Upper Gastrointestinal Bleeding in Children: The Role of *Helicobacter pylori* Infection and Non-steroidal Anti-inflammatory Drug Use

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ABSTRACT

Objective: *To study the role of non-steroidal anti-inflammatory drugs (NSAIDs) and* Helicobacter pylori *infection in the aetiology of upper gastrointestinal bleeding (UGIB) in children.*
Subjects and Methods: *One hundred and eighty-eight patients (82 girls, 106 boys; mean age 8.43 ± 5.24 years), admitted to the paediatric gastroenterology unit because of UGIB and who underwent endoscopic examination, were studied from their medical records, retrospectively.*
Results: *Upper gastrointestinal bleeding was observed in 188 (8.29%) of 2266 patients. The mucosal causes related to the oesophagus, stomach and duodenum were found at the rate of 37%, 58% and 24.5%, respectively with endoscopic examination. The location of bleeding could not be determined in 14.4% of the patients. History of drug intake before admitting to hospital was present in 40 patients (21.3%). When we examined these forty patients, 35% were on acetylsalicylic acid, 47.5% were on ibuprofen and 17.5% were on NSAIDs. Ibuprofen versus acetylsalicylic acid usage was found to be highly significant (*$p < 0.05$*) for UGIB.* Helicobacter pylori *was found in 20.7% of the patients. The relationship between* H pylori *and UGIB was not found statistically significant (*$p > 0.05$*). The relationship between drug intake and presence of* H pylori *infection was not found significant in our patients (*$p > 0.05$*).*
Conclusion: *Ibuprofen and acetylsalicylic acid intake were found significant in the aetiology of UGIB in children. There was no significant connection with* Helicobacter pylori *infection in children with UGIB. We did not find a significant relationship with drug intake and* H pylori *infection.*

Keywords: Bleeding in children, *Helicobacter pylori*, NSAIDs, upper gastrointestinal bleeding

Hemorragia Gastrointestinal Alta en Niños: El Papel de la İnfección por *Helicobacter pylori* y el Uso de Antiinflamatorios no Esteroideos

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RESUMEN

Objetivo: *Estudiar el papel de los antiinflamatorios no esteroideos (AINES), y la infección por* Helicobacter pylori *en la etiología de la hemorragia gastrointestinal alta (HGIA) en niños.*
Sujetos y métodos: *Novecientos ochenta y ocho pacientes (82 niñas, 106 varones; edad media 8.43 ± 5,24 años), ingresados en la unidad de gastroenterología pediátrica a causa de HGIA y sometidos a examen endoscópico, fueron estudiados de forma retrospectiva. a partir de sus registros médicos*
Resultados: *Se observó hemorragia gastrointestinal alta en 188 (8.29%) de los 2266 pacientes. Las causas mucosales relacionadas con el esófago, el estómago, y el duodeno se encontraron a razón de 37%, 58% y 24.5%, respectivamente con el examen endoscópico. No se pudo determinar la localización del sangrado en el 14.4% de los pacientes. Una historia de consumo de drogas antes del ingreso al hospital precedió a 40 pacientes (21.3%). Cuando examinamos a estos cuarenta pacientes, un 35% estaban siendo tratados con ácido acetilsalicílico, 47.5% con ibuprofeno, y 17.5% con AINES. Se halló que el uso del ibuprofeno frente al ácido acetilsalicílico fue altamente significativo (*$p < 0.05$*) para HGIS. La bacteria* Helicobacter pylori *fue encontrada en el 20.7% de los pacientes. La relación entre H pylori y*

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*HGIA no fue estadísticamente significativa (*p > *0.05). La relación entre el consumo de medicamentos y la presencia de infección por* H pylori *no fue significativa en nuestros pacientes (*p > *0.05).*
Conclusión: *Se halló que el consumo de ibuprofeno y ácido acetilsalicílico fueron significativos en la etiología de HGIA en niños. No hubo ninguna conexión significativa con la infección por* Helicobacter pylori *en niños con HGIA. No encontramos una relación significativa con el consumo de drogas y la infección por* H pylori.

Palabras claves: Sangrado en los niños, *Helicobacter pylori,* hemorragia gastrointestinal alta, AINE

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INTRODUCTION

Upper gastrointestinal (UGI) bleeding is defined as the bleeding in the gastrointestinal tract where the source of bleeding is proximal to the ligament of Treitz and usually presents with haematemesis, melaena or haematochezia (1). It remains an uncommon but important management problem usually requiring hospitalization in childhood. *Helicobacter pylori* (*H pylori*) infection and non-steroidal anti-inflammatory drug (NSAID) usage are frequent in children. They are also considered risk factors for gastrointestinal mucosal injuries (2). In this study, we aimed to evaluate the role of NSAID usage and *H pylori* infection in the aetiology of UGI bleeding in children who were admitted to the emergency room with acute UGI haemorrhage.

