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Comparison ondansetron and domperidon as antiemetic for gastroenteritis in children: a review

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ABSTRACT

Gastroenteritis (GE) is the leading cause of vomiting in children. It is the main reason children admitted into emergency departments (EDs). Vomiting can cause fluid loss therefore oral rehydration solution (ORT) is recommended as supportive care for mild to moderate dehydration. Antiemetic therapy for GE is not fully recommended by any management guidelines. However, in some studies, antiemetics including ondansetron and domperidone are used in vomiting-related GE. This review aimed to compare ondansetron and domperidone for the treatment of GE in children. The article search was performed to identify relevant publications using PubMed database PubMed. PRISMA flow diagram was used as protocol during the article screening process. Eight randomized control trials (RCTs) met the inclusion criteria. Treatment with ondansetron compared with domperidone increased the chance for vomiting cessation up to 24 hr after drug administration. Treatment with ondansetron compared with domperidone and placebo reduced the proportion of patients who needed IV rehydration. Moreover, ondansetron significantly reduced over 50% the proportion of patients requiring IV rehydration. Domperidone was lack of benefit for the vomiting treatment associated GE in children. Analysis comparing ondansetron with domperidone revealed that none of the patients experienced any major adverse effects. In conclusion, oral ondansetron shows greater efficacy in vomiting related GE in children up to 24 hr after administration compared to domperidone.

ABSTRAK

Gastroenteritis (GE) adalah penyebab utama muntah pada anak. Hal ini menjadi alasan utama anak dirawat di unit gawat darurat (UGD). Muntah dapat menyebabkan kehilangan cairan oleh karena itu larutan rehidrasi oral (ORT) direkomendasikan sebagai perawatan suportif untuk dehidrasi ringan hingga sedang. Terapi antiemetik untuk GE tidak sepenuhnya direkomendasikan di berbagai pedoman penatalaksanaan GE. Namun, dalam beberapa penelitian, antiemetik termasuk ondansetron dan domperidon digunakan pada GE yang berhubungan dengan muntah. Tinjauan ini bertujuan untuk membandingkan ondansetron dan domperidon untuk pengobatan GE pada anak. Pencarian artikel dilakukan untuk mengidentifikasi literatur relevan menggunakan database PubMed. Diagram alir PRISMA digunakan sebagai protokol selama proses penyaringan artikel. Delapan uji klinik secara acak (RCT) memenuhi kriteria inklusi. Pengobatan dengan ondansetron dibandingkan dengan domperidon meningkatkan kemungkinan berhentinya muntah hingga 24 jam setelah pemberian obat. Pengobatan dengan ondansetron dibandingkan dengan domperidon dan plasebo mengurangi proporsi pasien yang memerlukan rehidrasi IV. Selain itu, ondansetron secara signifikan mengurangi lebih dari 50% proporsi pasien yang memerlukan rehidrasi IV. Domperidon kurang bermanfaat dalam pengobatan muntah terkait GE pada anak. Analisis untuk membandingkan ondansetron dengan domperidon mengungkapkan bahwa tidak ada pasien yang mengalami efek samping serius. Kesimpulannya, ondansetron oral menunjukkan kemanjuran lebih besar pada muntah terkait GE pada anak hingga 24 jam setelah pemberian dibandingkan dengan domperidon.

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INTRODUCTION

Gastroenteritis (GE) is the leading cause of vomiting occurred in children which is the main reasons children admitted into emergency departments (EDs).[1] The prevalence of GE in children under 5 years old in low and middle income countries has been reported with result was 21.7% in India, 36% in Nepal, and 29-37% in Pakistan.[2-4] Prevalence of vomiting has been reported in 75% of children in the early stages of GE caused by rotavirus thereby causing distress for child and their caregivers. Vomiting can cause of fluid loss therefore oral rehydration therapy (ORT) is recommended as supportive care for patients with mild to moderate dehydration.[5]

Management of symptomatic therapy for emesis with GE has not been standardized yet by any management guidelines.[5] Antiemetic agents such as ondansetron and domperidone are prescribed as off-label drug in order to reduce episode of vomiting in GE-affected children. In European countries such as France, Spain, and Italy, the dopamine receptor antagonist domperidone is recommended for antiemetic therapy.[6] Meanwhile, only tiny of proportion children receive ondansetron, and are used for different indication among centers.[7-8]

