

## Reducing dyspeptic symptoms in children: proton pump inhibitor vs. H<sub>2</sub> receptor antagonist

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### Abstract

**Background** Dyspepsia is known as a leading cause of upper gastrointestinal tract morbidity. If left untreated, dyspepsia may become chronic. Dyspeptic symptoms manifest as epigastric pain, heartburn, nausea, hematemesis, or melena. Experimental studies have shown that omeprazole is more effective at reducing heartburn than ranitidine in adults. However, there have been few studies comparing the effects of proton pump inhibitors to H<sub>2</sub> receptor antagonists for reducing dyspeptic symptoms in children.

**Objective** To compare the effect of omeprazole with ranitidine for reducing dyspeptic symptoms.

**Methods** We performed a double-blind randomized controlled trial (RCT) at Sardjito Hospital and three community health centers in the Sleman District from June to November 2012. We recruited children aged 3–18 years with dyspepsia. Subjects were allocated into two groups using block randomization: the proton pump inhibitor (omeprazole) and the H<sub>2</sub> receptor antagonist (ranitidine) groups. According to the groups, either omeprazole (0.4–0.8 mg/kg/dose) or ranitidine (2–4 mg/kg/dose), respectively, were taken twice daily for 5 days. Dyspepsia was clinically diagnosed using the new Rome III criteria. Both groups were monitored for 5 days to assess for a reduction of dyspeptic symptoms.

**Results** Significantly more subjects in the omeprazole group recovered from dyspeptic symptoms than in the ranitidine group (RR= 4.87; 95%CI 1.5 to 15.3; P=0.005).

**Conclusion** Omeprazole was 4.87 (95% CI 1.5 to 15.3) times better than ranitidine in reducing dyspeptic symptoms on children aged 3–18 years with dyspepsia. [Paediatr Indones. 2014;54:198–201.].

**Keywords:** *dyspepsia, omeprazole, ranitidine*

Dyspepsia is defined as discomfort, or chronic or recurrent pain, centered in the upper abdomen. Functional dyspepsia is persistent or recurrent pain in the upper abdomen that does not go away after defecation. It is not associated with changes in the frequency or form of feces, and is experienced at least once a week for 2 months with no organic abnormality.<sup>1,2</sup>

Dyspepsia in children has not received much attention especially in Indonesia. Moreover, there is no treatment consensus for children, although some centers have defined therapeutic approaches. Treatment provided to children usually adopts protocols from studies conducted in adult patients with *Helicobacter pylori* infection.<sup>3,4</sup>

H<sub>2</sub> receptor antagonists reduce acid secretion by blocking histamine receptors in gastric parietal cells. The mechanism of action of proton pump inhibitors (PPIs) in controlling gastric acid secretion is by blocking the proton pump (K<sup>+</sup>/H<sup>+</sup> adenosine triphosphatase) that transports H<sup>+</sup> ions out of

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gastric parietal cells. Proton pump inhibitors (PPIs) inhibit three receptor types simultaneously, i.e., the histamine, muscarinic acetylcholine, and gastrin receptors. Therefore, its effect is faster than that of H<sub>2</sub> receptor antagonists.<sup>5,6</sup> The aim of this study was to compare the effect of omeprazole to ranitidine for reducing dyspeptic symptoms in children with dyspepsia.

## Methods

We conducted a double-blind, randomized, controlled trial at Dr. Sardjito Hospital and three community health centers in Sleman, Yogyakarta from June to November 2012. Inclusion criteria were children aged 3-18 years with dyspepsia whose parent consented to participate in this study. We excluded children with a history of surgery, pancreatic diseases, malignancy or renal failure. Diagnoses of dyspepsia were made based on the new Rome III criteria.<sup>2</sup>

The minimum required sample size was 80, as calculated with a power of 80% and  $\alpha=0.05$ , and an estimated 20% drop out rate. We allocated subjects to receive either PPI (omeprazole) or H<sub>2</sub>-receptor antagonist (ranitidine) using block randomization. Both treatments, omeprazole (0.4-0.8 mg/kg BW/dose) and ranitidine (2-4 mg/kgBW/dose) were taken twice daily for 5 days. During the 5-day trial, mothers recorded the medications taken by the children daily,

as well as their symptoms such as nausea, vomiting, headache, urticaria, rash, and diarrhea. The doctors in charge reconfirmed the symptoms when the child visited the hospital, until the new Rome III criteria were no longer fulfilled. On the 6<sup>th</sup> day following initiation of therapy we took histories and performed clinical examinations on subjects to evaluate for dyspepsia. A total of 74 children completed the 5-days of treatment.

Observers from four centers were tested for interrater reliability, yielding a kappa value of 0.725 (0.6-0.8). This study was approved by the Research Ethics Committee of the Universitas Gadjah Mada Medical School. Data were analyzed using statistical software for Windows, and included relative risk (RR) and 95% confidence intervals (CI). Results were considered to be statistically significant for P values < 0.05.

## Results

We randomized 79 children, 5 subjects were lost to follow up. The study flow chart is shown in **Figure 1**. Basic characteristics of subjects are shown in **Table 1**. Prior to the study, the most common symptom experienced by subjects was epigastric pain (**Table 1**). Significantly more patients recovered in the omeprazole group compared to the ranitidine group [(RR=4.87; 95%CI 1.5 to 15.3; P=0.005)] (**Table 2**).

