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Research Article

Acid Suppression Therapy for the Empirical Treatment of Nausea and Vomiting in Hospitalized Pediatric Patients

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Abstract

Objective: To investigate and compare the safety and efficacy of the empirical use of Histamine-2-receptor antagonists (H2RAs) and Proton pump inhibitors (PPIs), for the treatment of unspecified nausea and vomiting (NV) in hospitalized children.

Methods: The retrospective cohort study was conducted at King Abdulaziz Medical City in Riyadh (KAMC-R) and included pediatric patients ≤14 years who received acid suppression therapy (AST), H2RAs or PPIs, for the treatment of unspecified NV between April 30, 2018, and April 30, 2019. The primary outcome was the complete resolution of NV within three days of AST. The secondary outcomes were the frequency of rescue medication use, the number of vomiting episodes since starting the AST, and the adverse drug reactions (ADRs).

Results: Sixty-two patients were included in the study, 25 (40.3%) were in the H2RAs group and 37 (59.7%) in the PPIs group. The mean age was 3.69 ± 4.13 years, with the majority male (64.5%). Overall, 87% (n=54) of the sample had complete resolution of NV within 3 days of the AST therapy with no difference between the H2RAs and PPIs groups (p=0.344). The number of NV episodes from initiating the AST until the complete resolution was similar between the groups. In total, 14 patients (25.9%) required rescue therapy with granisetron, 6 (26.1%) in the H2RAs group compared to 8 (25.8%) in the PPIs group. There was no difference in the number of the required granisetron doses or the incidence of ADRs.

Conclusion: Both PPIs and H2RAs were effective and safe for the treatment of unspecified NV in hospitalized pediatric patients. The selection of either agent should be based on other factors.

Keywords: Pediatric; Nausea and vomiting; Proton pump inhibitor; Histamine-2-receptor antagonist; Granisetron.

INTRODUCTION

Nausea and vomiting (NV) are distressing symptoms in hospitalized children. They are frequent symptoms related to a wide range of gastrointestinal (GI) and non-GI disorders. The incidence of NV associated with general surgery in children is more than 40%, almost twice compared to the adult population. [1-4] Receiving chemotherapy is a well-documented risk of NV, estimated to occur in more than 70% of the pediatric population depending on the emetogenicity of the chemotherapy agent used.[5, 6] In addition, conditions that alter gastric emptying, such as hypokalemia and acidosis, or using medications such as nonsteroidal anti-inflammatory drugs, opioids, antibiotics, and anticholinergics are a frequent cause of NV related to gastropareses. [7, 8]

Several pharmacological agents are available to treat NV in children. Acid suppressive therapy (AST), such as Histamin-2-receptor antagonists (H2RAs), and Proton pump inhibitors (PPIs) are used empirically to treat unspecified NV. In addition to these agents, the 5-HT3 antagonists, such as granisetron, are used as rescue therapy. PPIs are ASTs with the potential of antiemetic properties, as they act on a receptor of the parietal cell on the gastric wall which plays a role in the sensation of nausea by mediating input via the vagal nerve to the nausea-vomiting center in the midbrain.[9] Premedication with PPIs reduces the overall incidence of vomiting post-anesthesia and lowers the total amount of vomit compared to a placebo.[10, 11] They are also successful in maintaining the gastric pH > 4, without adverse effects or significant drug interactions.[12] H2RAs also have the properties to treat GI symptoms by decreasing the production of gastric acids that increases the pH of the gastric content and improves symptoms.[13, 14] Both PPIs and H2RAs are effective in lowering the gastric pH and treating NV associated with different pediatric disease states, including gastrointestinal reflux disease (GERD).[13, 15, 16] However, using AST for acid-non-related NV is controversial.[17, 18] The current study aimed to investigate and compare the safety and efficacy of the empirical use of PPIs and H2RAs for the treatment of unspecified NV in hospitalized pediatric patients.