Ondansetron and domperidone have been studied in a number of observational studies and randomized controlled trials related to their efficacy and safety for children with GE. Evidence exists that ondansetron when administred orally in 10 trials (1479 participants) compared to placebo, increases the percentage of patients who had vomiting cessation, and lowers the rate of early hospital admissions.[9] However, not all of these studies evaluate an adequate comparative evaluation between domperidone and ondansetron.[5,10] Regarding the studies of domperidone, limited studies are available with small enrollment participants, lacking methodological quality, and inconsistent outcomes.[10]

MATERIAL AND METHODS

Article criteria and sources

The research article comparing domperidone versus ondansetron for vomiting in pediatric with GE was performed using the primarily database website, namely PubMed. The following key words were used to identified the relevant articles: “ondansetron”, “domperidone”, or “gastroenteritis”. All articles were screened for inclusion and exclusion criteria. The studies were included if they have full article access with relevant keywords, and randomized control trials (RCTs) that published during the last 10 yr. All antiemetic medications or placebos given orally, intravenously, or through suppository were eligible for inclusion in this study. Other inclusion criteria if children had at least 1 reported episode of nonbilious, non bloody vomiting with symptoms of GE (fever, nausea, diarrhea, abdominal pain, bloating or discomfort). Articles were excluded if they conducted in children who had severe dehydration, underlying chronic disease, such as gastroesophageal reflux, congenital heart diseases, malignancy, immunodeficiency, malnutrition, and known to hypersensitivity of ondansetron or domperidone. Additionally, studies identified as review type were also not included.

Article extraction

The PRISMA flow diagram was used as protocol during article screening process (FIGURE 1).

