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ORIGINAL ARTICLE

Impact of Intravenous Pantoprazole *versus* Oral Pantoprazole on Gastric pH in Pediatric Intensive Care Unit: A Randomized Trial

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KEYWORDS

Gastric Acid;
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ABSTRACT: Critically ill patients are at risk for development of stress-related mucosal damage (SRMD). Proton Pump Inhibiros (PPIs) like pantoprazole are extensively used to prevent SRMD in ICU settings. It is not known with certainty that either oral or intravenous pantoprazole is associated with a better response. Our goal was to compare effects of intravenous pantoprazole with oral pantoprazole on gastric pH in children admitted to PICU. In this blinded trial, 80 patients were randomly divided into two groups. Patients in in the first group received oral pantoprazole (1 mg/kg/day/divided) and patients in the second received IV pantoprazole (1 mg/kg/day/divided). The gastric pH was measured 48 hours after pantoprazole administration using litmus paper. The mean age was 990 days. After 48 hours, the gastric pH was 4.46 ± 1.48 in patients received pantoprazole orally and it was 4.85 ± 1.52 in patients received pantoprazole intravenously. There was no significant difference between two study groups ($P= 0.252$). Besides, no significant differences were noted in rate of diarrhea and nosocomial pneumonia between 2 study groups ($P > 0.05$). This study showed that both intravenous and oral pantoprazole had similar effects on gastric acid of children hospitalized in PICU. It seems reasonable to use oral pantoprazole to reduce the costs of treatment.

INTRODUCTION

Critically ill patients in the intensive care unit (ICU) are at risk for development of stress-related mucosal damage (SRMD), which may deteriorate the clinical status and increase mortality rate [1]. The prevalence rate of gastrointestinal bleeding due to stress-related wounds ranges from 6% to 43%, and the bleeding rate is usually from 1.6% to 5.3% [2]. Trauma, shock, burns, and sepsis are potential causes of visceral perforations and occurrence of SRMD [3, 4]. In such patients, low blood perfusion of the gastrointestinal tract may lead to SRMD [5]. Pharmacotherapy has a pivotal role in the management of patients with SRMD particularly for suppression of gastric pH [6]. In general, a combination of endoscopic and pharmacological therapies offers the best possible clinical

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outcomes [7]. Proton pump inhibitors (PPIs) such as lansoprazole, omeprazole, pantoprazole, and rabeprazole are considered as the most effective drugs in inhibiting gastric acid [8]. PPIs are currently drugs of choice for acid-related disorders of the gastrointestinal tract. Different studies in the intensive care unit illustrated that PPIs had a more effective role in inhibiting gastric acid secretion than H2 receptor antagonists. Of note, a high-dose intravenous infusion with proton pump inhibitors (PPIs) is often required to achieve complete and sustained acid suppression [2]. In addition, the IV form is much more expensive than oral form and may impose more costs to the patients. Pantoprazole as a PPI is widely used in adults and children. However, it is not known with certainty that which forms of pantoprazole is associated with more beneficial effects in children hospitalized in ICU. This was our purpose. This study was aimed at comparing oral with intravenous pantoprazole on gastric pH in pediatric ICU.

MATERIALS AND METHODS

Study design

This randomized, open-label, active-controlled, parallel-group and single center study was conducted in PICU of Mofid Children Hospital, Tehran, Iran. Randomization was done using a computer-generated sequence list. Local Ethics Committee approved the study and written informed consent was obtained from the parents prior to trial participation. The study was performed according to the World Medical Association Declaration of Helsinki and was registered at Iranian Registry of Clinical Trials (IRCT20120415009475N7). Eighty children aged from 0 to 15 years requiring GI prophylaxis were included. Patients in the first group received oral pantoprazole: 1 mg/kg q24hr (2 divided doses) through nasogastric tube [9]. Patients in the second group received IV pantoprazole: 1 mg/kg q24hr (2 divided doses). Participants were excluded if they had liver disorders (high liver function test values), severe renal failure (high creatinine levels according to age), bleeding, inability to receive drugs enterally, and history of hypersensitivity. Patients were discontinued from the study for these reasons: safety, lost to follow-up, and voluntary discontinuation. Patients were followed until discharge from PICU. The APACHE II scoring system was applied to get the measure of the patients' clinical status. The APACHE II scoring system was used in the intensive care unit to ascertain the severity of the disease and to gauge the mortality rate in the hospital. The maximum value of this score was 71, and the higher degree of the score indicated the worse condition of the patient so that the score of 25 predicted 50% mortality and a score above 35, 80% mortality.

Efficacy assessment

Forty-eight hours after drug administration, the gastric pH was measured. For this purpose, pH of the sample was immediately measured on-site and by litmus paper. Samples of gastric juice were taken from the patient’s nasogastric tube through a gavage syringe (50 ml syringe), and some of it was poured onto the litmus paper and then pH was recorded [10]. The litmus paper manufactured by Merck German Company was used in this study to measure the gastric pH.

Safety assessment

Untoward effects and vital signs were monitored during patients stay in PICU. For assessment of adverse effects of the drugs, patients were monitored for edema, rash, and constipation.