MATERIALS AND METHODS

Design and Setting

The retrospective cohort study included hospitalized pediatric patients who had unspecified NV and received AST (PPIs or H2RAs). The study was conducted at King Abdulaziz Medical City in Riyadh (KAMC-R), a governmental academic tertiary care hospital. The only available H2RAs in the hospital formulary were oral and parenteral ranitidine, and the available PPIs were oral omeprazole and parenteral esomeprazole. The medications were prescribed according to predefined templates, using the actual patient weight for dosing. Ranitidine was administered orally or intravenously at a dose of 2-6 mg/kg, divided every 8-12 hours. Intravenous esomeprazole and oral omeprazole are administered at a dose of 1 mg/kg once daily. Using 5-HT_3 receptor antagonists, granisetron, as a rescue therapy is a frequent practice for children with NV, despite optimal AST. The hospital had no guideline available for selecting a specific AST or using the rescue therapy. The choice was at the discretion of the clinical care team in each unit.

Population

A list of admitted pediatric patients with NV was requested from the Data Management Center of King Abdullah International Medical Research Center, and the patients' data were extracted through the hospital's electronic health information system. All the hospitalized patients between April 30, 2018, and April 30, 2019, who received either H2RAs or PPIs for NV, were screened for eligibility. The occurrence of NV was confirmed by reviewing the patient medical charts at the time the AST was ordered. The inclusion criteria were patients 14 years or younger, used H2RAs (Ranitidine IV or orally) or PPIs (Oral omeprazole or IV esomeprazole) for the treatment of NV that were not related to a specific patient condition. We excluded patients who had a history of GI bleeding, GERD, or a gastric ulcer, received chemotherapy or received AST for < 3 days.

Outcome Measures

The demographic data included age, weight, height, gender, BMI, and comorbidities. Information related to the prescribed AST included the type of AST, duration of therapy, and reported adverse reactions (cough, diarrhea, and thrombocytopenia). Data regarding the frequency of NV, in addition to the frequency of using granisetron as a rescue medication, were recorded. The primary outcome was the complete resolution of NV within 3 days of AST (i.e., zero incidence of NV after 72 hours of continuous AST). Episodes of NV were defined through the International Classification of Diseases, Ninth Revision (ICD-9-CM), Clinical Modification, code 787.01 (ICD-10-CM R11.2) that includes unspecified NV. The secondary outcomes were the frequency of rescue medication use during the first 3 days of therapy, the number of vomiting episodes reported since starting the AST, and the occurrence of ADRs.

Statistical Analysis

The data was entered in MS Excel 2010 and analyzed by using statistical software SPSS 20.0 version [IBM SPSS, USA], and a $p<0.05$ was considered as statistically significant. The continuous variables are presented as mean and standard deviation, and the categorical variables as frequency and proportions. To determine the association between the categorical variables, a Chi-Square test was used and the comparison of the mean of two continuous variables, an independent samples t-test. The study was approved by the Institutional Review Board (IRB) of the King Abdullah International Medical Research Center (KAIMRC) and was granted a waiver of informed consent.

RESULTS

In total, a sample of 206 participants were admitted to the hospital between April 30, 2018, and April 30, 2019, who received an AST (H2RAs or PPIs). Each participant's chart was initially screened for the indication of AST. Only pediatric patients (n=137) who had been diagnosed with NV and received AST were eligible for inclusion. After excluding patients who had GERD (n=42), GI bleeding (n=2), received chemotherapy (n=1), or received AST for <72 hours (n=30), 62 patients were included in the analysis (Figure 1). Of those, 25 (40.3%) were in the H2RA group and 37 (59.7%) in the PPI group.

In the H2RAs group, ranitidine was administered intravenously in 16 (64%), and orally or via nasogastric tube (NGT) in 9 (36%) patients. The PPIs included esomeprazole intravenous in 18 patients (48.6%), and omeprazole orally or via NGT in 19 patients (51.3%). The duration of therapy for the H2RAs group was longer than the PPIs group (8.24 ± 7.16 days vs. 5.41 ± 4.58 days); however, comparing the mean was not statistically significant (p=0.402).

The demographic characteristics and comorbidities of the sample are displayed in Table 1. There were no statistically significant differences between the two groups. The majority of the samples were male (64.5%), with an average age of 3.69 ± 4.13 years, and 4.24 ± 3.13 years for the H2RAs and PPIs groups respectively. Dehydration as a complication of NV was reported in 12 children (19.4%), however, the difference between the two groups was not statistically significant, (28% in the H2RAs group and 13.5% in the PPI group) (p=0.157).