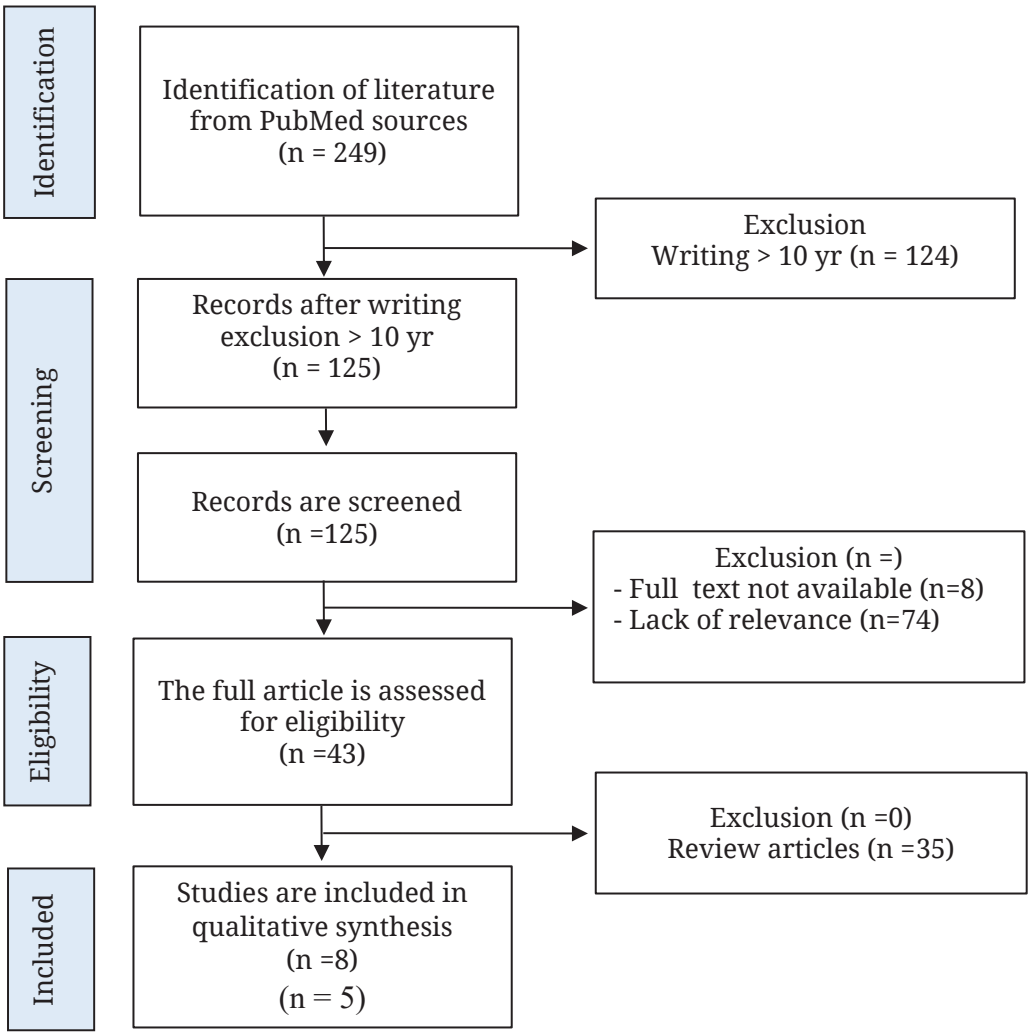

FIGURE 1. Protocol PRISMA flowchart for identified and screened article process.

TABLE 1. The outcome in clinial trial of ondansetron vs domperidone for GE in pediatric patients

Author	Treatment	Participants/ Subjects	Outcome target	Result	
				Efficacy	Safety
Oral administration ondansetron versus domperidone					
Hanif *et al.*[11]	Children are given ondansetron 0.15 mg/kgBW (group A) or domperidone oral at a dose of 0.5 mg/kgBW (group B) randomly	Patient under 5 years old with no blood vomiting and symptom of gastroenteritis (bloating, diarrhea, stomach pain, bloating with or without fever)	Primary outcome is the number of patients with cessation of vomiting in each group after 24 hours post intervention	The frequency of vomiting cessation after 6 hr in ondansetron group was 87% compared to 81% in domperidone group. It was not significantly different ($p<0.05$). After 24 hr, cessation of vomiting episodes was greater in ondansentron group (95%) than domperidone group (85%).	There was no adverse event reported in both groups.
Ahmad *et al.*[12]	Oral ondansetron, metoclopramide, and domperidone were administered at doses of 0.15, 0.1-0.2, and 0.5 mg/kgBW, respectively	Children under 10 years old with non-bloody vomiting and minimum 3 episodes of vomiting in last 24 hr.	The major outcome is the number of patients with cessation of vomiting in each group after 24 hr post treatment	Within 6 hr of starting therapy, the rate of vomiting cessation for metoclopramide (n=27) was 67.5%, domperidone (n=29) was 72.5%, and ondansetron (n=32) was 80.0% ($p = 0.29$). Vomiting cessation significantly greater in the ondansetron group (92.5%; n=37) after 24 hr than domperidone (82.5 %; n=33) and metoclopramide (77.5%; n=31; $p=0.03$) groups.	Ondansetron, domperidone and metoclopramide were well tolerated, with most of participant not have side effect. Headache, reported in a few of participant for each medication. Drowsiness and mild gastrointestinal issues such as diarrhea and constipation occurred in limited cases.
Tauseef *et al.*[13]	Children received randomly oral ondansetron at a dose of 0.15 mg/ kg BW or oral domperidone at a dose of 0.5 mg/ kgBW	Children below the age 12 yr, having ≥ 3 episodes of non-billious, non-bloody vomiting episode in last 24 hr and having signs of gastroenteritis	The primary outcome are the number of patients that needed 2nd dose within 15 min, vomiting cessation in each group after 6 and 24 hr post treatment.	Total 38 (25.3%) patients in domperidone group needed 2nd dose within 15 min than 27 patients in ondansetron group (18%). After 6 hr of treatment, 126 (84.0%) patients in ondansetron group had ceased vomiting patients in ondansetron have vomiting cessation higher than 118 (78.7%) in domperidone group ($p=0.2359$). The proportion patients who had cessation of vomiting in ondansetron was greater than domperidone (127 or 89.4%) vs 108 (80.6%) ($p=0.0390$)	Not reported

TABLE 1. cont.