SUBJECTS AND METHODS

A total of 2266 cases between the ages of two and 17 years who underwent UGI endoscopy over a period of two years between January 2010 and December 2012 were evaluated retrospectively. One hundred and eighty-eight of these children underwent UGI endoscopy because of UGI bleeding. Data retrieved from the records of these 188 patients included age, gender, history of drug intake, clinical presentation, endoscopic findings and treatment modalities.

The mean age of the patients was 8.43 (5.24) years and 43.6% (n = 82) of the patients were females and 56.4% (n = 106) of them were males. Newborns, patients with sepsis, bleed diastasis, patients who ingested corrosive substances and patients in intensive care units were excluded from the study. History of drug intake was noted and doses of drugs were appropriate for their age.

The complete blood count, coagulation tests (prothrombin time, partial thromboplastin time), liver function tests (aspartate aminotransferase, alanine aminotransferase), stool guaiac and BUN/Cr (blood urea nitrogen/creatinine) ratio were assessed in all patients.

Upper gastrointestinal endoscopy (Olympus EVIS CV-160) was performed within 12–24 hours after bleeding after vital signs were stabilized with intravenous midazolam (0.1 mg/kg). Before endoscopy, informed consent was obtained from all patients' parents. Gastric and duodenal biopsies (two biopsy specimens from corpus, antrum and duodenum) were taken during the endoscopic procedure and the findings at UGI endoscopy and course of the disease were recorded. In the stomach, the level of inflammation, activity, atrophy, metaplasia and presence of *H pylori* was established by the visual analogue scale given in the updated Sydney classification (3). The intensity of the infection with *H pylori* was classified as Gram-negative bacillus absent (grade 0), mild or rare (grade 1), moderate (grade 2) and marked (grade 3).

Statistical analysis

For statistical analyses, NCSS (Number Cruncher Statistical System) 2007 and PASS (Power Analysis and Sample Size) 2008 statistical software (Utah, USA) was used. During evaluation of study data, for comparison of definitive statistical methods (mean, standard deviation, frequency, rate) as well as quantitative data, Chi-square test was used in single dimensional array and Yates continuity correction and Fisher's exact tests were used in four dimensional arrays. Significance was evaluated at $p < 0.05$ level.

RESULTS

One hundred and eighty-eight of 2266 patients, who underwent UGI endoscopy, were brought in due to UGI bleeding (8.29%). Haematemesis was observed in 91.48% of the cases (172 patients) and melaena in 60.1% (113 patients).

Oesophageal varices were detected in 2.65% of all cases and nonvariceal (mucosal) causes were found in 82.9% of them. When nonvariceal endoscopic results were examined, we detected oesophagus-related causes (oesophagitis and oesophageal ulcer, Mallory-Weiss syndrome) in 36.7% (n = 69) of patients, stomach-related causes (erosive gastritis, nodular gastritis, gastric ulcer, pancreatic rest and antral polyp) in 58% and duodenum-related causes (duodenal ulcer, duodenitis) in 24.5% (Table 1). In 14.4 % of patients (n = 27), endoscopic findings were considered normal.

History of drug usage was noted in 40 patients (21.3%). Of these 40 cases, 35% had used acetylsalicyclic acid, 47.5% had used ibuprofen and 17.5% had used other NSAIDs. A statistically significant relation was found between use and UGI bleeding. Use of ibuprofen and acetylsalicylic acid was significantly high ($p < 0.05$). Endoscopic findings of patients who had a history of medication use are given in Table 2.

Although detecting stomach-related causes through endoscopy was remarkably high, these were not found to be statistically significant. In our study, oesophagus-related causes

Table 1: Endoscopic findings of the children in the study group

	Endoscopic findings	n
Oesophagus-related causes (36.7%)	GER+oesophagitis	59
	Oesophageal ulcer	8
	Mallory-Weiss tear	2
Stomach-related causes (58%)	Erosive gastritis	46
	Gastric ulcer	27
	Nodular gastritis	17
	Pancreatic rest	2
	Antral polyp	1
Duodenum-related causes (24.5%)	Duodenal ulcer	34
	Duodenitis	15
Normal endoscopic findings (14.4%)		27

GER: gastroesophageal reflux

Table 2: Endoscopic findings of the children with non-steroidal anti-inflammatory drug (NSAID) history

Medicine	Endoscopic result	n
Ibuprofen	Gastric ulcer	4
	Duodenal ulcer	2
	Erosive gastritis	8
	Duodenitis	2
	Oesophagitis+gastritis	1
	Normal	2
Acetylsalicyclic acid	Gastric ulcer	6
	Duodenal ulcer	3
	Oesophagitis	2
	Erosive gastritis	2
	Normal	1
Other NSAIDs	Gastric ulcer	2
	Duodenal ulcer	1
	Erosive gastritis	3
	Ulcer of pancreatic rest	1

