
<td>0.031</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>3.14 ± 1.16</td>
<td></td>
<td>2.37 ± 1.62</td>
<td></td>
<td>1.96 ± 1.67</td>
<td></td>
<td>1.66 ± 1.30</td>
<td></td>
</tr>
<tr>
<td>37-48 month</td>
<td>Intervention</td>
<td>3.14 ± 1.15</td>
<td>0.661</td>
<td>2.04 ± 1.93</td>
<td>0.499</td>
<td>1.19 ± 1.07</td>
<td>0.016</td>
<td>2.66 ± 1.49</td>
<td>0.557</td>
</tr>
</tbody>
</table>
Results obtained from t-student test

No complications related to metoclopramide in the children of the intervention group were seen.

**DISCUSSION**

In this single-blinded clinical trial performed on 240 children with moderate dehydration resulted from gastroenteritis, the effectiveness of metoclopramide was investigated on vomiting episodes of the patients and compared with conventional serum therapy. The results showed that metoclopramide significantly reduced children’s vomiting episodes in the first day, while when metoclopramide was withdrawn at the fourth day, vomiting episodes increased significantly. This finding reveals the impact of metoclopramide in reduction in vomiting episodes in children with gastroenteritis. Few research have been carried out on the effect of metoclopramide on reduction in nausea and vomiting induced by gastroenteritis and according to the knowledge of the researchers, only 3 papers exist on the role of metoclopramide in reduction in gastroenteritis-induced vomiting. Van Eygen et al. carried out a study to compare the effect of domperidone (30 mg) and metoclopramide (10 mg) suppositories on nausea and vomiting in children with gastroenteritis. Their results showed that in a period of 24 h, metoclopramide significantly reduced vomiting episodes as compared to placebo (27). This is consistent with the present study. However, they followed their patients for only 24 h and their way of drug administration and its dose varied with our study. The sample size does not seem enough for an ultimate conclusion as well. In their study on the antiemetic effects of ondansetron in acute gastroenteritis, Cubeddu et al. evaluated 36 patients in three 12-peopled groups of ondansetron (0.3 mg/kg), metoclopramide (0.3 mg/kg), and placebo (sterile saline). Their results revealed that metoclopramide had no significant difference with placebo in control of vomiting in children with gastroenteritis (28). This finding was against the results of Al-Ansari et al., who studied the effects of ondansetron and metoclopramide on 167 children with gastroenteritis (26). In this study, vomiting episodes ceased sooner in ondansetron and metoclopramide groups than placebo group and both medicines had no superiority to the other (26). This result is also consistent with our study; however, we followed the patients for four consecutive days while the mentioned studies followed their patients for only 24 h. Among three mentioned studies, only the study of Al-Ansari et al. had a reliable sample size. Side effects of metoclopramide were seen in any of the above studies. Two systematic studies were performed about the side effects of metoclopramide in children to reveal its safety in the treatment of gastroenteritis. Alhashimi et al. systematically reviewed antiemetics and stated that metoclopramide can significantly decrease vomiting episodes in children with gastroenteritis and that diarrhea occurring after consumption of metoclopramide is due to fluid retention and toxins which would be excreted from the body if the drug was not consumed. Therefore, the resulting diarrhea cannot be attributed to metoclopramide (25). According to appropriate sample size and longer follow-up in the present study compared to previous studies, it seems that our results are more reliable. Significant increase in vomiting episodes after withdrawing the drug at the fourth day reflects the causative role of metoclopramide in reduction in vomiting episodes. In addition, no side effects attributed to metoclopramide were observed in the present study which demonstrates the safety of the drug for limited use for preventing vomiting in children. However, due to severe scarcity in this field of study, it is recommended to carry out a multi-centric research and follow patients until complete cessation of vomiting, while comparing
metoclopramide and ondansetron [as the first choice antiemetic but more expensive than metoclopramide and thus low accessible (9, 29-31)], in terms of treatment effects and side effects.

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REFERENCES