Author	Treatment	Participants/ subjects	Outcome target	Result	
				Efficacy	Safety
Oral administration ondansetron versus domperidone					
Marchetti *et al.*[14]	Oral ondansetron 0.15 mg/ kgBW, oral domperidone 0.5 mg/kgBW, or a placebo will be given to children randomly	Children diagnosed with gastroenteritis aged 1 years to 6 years and admitted to the pediatric emergency department (ED)	The major outcome was rate of children receiving nasogastric or IV rehydration solution. Secondary outcome were the safety profile, number of episodes vomiting during ED stay and 48 hours after intervention	Total 356 patients were divided to placebo (n= 118), domperidone (n= 119), and ondansetron (n = 119). Patients who needed IV rehydration in ondansetron group is 14 (11.8%) lower than domperidone and placebo 30 (25.2%) and 34 (28.8%). When compared to placebo (RR=0.41; 98.6% CI: 0.20–0.83) and domperidone (RR=0.47; 98.6%CI:0.23–0.97), ondansetron significantly reduced over 50% of patients requiring IV rehydration. Moreover, ondansetron significant decreased vomiting episodes during ED stay.	No severe adverse event was reported. 13 patients experienced mild adverse effect (6 ondansetron, 5 domperidone and 2 placebo). Drowsiness, asthenia, abdominal pain, or diarrhea were reported and comparable among groups.
Rang *et al.*[15]	Patients randomly given single bolus ondansetron at dose 0.2 mg/kgBW (maximum dose 8 mg) vs 0.9 % saline solution as placebo	61 pediatric inpatients, aged 11-60 mo with acute diarrhea with more than 3 stools in last 24 hr, non-bloody feces, having dehydration in mild to moderate stage, having 3-4 of vomiting within 4 hr and taking antiemetics yet.	The primary outcome is proportions of pediatric who needed IV rehydration. The number of patients who had ceased vomiting, the proportion of patients receiving oral rehydration solution, the length of stay (LoS), and duration of diarrhea are secondary outcomes.	Among the 30 patients in the ondansetron group, 22 patients experienced a complete cessation of vomiting. Meanwhile only 7 patients in the placebo group who had ceased vomiting (RR= 0.32; 95%Cl:0.16-0.63: p<0.001). Proportion patients who needed IV rehydration in placebo was greater than ondancetron (3 or 10% vs 12 or 39%). In the ondansetron group, the median amount of patients who took oral rehydration solution in a 24 hr period was considerably higher than in the placebo group (450 vs. 350 mL; p = 0.019). There were not different between duration of diarrhea and LoS in both groups.	No adverse effect was reported

TABLE 1. cont.

Author	Treatment	Participants/ subjects	Outcome target	Result	
				Efficacy	Safety
Oral ondansetron versus placebo					
Bonvanie *et al.*[16]	Patient split into two groups at random i.e. the intervention group and the control group. The control group received CAU (care of usual), namely oral rehydration solution and the intervention group was given CAU also a single oral ondansetron dose (0.1 mg/ kgBW).	Pediatric inpatients aged 6 mo-6 yr, diagnosed with GE, having ≥ 4 vomiting episodes in last 24 hr, ≥ 1 vomiting episodes in last 4 hr.	The primary outcome was number of patients who vomiting after 4 hr randomization. The total amount of vomiting and oral rehydration solution intake per patient were secondary outcomes after a 4 hr randomization. Proportion of visiting again to specialist care and hospital admission were assessed after 7 d randomization.	194 participants were included in this trial. The number of patients who continued vomiting decreased with one dose oral ondansetron from 42.9 to 19.5% in 4 hr (OR=0.37; 95%CI: 0.20 - 0.72; number needed to treat: 4). Proportion of vomiting episodes also decreased with ondansetron after a 4 hr intervention (incidence rate ratio 0.51 [95% CI = 0.29 to 0.88]). The median parenteral satisfaction with therapy was significantly greater in the intervention group. However, there were no significantly different between intake of oral rehydration solution, and number of hospital admissions in both groups.	No adverse effect was reported
Suppository domperidone versus placebo					
Kita *et al.*[17]	Participant randomized to receive ORT or ORT + domperidone suppository at a dose 1 mg/kgBW.	Participants aged 6 mo - 6 yr with at least 1 episode of non-bilius, non-bloody vomiting in last 4 hr and mild to moderate dehydration	The portion of patients who had vomiting within two hours of the intervention in each group was the primary endpoint.	56 children included in randomization; 24 received ORT and 32 received ORT+ domperidone suppository. The rate of patient vomiting in ORT group (27.3%) greater than those in the ORT+ domperidone group (20.7%; p=0.41).	Not reported
Oral domperidone versus placebo					
Leitz *et al.*[18]	A placebo or oral domperidone 0.25 mg/kg plus ORT was randomly assigned to each participant.	Children with acute gastroenteritis ages 6 mo to 12 yr.	The major outcome was the number of patients with no vomiting episodes. The number of patients who were ≥ 4 y.o. and had no nausea episodes within 48 hr following the initial administration of treatment was the secondary endpoint.	No significant difference in the number of vomiting cessations between domperidone (32%) and placebo (33.8%) group within 48 hr after first administration. Patients ≥ 4 yr, the proportion of patients without any nausea episodes in 48 hr was comparable for both domperidone (35.7%) and placebo (38.6%).	Adverse events were similar in the domperidone and placebo groups (3.4% vs. 5.5%), 1 patient experienced a major side event in each group; dehydration in the placebo group and GE caused by *Salmonella* in the domperidone group. During this investigation, no particular side effects of domperidone (such as extrapyramidal symptoms or QT prolongation) were reported.