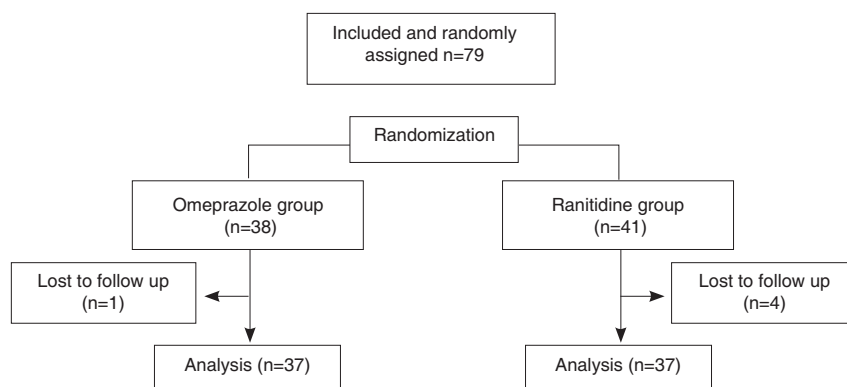


Figure 1. Study flow chart

**Table 1.** Baseline characteristics of subjects

| Characteristics                                               | Omeprazole<br>(n=38) | Ranitidine<br>(n=41) |
|---------------------------------------------------------------|----------------------|----------------------|
| Age by grouping, n (%)                                        |                      |                      |
| 3-5 years                                                     | 5 (13)               | 3 (7)                |
| 5-10 years                                                    | 12 (32)              | 21 (51)              |
| 10-18 years                                                   | 21 (55)              | 17 (42)              |
| Gender, n (%)                                                 |                      |                      |
| Male                                                          | 17 (45)              | 19 (46)              |
| Female                                                        | 21 (55)              | 22 (54)              |
| Distribution of symptoms based on New Rome III criteria, n(%) |                      |                      |
| Full after a meal                                             | 16 (42)              | 11 (27)              |
| Early satiety                                                 | 10 (26)              | 10 (24)              |
| Epigastric pain                                               | 32 (84)              | 38 (93)              |
| Heartburn,                                                    | 12 (32)              | 10 (24)              |

**Table 2.** Bivariate analysis of factors affecting recovery\*

| Variables       | Not recovered<br>n (%) | Recovered<br>n (%) | P<br>value | RR   | 95%CI        |
|-----------------|------------------------|--------------------|------------|------|--------------|
| Duration, n (%) |                        |                    |            |      |              |
| 3-6 months      | 7 (33)                 | 21 (40)            | 0.615      | 1.3  | 0.45 to 3.79 |
| >6 months       | 14 (67)                | 32 (60)            |            |      |              |
| Drug, n (%)     |                        |                    |            |      |              |
| Omeprazole      | 5 (24)                 | 32 (60)            | 0.005      | 4.87 | 1.5 to 15.3  |
| Ranitidine      | 16 (76)                | 21 (40)            |            |      |              |

\*Chi square test

## Discussion

We found dyspepsia incidence to be most common in 10 to 18 year age group. Similarly, Ali *et al.* reported that the most common age group of children with dyspepsia was over 10 years old.<sup>7</sup> Our results suggest that omeprazole was 4.87 times more likely than ranitidine for resolving dyspeptic symptoms. Armstrong *et al.* found that in a study of 390 adult dyspeptic patients from 46 hospitals in Canada, there were fewer complaints of heartburn in the omeprazole group than in the ranitidine group after 14 days of therapy.<sup>8</sup> The mechanism of action of PPI for controlling gastric acid secretion is by blocking the proton pumps ( $K^+/H^+$  adenosine triphosphatase) that transports  $H^+$  ions out of the gastric parietal cells. Proton pump inhibitors (PPIs) inhibit three types of receptors simultaneously, i.e., the histamine, muscarinic acetylcholine and gastrin receptors. Therefore, the inhibitory effect of PPIs is faster than that of the  $H_2$  receptor antagonists.<sup>5,6</sup>

Acid secretion can be stimulated by three principal "secretagogues," namely, histamine, acetylcholine, and gastrin. The actions of these three

substances are synergistic. Therefore, a small dose of one substance potentiates the effect of a small dose of another. Each has a specific receptor site on the basolateral membrane of parietal cells. Activation by the cAMP pathway for histamine, or by calcium sensitive pathways for the muscarinic and gastrin receptors triggers the  $K^+/H^+$  ATPase pump, and through an active transport mechanism, is able to increase the hydrogen ion concentration within the lumen of the stomach. By selectively blocking the  $K^+/H^+$  ATPase pump, which represents the final step of gastric acid secretion, PPIs act as a novel class of efficient anti-secretory agents.<sup>6</sup>

A study in 1993 compared  $H_2$ -receptor antagonists to omeprazole for reducing gastric pepsin and pepsinogen A in the gastric mucosa. Patients with active duodenal ulcers were evaluated by endoscopy after 4 weeks of drug administration. This study reported no significant decrease in gastric pepsin or pepsinogen A in the gastric mucosa.<sup>9</sup> This might be due to the difference of the severity of disease and the number of subjects was too small, thus affecting the results of the study.

Side effects of omeprazole and ranitidine were

not found in our study subjects. The therapy was short-term, and side effects usually appear after prolonged use. Side effects of PPIs often include headache, nausea, abdominal pain, constipation, flatulence, and diarrhea. Side effects are usually mild, self-limiting and not related to dose or age. A study has shown adverse effects that may be associated with various long-term durations of PPI use.<sup>7</sup> A Scottish study found that acid hypersecretion was a side effect of omeprazole after 15 days of drug administration, and was associated with the increased gastric pH.<sup>10</sup> Side effects of ranitidine included headache, anxiety, dizziness, somnolence, and depression.<sup>11</sup>

In conclusion, omeprazole reduced dyspepsia symptoms 4.87 (95%CI 1.5 to 15.3) times better than ranitidine

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