Data analysis

With a consideration of 10% out drop, a total 85 patients were estimated for sample size. Individuals divided into two equal groups through random allocation. X^2 test was used to study differences between groups and we used repeated measures student *t* test was used to compare mean difference between groups. Level of 0.05 ($P < 0.05$) was statistically significant. Analysis was carried out using SPSS software version 19.0, Chicago, USA.

RESULTS

Baseline Characteristics

Of the 85 individuals who were included 5 children met the exclusion criteria. Eighty participants had complete observation over the course of treatments. Table 1 shows baseline characteristics of subjects. The mean age was 990.69 ± 192.2 days. Age range was from 43 days to 13 years.

Distribution of APACHE II Score among the Studied Patients

As shown in Figure 1, the mean APACHE II score in intravenous (IV) pantoprazole group was 24.9 ± 6.6. The mean APACHE II score among in oral (PO) pantoprazole group was 24.8 ± 4.3.

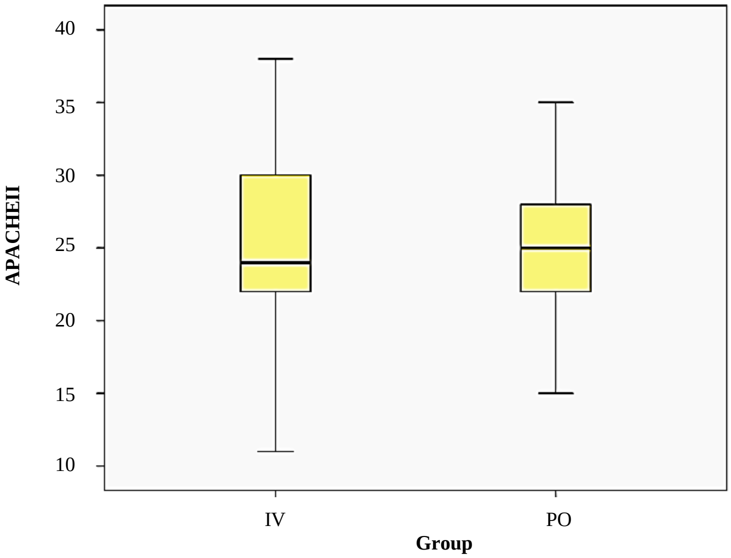

Figure1. Distribution of APACHE II score

Table 1. Baseline characteristics of patients

Characteristics	Oral pantoprazole (n=40)	IV pantoprazole (n=40)	P value
Age, days	984.4 ± 118.3	998.7 ± 119.5	0.4
Age (range)	43d-11 yr	51d-11 yr	0.5
Girl	19 (47.5)	21 (52.5)	0.6
Admission diagnosis			
Sepsis	14 (35)	11 (27.5)	0.7
Trauma	9 (22.50)	9 (22.5)	0.7
Surgery	10 (25)	15 (37.5)	0.5
Other	8 (20)	7 (17.5)	0.6
Lab tests			
Hemoglobin, g/L	102 ± 4.9	102 ± 4.2	0.3
Total WBC count, 10^9/L	8.1 ± 3.3	8.9 ± 2.9	0.9
Platelets, 10^9/L	243 ± 110	283 ± 169	0.8

Data are shown as mean ± SD or number (%)

Levels of creatinine and BUN

The mean serum creatinine (Sr Cr) was 0.8 ± 0.9, in IV group and it was 0.6 ± 0.5 in the oral group. BUN was 15 ± 21.7 in IV group and it was 15 ± 11.9 in oral group.

Levels of pH

As shown in Figure 2, the mean pH was 4.5 ± 1.5 in IV group. Of note, the gastric pH of 7 patients (17.5 %) patients was under 4. The mean gastric pH among patients under the treatment 4.46 ± 1.4 in oral group. In addition, the gastric pH of 13 patients (31.7 %) was under 4.

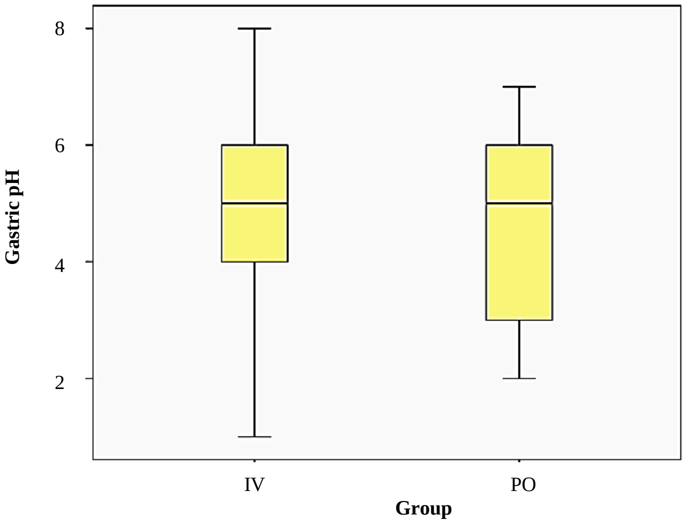

Figure 2. Distribution of gastric pHof patients

The frequency of diarrhea, nosocomial pneumonia, and mortality rate

As presented in Table 2, there were differences in the frequency of diarrhea, nosocomial pneumonia, and rate of mortality in study groups. Diarrhea was more common in patients receiving IV form (15 % vs 5 %). In addition, nosocomial pneumonia was observed more frequently in patients receiving oral form (30 % vs 12 %). Finally, rate of death was higher in group who received oral pantoprazole (42 % vs 15 %). None of the mentioned differences were statistically significant.

