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Original Article

The addition of omeprazole to ondansetron for treating chemotherapy-induced nausea and vomiting in pediatric cancer patients

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Abstract

Background Chemotherapy-induced nausea and vomiting are some of the most disturbing side effects in pediatric cancer patients. The standard recommendation is the use of 5-hydroxytryptamine 3 receptor antagonist, such as ondansetron, to treat these symptoms. Despite this treatment, more than 50% of patients still experience nausea and vomiting.

Objective To evaluate the effect of the addition of omeprazole to ondansetron in the treatment of chemotherapy-induced nausea and vomiting.

Methods A double-blind, randomized, controlled trial was conducted at Haji Adam Malik Hospital, Medan, North Sumatera, from March to May 2016. Subjects were children aged 1 to 18 years, diagnosed with cancer, and who received intravenous chemotherapy. Patients were randomized to receive either a single dose of ondansetron (0.5 mg/kg) plus placebo or ondansetron (0.5 mg/kg) plus omeprazole (0.5 mg/kg). The severity of nausea and vomiting were measured using the Rhodes index of nausea, vomiting, and retching during the 24 hours after initiation of emetogenic chemotherapy. The primary outcome of efficacy was the proportion of patients who achieved complete response (lack of nausea/vomiting). Statistical analysis was performed by Chi-square and Fischer's exact tests.

Results Seventy eligible pediatric patients were randomized into two groups: 32 subjects in the ondansetron + placebo group and 38 others in the ondansetron + omeprazole group. The therapy failed in 50% (16/32) of the ondansetron + placebo group and 18.4% (7/38) of the ondansetron + omeprazole group. There was a significant difference in the clinical response between groups (P=0.01).

Conclusion The addition of omeprazole to ondansetron for the treatment of chemotherapy-induced nausea and vomiting is more effective than administration of ondansetron alone. **[Paediatr Indones. 2018;58:42-7 ; doi: http://dx.doi.org/10.14238/pi58.1.2018.42-7]**.

Keywords: *omeprazole; ondansetron; chemotherapy; vomiting; pediatric cancer*

Cancer is the second most common cause of death in children aged less than 15 years.[1,2] Cancer treatment generally consists of surgery, radiotherapy, and/or chemotherapy.[1] Chemotherapy is remains the first choice for cancer treatment in children.[1,2] Treatment with chemotherapy can cause side effects, the most common being nausea and vomiting.[3] Chemotherapy-induced nausea and vomiting (CINV) causes stress, dehydration, electrolyte disturbance, malnutrition, and anorexia, often resulting in patients refusing treatment at the next chemotherapy cycle.[4]

Serotonin receptor antagonists (ondansetron) are commonly used in the management of CINV in

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children.[5-9] Study on the use of antiemetics in children is still scarce, and more than 50% of patients continue to have vomiting, despite taking 5-hydroxytryptamine 3 receptor antagonists.[5,7,10] In general, chemotherapy causes nausea and vomiting through direct stimulation of the vomiting center, or indirectly through the chemoreceptor trigger zone (CTZ) and the peripheral vomiting center of the gastrointestinal tract.[11] Chemotherapy also results in damage to the gastrointestinal mucus,[12] increased gastrin hormone secretion,[13] delayed gastric emptying causing gastric distension,[14] and stress (psychological),[15-18] ultimately leading to an increase in gastric acid.[13-14] Proton pump inhibitors (such as omeprazole) function to reduce gastric acid[19] in dyspepsia syndrome, so we aimed to assess its effect in children with cancer who received chemotherapy.

Methods

A double-blind, randomized, controlled trial was conducted at Haji Adam Malik Hospital, Medan, North Sumatera, from March to May 2016. Subjects were children aged 1 to 18 years, diagnosed with cancer, who received intravenous chemotherapy, and with moderate to severe emetogenic risks. The exclusion criteria were patients with malignancy of the gastrointestinal tract, nausea or vomiting in the 24 hours before chemotherapy, other known causes of nausea or vomiting, or severe comorbidities such as malnutrition, encephalitis, meningitis, sepsis, bronchopneumonia, pulmonary tuberculosis, neutropenia, severe anemia, or severe hemorrhage. All patients were hospitalized during chemotherapy administration.

The minimum required sample size was calculated by using the sample formula for hypothesis testing of two independent proportions. The proportion of complete control of standard drugs (ondansetron) was 50%,5,8 and the difference in proportion of complete control between groups was expected to be 30%. Data on subjects' age, sex, type of cancer, and emetogenic levels of chemotherapy were collected along with demographic information as well as severity of nausea and vomiting. Data analysis was done with using the statistical package for social science (*SPSS), version 19.0* and the results presented in tables. This study was approved by the Health Research Ethics Committee at the University of Sumatera Utara Medical School.