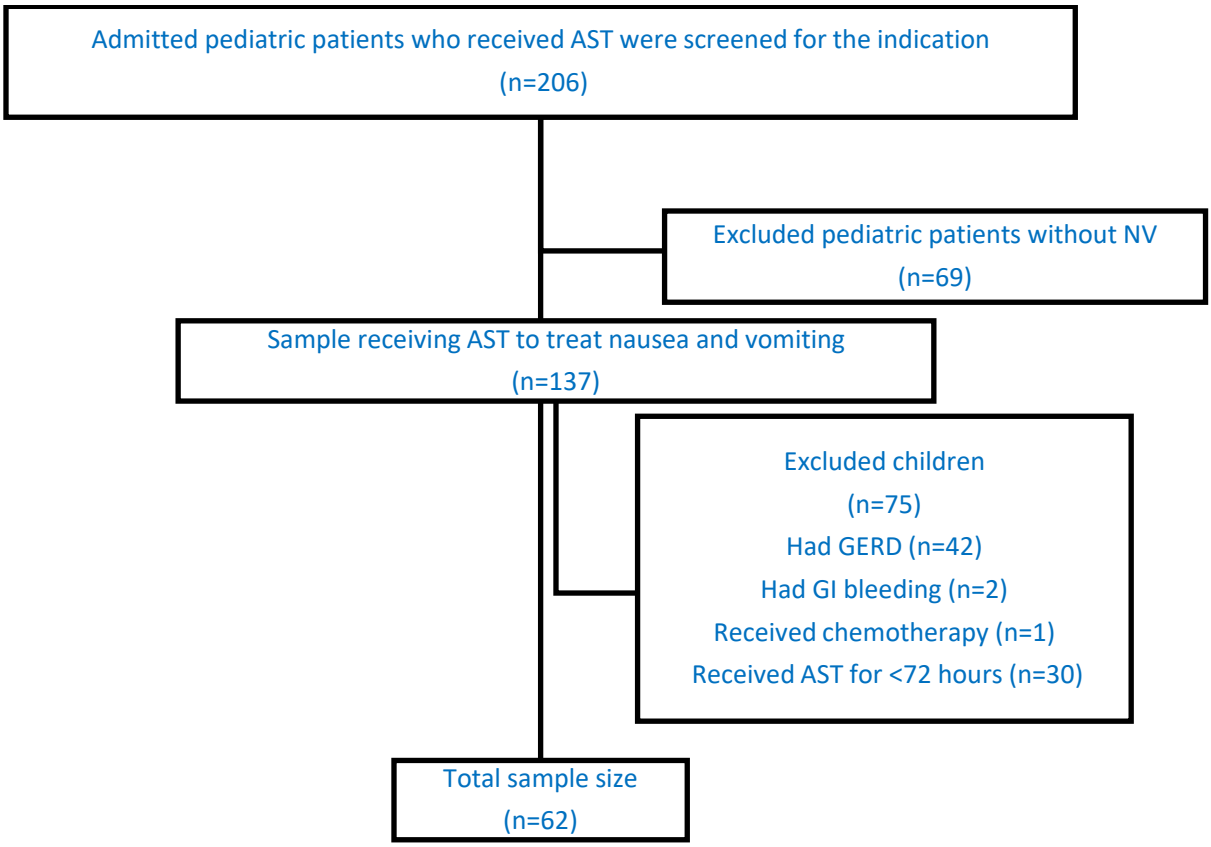

Figure 1: Patient's enrollment

Table 1: Demographic and clinical characteristics (n=62)

	Total (n=62)	**H2RA 25 (40.3%)**	**PPI 37 (59.7%)**	**p – value**
Demographic Variables				
Female n (%)	22 (35.5)	6 (24.0)	16 (43.2)	0.120
Male n (%)	40 (64.5)	19 (76.0)	21 (56.8)	
Age (mean ± SD) in years		3.69 ± 4.13	4.24 ± 3.13	0.551
Weight (mean ± SD) in Kg		12.09 ± 7.87	14.93 ± 10.53	0.256
Height (mean ± SD) in cm		85.00 ± 31.16	96.58 ± 21.07	0.085
BMI (mean ± SD) Kg/m^2		14.7 ± 2.5	14.3 ± 2.3	0.512
Comorbidities n(%)				
Hypertension	4 (6.5)	1 (4.0)	3 (8.1)	0.642^
Diabetes mellitus	1 (1.6)	0 (0)	1 (2.7)	1.000^
Heart failure	2 (3.2)	2 (8.0)	0 (0)	0.159^
Chronic kidney disease	7 (11.3)	1 (4.0)	6 (16.2)	0.225^
Hepatic	2 (3.2)	1 (4.0)	1 (2.7)	1.000^
Dehydration (as a complication of NV)	12 (19.4)	7 (28.0)	5 (13.5)	0.157