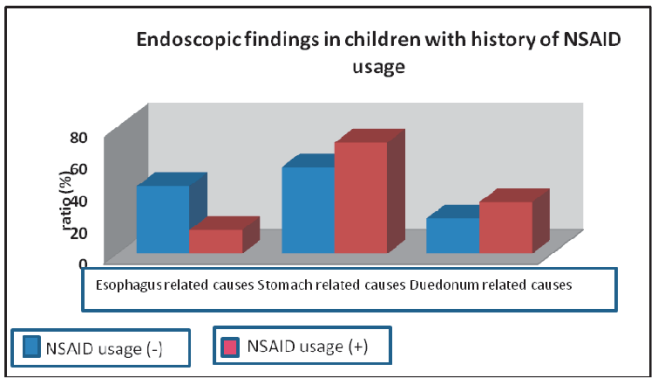

Figure: Endoscopic results in children with history of non-steroidal anti-inflammatory drug (NSAID) usage.

were found to be significantly high in patients who did not have a medication use history ($p < 0.01$) [Figure].

Helicobacter pylori was detected in 20.7% of patients, but no significant difference between presence of *H pylori* and UGI tract bleeding was found ($p > 0.05$). When medication use and presence of *H pylori* in our patients were evaluated, no statistically significant relation was found ($p > 0.05$). *Helicobacter pylori* was found to be positive in 72.5% of those who had not used medication, and in 83.3% of those who had (Table 3).

Table 3: The relationship between non-steroidal anti-inflammatory drug (NSAID) usage and *H pylori* infection

H pylori	**NSAID usage**		*P*
	(-)	**(+)**	
	n (%)	n (%)	
Positive	29 (72.5%)	10 (83.3%)	0.706
Negative	11 (27.5%)	2 (16.7%)	

Fisher's exact test

DISCUSSION

Upper gastrointestinal tract bleeding is the cause of 5% of upper gastrointestinal tract endoscopy indications in children (4). In our study, this rate was detected as 8.29% and found to be similar with other studies from Turkey (5, 6).

Non-steroidal anti-inflammatory drugs have antipyretic, analgesic and anti-inflammatory effects and their mode of action is through suppression of prostaglandin synthesis. Ibuprofen is an NSAID, widely used in children as an antipyretic and analgesic, and is safe in lower doses in the short term (7, 8). Aspirin is an NSAID with an antithrombotic effect, and is used as a prophylactic in lower doses in cardiovascular diseases and in strokes (9).

Helicobacter pylori infection is a frequently detected infection among the frequently observed peptic ulcer causes in Turkey (10).

The association between *H pylori* infection and NSAIDs in gastroduodenal pathologies is complicated: *Helicobacter pylori* and use of NSAIDs increase peptic ulcer bleeding 1.79 and 4.86 times, respectively (11). In our study, use of ibuprofen and aspirin was found to be significant in the aetiology of UGI tract bleeding. While there are adult studies which show that risk of *H pylori* eradication and bleeding decreases in chronic NSAID users, results are mixed in studies published on this subject (12, 13). Aygun *et al* (6), in a Turkish study conducted in children, detected medication use as aetiology in 26.6% and NSAID and aspirin as 40.5% and 27%, respectively. No association was found between *H pylori* and UGI tract bleeding in the same study. In a similar study by Eren and Hekim (14), aspirin use history was reported as 43.8% and NSAID use as 18.8%. A causal association with *H pylori* was not detected. In our study, rate of medication use was found to be 21.3% and ibuprofen use was prominent (47.5%). Use of aspirin was also significantly frequent (35%). In endoscopic findings, while erosive gastritis was more prominent in ibuprofen users, gastric ulcer was more frequently observed with acetylsalicylic acid use. In studies conducted on this subject, haemorrhagic gastritis was the most prominent, with gastric ulcer following it (6, 14). In the present study, as well as in the aforementioned studies, no association with *H pylori* was

found. Also, distinctively in our study, the presence of *H pylori* and medication use history were compared but no significant association was detected. Studies on this subject are mostly from adult patients and associated with long-term NSAID use. In a study by Kalyoncu *et al* (15), antipyretic use in children younger than two years was reported as a cause of UGI tract bleeding with a rate of 56%. In our study, we emphasize that antipyretic and analgesic drugs, particularly ibuprofen and aspirin, were more prominent in gastric involved endoscopic findings, while oesophageal findings were less frequently observed with these drugs.

Although *H pylori* is frequently observed and its association with peptic ulcer more frequently detected in Turkey, aetiologically, *H pylori* was not found to be significant in our study (12). No association between NSAID and *H pylori* was detected. Because of excessive use of ibuprofen, and of aspirin, though in lower doses, in children and because we live in a country where *H pylori* is abundant, more studies, in which UGI tract bleeding is considered with this respect and its association with *H pylori* is examined, should be conducted.

CONCLUSION

In the aetiology of upper gastrointestinal tract bleeding, use of ibuprofen and aspirin was found to be frequent, but was not associated with *H pylori*. Gastric causes were found to be more prominent in those who had a medication use history.

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