All children who fulfilled the inclusion criteria were enrolled in this study. Subjects were divided into two groups by simple randomization. Group I received intravenous 0.5 mg/kg ondansetron and 0.9% NaCl 30 minutes before chemotherapy. Group II was given 0.5 mg/kg ondansetron 30 minutes before chemotherapy, and 0.5 mg/kg omeprazole (administered intravenously) shortly before chemotherapy. The treatments were carried out in a disguised manner in which the 0.9% NaCl and omeprazole (40 mg dry powder) were placed in new vials (labeled A for 0.9% NaCl and B for diluted omeprazole) with 8 mL (1 mL solution in vial B containing 5 mg omeprazole) each given at a dose of 0.1 mL/kg. The severity of nausea and vomiting was measured by the *Rhodes* index of nausea vomiting and retching (RINVR) during the 24 hours after initiation of emetogenic chemotherapy.20 We tested the validity RINVR by Pearson's correlation test and obtained Cronbach's coefficient alpha of 0.97. We interviewed children and parents to obtain demographic data. Nausea and vomiting indices were documented by a research assistant during chemotherapy, and by parents for 24 hours after chemotherapy.

Analyses of nausea and vomiting were done separately for the 24 hours after initiation of emetogenic chemotherapy. Severity of nausea vomiting based on 0-32 score range where no nausea vomiting: 0, mild: 1-8, moderate: 9-16, severe: 17-24, very heavy: 24-32. Clinical antiemetic response is divided into 3 groups: complete control (no nausea, vomiting), partial (mild and moderate), and failure (severe and very severe). In this study, the clinical response of the drug was divided into 2 groups: successful (complete control) and failed therapy (partial and failed control). The X test and Fischer's exact test were used to compare the difference in efficacy of the two antiemetic treatments. A P value of < 0.05 was considered to be statistically significant.

Results

Seventy eligible pediatric patients were randomized by simple randomization: 32 subjects in the ondansetron + placebo group and 38 in the ondansetron + omeprazole group. **Table 1** shows the baseline

characteristics of subjects by group, including sex, mean age, type of cancer, and emetogenic levels of chemotherapy. Both groups had more boys than girls. The most common types of cancer were leukemia (62.5% *vs.* 52.6%). The emetogenic levels of chemotherapy were mild 3/32 *vs.* 2/38, moderate 23/32 *vs.* 29/38 and high 6/32 *vs.* 7/38. Subjects' mean ages were 7.0 (SD 4.14) years in the ondansentron + placebo group, and 7.7 (SD 4.80) years in the ondansentron + omeprazole group.

Table 1. Demographic characteristics of subjects

Characteristics	Ondansetron + placebo (n = 32)	Ondansetron + omeprazole (n = 38)
Mean age (SD), years	7 (4.14)	7.7 (4.80)
Sex, n		
Male	20	22
Female	12	16
Malignancy type, n		
ALL	16	19
AML	3	1
CML	1	0
HL	2	4
NHL	2	3
Retinoblastoma	7	6
Rhabdomyosarcoma	1	1
Sarcoma	0	1
Teratoma	0	2
Testicular tumor	0	0
Chemotheraphy agent, n		
Carboplatin	7	3
Cysplatin	0	3
Cytarabin	2	0
Cyclophosphamide	6	7
Doxorubicin	13	23
Danurubicin	1	1
Vincristine	3	2
Emetogenic level, n		
Mild	3	2
Moderate	23	29
Severe	6	7

ALL: acute lymphoblastic leukemia, AML: acute myeloblastic leukemia, CML: chronic myeloblastic leukemia, HL: Hodgkin's lymphoma, NHL: non-Hodgkin's lymphoma

Table 2 shows the clinical response to the drugs in both groups. The treatment failed in 16/32 subjects in the ondansetron + placebo group, and 7/38 in the ondansetron + omeprazole group. The addition of omeprazole to ondansetron in managing CINV in pediatric cancer patients was more effective than ondansetron administration alone (RR 1.6; 95%CI 0.18 to 0.42; P=0.01). Kolmogorov-Smirnov test showed that the indices of nausea and vomiting were normally distributed.

Table 2. Clinical response to medication

Intervention	Clinical response		Total	P value
	Complete response	Failed response		
Ondansetron + placebo	16	16	32	0.01*
Ondansetron + omeprazole	31	7	38	
Total	47 (67.1)	23 (32.9)	70	

*Chi-square test

Discussion

The results of this study showed that the addition of omeprazole to ondansetron in the management of nausea and vomiting due to chemotherapy was more effective than (or superior to) ondansetron alone.