Table 2. Comparison on frequency of diarrhea, nosocomial pneumonia, and mortality rate in 2 study groups

Characteristics	Oral pantoprazole (n=40)	IV pantoprazole (n=40)	P value
Diarrhea	2 (5)	6 (15)	0.3
Nosocomial Pneumonia	12 (30)	5 (12)	0.08
Death	17 (42)	6 (15)	0.06

Data are shown in number (%)

DISCUSSION

The current study addressed the 80 pediatric patients admitted in the pediatric intensive care unit of Mofid Children's Hospital, and its purpose was to compare the efficacy of intravenous with oral pantoprazole on gastric pH. We showed that oral and intravenous administrations of pantoprazole had similar effects on gastric pH in children hospitalized in PICU. Chen et al. conducted a study on omeprazole and famotidine and perceived that the patients under the treatment of famotidine had more gastrointestinal symptoms compared to those under the treatment of omeprazole. 5 out of 55 patients under the treatment of omeprazole and 15 out of 49 patients under the treatment of famotidine were suffering from recurrent ulcer [11]. Taubel et al. compared the effect of intravenous lansoprazole suspension and intravenous pantoprazole on patients' gastric pH after 24 hours. The result of this study indicated that Lansoprazole was more able to keep the pH above three higher than the time. Therefore, lansoprazole had more powerful pH control than pantoprazole [12]. Dabiri et al compared oral omeprazole, oral pantoprazole, and intravenous pantoprazole in terms of their effects on the gastric pH. They monitored 56 critically ill adult patients to control their gastric pH. Then they treated the patients randomly with one of the three mentioned drugs, and ultimately, they observed that the mean gastric pH in the groups receiving oral omeprazole and oral pantoprazole were significantly higher than the group on intravenous pantoprazole. Therefore, they concluded that the pantoprazole oral suspension and omeprazole were more effective than intravenous pantoprazole [13]. A study conducted to investigate the effectiveness of pantoprazole oral suspension on 1 to 11 months infants affected by GERD; 128 patients were on pantoprazole therapy for four weeks. After this period, 106 of them were treated with a placebo in the double-blinded study. Consequently, the results of the study revealed that pantoprazole significantly improved GERD symptoms and was withdrawn thoroughly. While in the double-blinded treatment phase, there was no significant difference between pantoprazole and placebo in the withdrawal period due to a lack of efficacy. The deterioration of the patient's GERD symptoms in the fifth week of treatment with placebo was the most significant difference between two groups [14]. In spite of the powder forms of PPI drugs for producing suspension in the global market, the suspension was not provided in the form for industrial pharmacy in Iran. In ICU the powder is dissolved in water and is given to patients by NG tube. However, dissolved pantoprazole is not resistant against gastric acid and its great portion is degraded. To solve this problem, sodium bicarbonate is usually added to the solution to increase pH of the stomach and protect pantoprazole. It is also able to activate the parietal cells. Bigoniya et al. compared the difference between anti-ulcer activity of buffered pantoprazole and plain pantoprazole in rat. The results indicated that sodium bicarbonate buffered pantoprazole effectively increased gastric pH above 4 for up to 6 hours. Moreover, this study specified that the concentration of pantoprazole in rat gastric content was higher than that of plain pantoprazole [15]. Current evidence shows that gastric pH above 4 is usually accompanied by bacterial colonization and high rate of nosocomial pneumonia. For this reason, it was very likely that respiratory infections would occur following gastric ulcer treatments [16,17]. The patients in this study were examined for pneumonia. We did not observe a significant relationship between nosocomial pneumonia and gastric pH. In general, PPIs are effective to suppress the acid production. They have long duration of action and their untoward effects are predictable. It has been shown that long-term PPI treatment may affect the absorption of calcium, iron, magnesium, and vitamin B12 [18-20]. The half-life of pantoprazole is 1 its duration of action will last for 24 hours. It is extensively metabolized by hepatic P450 enzymes and its main route of elimination is urine [21]. Diarrhea, abdominal pain, constipation, and facial edema are reported in 1–5% of patients using PPIs (23). Long-term use of PPIs has been associated with an increased risk of dementia, pneumonia, and kidney disease (22-24). Our previous experience showed that long-term pantoprazole therapy can reduce serum ferritin in patients with thalassemia major (25).

CONCLUSIONS

This randomized and single-blinded study showed that both intravenous and oral suspension of pantoprazole had similar effects on gastric pH of children in PICU. It seems reasonable to use oral pantoprazole to reduce the costs of treatment.

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Conflict of interests

None.

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