DISCUSSION

The management therapy of GE in children is mostly concerned about potential event to cause dehydration and worsen the illness. Vomiting, a common symptom of AGE, can lead to fluid loss and electrolyte imbalances. Oral rehydration therapy is the first recommendation of treatment among cases of mild to moderate dehydration because of AGE.[19-20] World Health Organization states that antiemetic have no practical benefit for children in gastroenteritis therapy.[19] Moreover, routine use of antiemetic in children can increase potential side effects of these drugs.[20] Ondansetron, and domperidone have emerged as effective options for controlling vomiting in children. However, the comparative efficacy of these treatments, particularly in the context of acute gastroenteritis in children, has not been well-studied. Therefore, we presented several randomized controlled trials of ondansetron comparing with domperidone in pediatric with gastroenteritis.

Clinical trials conducted by Ahmad *et al.*[12] oral ondansetron showed greater efficacy in vomiting cessation during 24 hr follow-up. Meanwhile at shorter interval of 6 hr, ondansetron showed no significantly different with domperidone. These results mirrored outcomes reported in previous research studies conducted by Hanif *et al.*[11] Another study conducted by Tauseff *et al.*[13] with larger participant, showed that ondansetron significantly more effective than domperidone in cessation of vomiting at 24 hr follow up (89.4% versus 80.6%; p=0.0390). On the other hand, using a single dose of oral ondansetron successfully decreased the proportion of patients needed rehydration, reduced the LoS by 50%, and also reduced vomiting episodes in ED-stay as compared to domperidone in a multicenter double-blind RCT related to the Study ONdansetron vs. DOmperidone (SONDO).[14.] All these studies, strengthening and growing body of evidence in favor of ondansetron's efficacy.

Two studies investigated administration of ondansetron versus placebo. One study compared single bolus ondansetron (0.2 mg/kgBW) and placebo conducted by Rang *et al.*[15] showed significant in reducing the frequency of vomiting episodes after 4 hr administration in pediatric ward. The results additionally show that the ondansetron IV effect on vomiting lasted for 4 hr. Moreover, this study also reported reduction in the use of IV rehydration in ondansetron group than placebo.[15] In Bonvanie *et al.*[16] administration of oral ondansetron (0.1 mg/kgBW) lowers the frequency of vomiting and the number of vomiting episodes that occur within 4 hr of presentation. The findings showed that an ondansetron dosage of 0.1 mg/kgBW administered in primary care is at least as effective as a greater dose administered in pediatric ward to provide cessation of vomiting.[16]

Two studies investigated administration of domperidone versus placebo. Randomized clinical study conducted by Kita *et al.*[17] to evaluate the effect of administration ORT alone and domperidone in combination with ORT. This study showed higher number of vomiting cessation in domperidone plus ORT groups compared to ORT alone (79 vs. 73%). However, this study did not observe effect of domperidone on the number of vomiting episodes in patient within short period. Therefore, effect domperidone combined with ORT to prevent emesis-related gastroenteritis remains unclear. These finding were also strengthened by the current study of Leitz *et al.*[18] where a low dose of domperidone combined with ORT for children aged 6 mo -12 yr showed inconsistent results and did not significantly different from placebo in decreasing nausea and vomiting-related gastroenteritis.