The gastrointestinal tract is involved in the mechanism of CINV through impulses carried to the peripheral vomiting center through the vagus and sympathetic nerves.[11] This system contributes to autonomic sensations such as gastric distension, gastric acid, anxiety, depression, and pain.[17,21] Increased autonomic activity against stress triggers an increase in gastric acid, in which the vagus nerve stimulates parietal cells directly or through gastrin antral effects by releasing gastric-releasing peptide (GRP), acetylcholine bound to M3 muscarinic receptors, and histamine.[22] Serotonin release from enterochromaffin cells due to chemotherapy leads to stimulation of peripheral vomiting centers and stomach muscle dysmotility.[11] Increased gastric acid secretion directly stimulates the vomiting center.[21-22]

Riezzo *et al.* showed that abnormalities in gastric motor activity result from loss of regular activity of slow waves.[13] Also, Nelson *et al.* reported that gastric dysrhythmias were associated with anterior hypomotility and delayed gastric emptying times, with symptoms such as nausea and vomiting.14 These findings suggest that changes in gastric electrical activity are associated with symptoms of dyspepsia, rather than symptoms of vomiting. The conclusion to

the studies was that chemotherapy causes symptoms of nausea and vomiting related to a dyspepsia syndrome.[13,23] The distension that occurs in the stomach stimulates tense receptors that eventually stimulate gastric acid secretion by parietal cells.[22,24]

During chemotherapy, cell injury in the gastrointestinal tract causes release of several inflammatory factors including cyclooxygenase-2 (COX-2), interleukin-6 (IL-6), and nuclear factor kappa-B (NF-kB).[21,25-26] The end result of this pathway is tissue damage and potential mucositis that continues along the gastrointestinal tract.[12] Inflammation and cell injury are thought to be heavily involved in delayed CINV.[21]

A randomized, cross-over, and double-blinded study in India by Sontakke et al. treated CINV with ginger and obtained complete control of 62%.[27] Pillai *et al.* reported that ginger powder was effective in reducing severity of acute and delayed CINV in patients receiving highly emetogenic chemotherapy. They concluded that ginger improved gastric motility.[28] The secretion of gastric acid decreased such that stimulation of the vomiting center was reduced.[22,24] This is consistent with the foundation of our research theory.

Deghani et al. reported that the omeprazole dose of 1 mg/kg/day in children was superior to ranitidine, famotidine, and cimetidane in reducing dyspepsia symptoms of nausea (86.2%), vomiting (80.8%), and flatulence (79.5%).19 In addition, Sartori *et al.* reported that 20 mg of omeprazole reduced gastric acid production by 97% and maintained gastric pH for 18 to 20 hours. They also suggested that gastric mucosal injury due to chemotherapy can be prevented with omeprazole (P=0.001).[29] In our study, a dose of 0.5 mg/kg omeprazole was administered intravenously before chemotherapy. We chose this dose in consideration of the severity of stress conditions from cancer, while still in the drug dose range.

Standard treatment of CINV is based on the emetogenic potential of the chemotherapy used.[5,6,10] Holdsworth *et al.* found moderate emetogenic risk in 63.4% of girls and 64.1% of boys, and high risk in 36.6% of girls and 35.9% boys.[8] Similarly, Hilarius *et al.* found moderate emetogenic risk of 63% and high risk of 37% in a community-based hospital study.[30] Female and younger patients are more likely to experience CINV than male and older patients.[5,10] In our study, we found no significant differences in emetogenicity between the ondansetron + placebo and ondansetron + omeprazole groups: low risk 9.4% *vs.* 5.3%, respectively, moderate risk 71.9% *vs.* 76.3%, respectively, and high risk 18.8% *vs.* 18.4%, respectively (P=0.795). In other studies, children undergoing moderate and high emetic risk chemotherapy were recommended to receive a serotonin receptor antagonist (ondansetron) in combination with an NK-1 receptor antagonist (aprepitant) and dexamethasone.[5,6,10] To date, no randomized trial of aprepitant has been performed in children.[5] Our study was a pilot study to assess the effectiveness of the addition of omeprazole to ondansetron for treating CINV in pediatric cancer patients.

A double-blind, randomized study by Siddique *et al.* reported that complete and partial responses to CINV in ondansetron administration alone were 70% and 30%, respectively, for the acute type, and 43% and 50%, respectively, for the delayed type.[31] Jaing *et al.* reported that administration of 0.15 mg/kg ondansetron gave a complete response of 45.5%.[7] In addition, Holdsworth *et al.* reported that complete response to ondansetron (0.45 mg/kg IV) was seen in 65.5% of patients.[8] Also, Kurucu *et al.* noted that 5 mg/m^2 intravenous ondansetron gave a complete response for the acute type in 55% of patients.[9] These findings suggest that ondansetron is not optimal in the management of CINV, the experience of nausea and vomiting is highly subjective,[32] and appropriate dosing strategies for children and a combination of drugs are needed.[33]

In our study, successful therapy (complete response) with 0.5 mg/kg ondansetron was 50% (16/32). However, the addition of 0.5 mg/kg body weight omeprazole to ondansetron yielded an 81.6% (31/38) therapy success (RR 1.6; 95%CI 0.18 to 0.42; P=0.01). The addition of omeprazole to ondansetron was very effective in the management of nausea and vomiting due to chemotherapy. The strength of this study was its experimental design: randomized, controlled, and double-blinded. The limitation of this study was the small sample size. As this was a pilot study, further investigation is needed to determine the efficacy of other proton pump inhibitors in pediatric cancer as an addition to standard treatment for CINV with a larger study sample size.

In conclusion, the addition of omeprazole to ondansetron for treatment of chemotherapy-induced nausea and vomiting is more effective than administration of ondansetron alone.

Conflict of Interest

None declared.

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