p – value > 0.05; ^Fishers' Exact Test p – value

Overall, the primary outcome occurred in 87% (n=54) of the sample. H2RAs and PPIs showed no significant difference (p=0.344) in the complete resolution of NV within three days of AST therapy. The study's primary outcomes were observed in 92% (n=23) of the H2RAs group and 83.8% (n=31) in the PPIs group. For the majority (64.8%), the NV resolved within the first 48 hours of therapy, with no difference between the two groups (p=0.861) (Table 2).

Table 2: Comparison of time to nausea and vomiting resolution since starting the AST therapy

Time (in hours)	Total n=54	Groups		p-value
		H2RA 23 (42.6%)	PPI 31 (57.4%)	
24 n (%)	6 (11.1)	3 (13.0)	3 (9.7)	0.861
48 n (%)	35 (64.8)	14 (60.9)	21 (67.7)	
72 n (%)	13 (24.1)	6 (26.1)	7 (22.6)	

Of the group achieving the primary outcome (n=54), the frequency of reported NV, from starting the AST until the complete resolution, was similar between the two groups. A quarter (n=14, 25.9%) required rescue therapy with granisetron (n=6, 26.1%) in H2RAs group and 8 (25.8%) in the PPIs group), with no statistically significant difference between the two groups **(Table 3**).

Table 3: Characteristics of the sample with complete resolution of nausea and vomiting within three days of AST therapy

Variables	Total (n=54)	H2B (n=23)	PPI (n=31)	p-value
Episodes of nausea and vomiting within 72h* of therapy n (%)				
<3	38 (70.4)	15 (65.2)	23 (74.2)	0.335^
4 – 6	11 (20.4)	7 (30.4)	4 (12.9)	
7 – 9	1 (4.3)	3 (9.7)	4 (7.4)	
>9	1 (1.9)	0 (0)	1 (3.2)	
Patients requiring rescue therapy (granisetron)	14 (25.9)	6 (26.1)	8 (25.8)	0.981
Frequency of rescue therapy administration	4.3 ±3.07	2.17 ± 1.94	2.13 ± 1.13	0.960#

**Since starting the medication, for those who achieved the primary endpoints #1 ^p – value > 0.05, ^Fishers' Exact Test #t – test p-value*

There were no differences between the two groups in the reported adverse drug reactions (Table 4)

Table 4: Adverse drug reactions (ADRs)

ADR n (%)	Total (n=62)	H2RA 25 (40.3%)	PPI 37 (59.7%)	p-value
Cough	1 (1.9)	1 (4.3)	0 (0)	0.241^
Diarrhea	2 (3.7)	1 (4.3)	1 (3.2)	1.000^
Thrombocytopenia (decrease platelet by <50%)	2 (3.7)	2 (8.7)	0 (0)	0.177^

^Fishers' Exact Test

DISCUSSION

In the current study, we compared the safety and efficacy of short-term, empirical use of AST for treating unspecified NV in hospitalized pediatric patients. Vomiting is defined as a coordinated autonomic and voluntary motor response, leading to forceful expulsion of gastric contents through the mouth. It can be differentiated from regurgitation or spitting-up, as these two conditions are characterized by effortless retrograde flow of duodenal or gastric fluids into the esophagus and oral cavity. Vomiting in pediatrics is often a self-limiting condition, managed with only supportive measures.[19, 20] However, in our institution, many clinicians elect to use AST without supporting evidence of the efficacy or safety for this specific indication. Overuse of AST in the pediatric population has been recognized in the pediatric population, especially in infants with unproven GERD.[21, 22] This can be attributed, in part to the imprecise definition and challenging diagnosis of GERD in the pediatric population, particularly in young infants and neonates.[20] In the current study, we excluded patients for whom an AST was

prescribed for an approved indication, such as GI bleeding, GERD, gastric ulcer, or who received chemotherapy.