The current study revealed that ondansetron demonstrates greater efficacy compared to domperidone

in cessation of vomiting episode in children with gastroenteritis, likely due to its role as a serotonin 5-HT3 receptor antagonist. The mechanism of reducing emesis by inhibiting the vomiting centers in the brain and inhibiting afferent depolarization of peripheral vagal nerves in the intestine, which can trigger emesis in gastroenteritis patients. By decreasing emesis, ondansetron may increase patient to increase oral fluid intake, potentially decreasing the requirement for hospitalization and intravenous rehydration.[21]

Analysis comparing ondansetron with domperidone revealed that none of the patients experienced any major adverse effects. There was a greater median number of diarrhea episodes in the ondansetron group, but this appears to have no clinical significance especially when compared with the drug's significant reduction in vomiting.[11] According to Ahmad *et al.*[12] the incidence of side effects was generally well-tolerated; headache and general drowsiness reported as adverse effects for domperidone and ondansetron.[12] Despite this, the risk of developing prolongation of the QT interval, which can result in an abnormal and potentially fatal heart rhythm, has been published by the Food and Drug Administration (FDA) in September 2011 and recommend electrocardiogram monitoring in patients receiving ondansetron who had electrolyte abnormalities.[22] Nonetheless, there is evidence that routine electrolyte and ECG monitoring is not required in children without known risk factors such as a history of arrhythmias or concurrent use of QT-prolonging medications prior to the administration of a single oral ondansetron dose.[23]

Leitz *et al.*[18] reported adverse events were similar in the domperidone and placebo groups (3.4 vs. 5.5%), with just 1 patient experiencing a major adverse event in each group: dehydration in the placebo group and gastroenteritis caused by *Salmonella* in the domperidone group.[18] During this investigation, no particular side effects of domperidone (such as extrapyramidal symptoms or QT prolongation) were reported. Meanwhile, most of these studies reported domperidone are well-tolerated, post-marketing surveillances have reported the incidence of extrapyramidal events linked to domperidone use. Furthermore, there is evidence that a small percentage of newborns had QTc intervals, which lead to potential possibility that domperidone may increase the risk of a prolonged QTc interval.[24] Considering the potential severity of QT interval prolongation, pediatric patients with multiple risk factors for torsades de pointes (e.g., hypokalemia, heart rate or rhythm disorders, structural heart abnormalities, concurrent use of CYP3A4 inhibitor drugs or potassium-depleting diuretics, or domperidone therapy at a dose exceeding 30 mg/d) should be assess and routine ECG monitoring both at baseline and after 3 to 7 d of therapy.[25]

This narrative review did not involve in a formal cost-benefit or cost-effectiveness study. However, ondansetron use likely to be cost-effective based on the outcomes during the hospital stay from the studies. As an example, based on result data, one dose of oral ondansetron had significantly greater of vomiting cessation than domperidone due to acute GE over the first 6 hr after assessment over domperidone.[11-13] Given this outcome, ondansetron may be used to save overall cost, which makes it cost effective treatment for children with acute gastroenteritis. However, there are still unanswered questions If oral ondansetron does lower hospital admission rates in the 72 hr after hospital release. This could affect how the cost-effectiveness of ondansetron is calculated. To validate these impressions, cost-effectiveness and cost-utility evaluations had to be conducted.

CONCLUSION

Ondansetron have greater efficacy

than domperidone in vomiting cessation associated GE without severe dehydration in children of age 6 month to 12 years. Ondansetron significantly reduces the number of vomiting episodes and decreased the need for IV rehydration solution in children with GE. Domperidone is lack of benefit for vomiting treatment associated GE in pediatric patient.

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