The current results provided evidence of the efficacy of both PPI and H2RA for the treatment of unspecified NV in hospitalized pediatric patients. The complete resolution of NV has been achieved within three days of AST therapy, for the majority of the sample. This is consistent with literature indicating the efficacy of both PPIs and H2RAs in treating NV associated with various clinical conditions and disease states.[10, 11, 14] Raeder et al. investigated the impact of esomeprazole on reducing postoperative nausea and vomiting (PONV) in a randomized study using either esomeprazole or placebo. Although there was no significant difference between the two groups with PONV ($p = 0.3$), the overall incidence of vomiting was lower in the esomeprazole group with a significantly lower total amount of vomit than the placebo group ($p < 0.05$) (10). In another study by Kwon et al., the effects of PPI on PONV were studied retrospectively. The preoperative administration of PPIs was associated with a reduced incidence of PONV, especially in patients without GERD.[11] In addition, Doenicke et al. investigated providing a premedication of H1 and H2 blockers to minimize the incidence of PONV in a prospective randomized placebo-controlled study, including patients undergoing surgery. The effect of the H1 and H2 blockers in PONV was compared to placebo and indicated that the use of different combinations of H1 and H2 blockers was successful in reducing PONV.[14] The efficacy of PPIs for the treatment of overt regurgitation in infants with GERD was evaluated in several studies. None of these studies identified significant differences in the frequency of overt regurgitation compared to placebo.[23-26]

To the best of our knowledge, there is no literature reporting the efficacy of AST for the treatment of unspecified NV in hospitalized pediatric patients. Contrary to expectations, this study did not find a significant difference between the PPI and H2RA. Previous evidence reported that PPIs have a greater efficacy than H2RAs in acid-related NV.[27, 28] As an example, Ummarino et al. evaluated children with GERD who presented with extraesophageal symptoms. Omeprazole and ranitidine were compared in an intention-to-treat analysis. Omeprazole showed a greater reduction in vomiting episodes, compared with ranitidine (0.21 vs 1.75, P=0.0003).[27] There are several possible explanations for this result. The tendency of clinicians to prescribe PPIs for severe cases could explain the under predicted effect of PPI. Moreover, another plausible explanation for these findings is the small sample size in each group.

The safety profile of both groups was comparable. No serious adverse reactions were observed in the sample. Numerous adverse reactions could result from suppressing acid secretion. Gastric acidity is a primary line of defense against infection and, at the same time, plays an important role in the absorption of some nutrients. Several adverse effects might be associated with using AST. The reported adverse effects in pediatric literature include gastroenteritis[29], pneumonia[24, 29], and Clostridium difficile infection[30, 31] with both PPIs and H2RAs. Necrotizing enterocolitis[32] and candidemia[33] has been linked to H2RAs use in neonates and infants. Furthermore, a recent and large multicenter retrospective cohort study found that the use of PPIs was also associated with an increased risk of hospital-acquired acute kidney injury in hospitalized children.[34] We did not observe any of these adverse reactions in our study, which may be due to the small sample size and the retrospective study design.

The evidence from this study, while preliminary, suggests that the AST can be considered in pediatric patients with isolated NV. When selecting between PPIs and H2RAs, several factors need to be taken into account, including the availability of age-appropriate preparations, the preference of the parent or child, local procurement costs, in addition to the dosage frequency of the medication.[35]

Study limitations

The current has some limitations. First, the small sample size and the possibility of the study being underpowered. The second is the retrospective design with all its limitations. Third is the mixed population of medical and surgical patients. Fourth is the subjective definition of vomiting which can be easily confused with regurgitation or spitting up. Fifth is the lack of insight of the role of non-pharmacologic treatment options, including thickened feeding and positioning therapy. Regardless of these limitations, the current study could be the basis for future large randomized controlled trials to confirm these findings.

CONCLUSIONS

Both PPIs and H2RAs are effective and safe in the treatment of unspecified NV in hospitalized pediatric patients. In addition, the rate of NV resolution, the frequency of rescue therapy use, and the number of rescue doses required were similar with both medications. The selection of either medication should be based on other factors, such as cost.

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Conflict of Interest

The authors have no conflicts of interest to declare concerning the research, authorship, and/or publication of this article.

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