



## The Role of Helicobacter Pylori in Upper Gastrointestinal Bleeding after Using Ibuprofen in Children Aged 1-14 Years Old

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### Abstract

#### Background

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) including Ibuprofen is one of the most currently used drugs in all age groups and finding the relation between upper gastrointestinal bleeding and Helicobacter pylori (H. pylori) in children who used Ibuprofen, is our topic of research.

#### Materials and Methods

During the two years of the study, ten children with upper GI bleeding after Ibuprofen were selected as case group and twenty children with upper GI bleeding without history of drug usage were the control group. Their histories were obtained and compared. Helicobacter pylori (H. pylori) infection prevalence and other factors were compared by means of SPSS software, T independent test and chi square, P value less than 0.05 was significant.

#### Results

H. pylori was detected in 40% of case group and 8% of control group (P= 0.1) haemoglobin (mean  $\pm$  standard deviation) in case group was lower than control group  $10.5 \pm 2.1$  vs  $11.9 \pm 1.2$  g/dl (P= 0.08). This level (Hb) in H pylori infected was  $8.3 \pm 1.3$  vs.  $12 \pm 0.5$  (P= 0.0001) in non- infected children.

#### Conclusion

Upper GI bleeding following Ibuprofen prescription is a complex matter in children. H pylori infection is more common in bleeding episodes following Ibuprofen users which show lower haemoglobin levels compared to non- infected patients.

**Key Words:** Bleeding, Children, NSAIDs, Peptic ulcer.

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## 1- INTRODUCTION

Upper gastrointestinal bleeding (UGIB) is one of the most important gastrointestinal emergencies in children (1). Endoscopy is the standard diagnostic method for UGIB and it should be done within the first 24 hours after bleeding (1). Non-steroidal anti-inflammatory drugs (NSAIDs) such as Ibuprofen is well known widely used as pain killers or antipyretic. NSAIDs are commonly prescribed in children. However the drugs can produce gastrointestinal complications such as ulcers and erosions. The pathophysiology of these complications has mostly been ascribed to NSAID's action over the cyclooxygenase (COX) inhibition and prostaglandin (PG) deficiency but its mechanism has not been known completely because the intestinal mucosa can also be injured directly by NSAIDs. The latter shows the induced mucosal injuries may be not related essentially to the effects of the acid (2).

Ibuprofen is commonly used with paracetamol for fever management in children and Ibuprofen has been considered as safe NSAIDs that can be associated with Upper Gastrointestinal bleeding (UGIB) infrequently (3, 4). Helicobacter pylori infection and NSAIDs use are a risk factor for UGIB in children (5- 7). In this study we try to describe role of Helicobacter pylori (H. pylori) infection in gastric bleeding after ingestion of Ibuprofen, a prototype NSAID used in children, by a document based study on 12 cases that developed Upper GI bleeding after use of Ibuprofen.

## 2- MATERIALS AND METHODS

### 2-1. Study design

This is a cross sectional retrospective study. Children's aged 1-14 years old with Upper GI bleeding following use of Ibuprofen were enrolled as case group, they were admitted at the Tabriz

Children's hospital (Iran) during two years from November 2014 to October 2016. Their data include, age, gender and dose and duration of Ibuprofen treatment. Twenty patients that had upper GI bleeding without history of using caustics or drug abuse were matched as control group and the information was compared with the case group. The inclusion criteria were: healthy children aged 1-14 years old with Upper GI bleeding following use of Ibuprofen. The exclusion criteria were: children with previous history of ulcer disease, drug consumption (corticosteroid, anti-coagulants drugs), liver, renal or neurological disorders, burns, trauma, caustic or foreign body ingestion and any coagulopathy disorders. After stabilizing the vital signs of children with UGIB, upper GI endoscopy was done by a pediatric gastroenterologist with pediatric endoscope (Pentax model made in Japan), site and size of bleeding were marked. Tissue samples were taken from the stomach and H. pylori infection was investigated by Giemsa staining in the samples. Family history for GI bleeding and other peptic disorders was obtained and recorded in questionnaires filled by a pediatric gastroenterologist. All data were kept secret and the protocol of the study was approved by the Ethical committee of Tabriz University of Medical Sciences.

### 2-2. Statistical methods

The results of the study were analysed by SPSS software (version 20.0). All data expressed by ratio and percent and mean  $\pm$  standard deviation, maximum and minimum values, comparison between mean of quantity values was one by T independent test and qualified data compared by Chi square test. P- value less than 0.05 were considered significant.

## 3- RESULTS

During the study, 10 children were admitted due to Upper GI bleeding after

Ibuprofen ingestion mainly for its anti-febrile effects. Twenty patients with upper GI bleeding mainly due to gastric prolapse or Mallory Weiss syndrome was considered as control group. They had not history of caustics or drug use. The groups matched in age and gender (**Table.1**). In our study the duration of Ibuprofen use was from 1 to 3 days. The mean  $\pm$  standard deviation [SD] (Minimum, Maximum) of dose (mg/kg/d) in our cases with bleeding was  $7 \pm 9$  (4, 23). The gastric antrum was affected in 70% and body was involved in 30%. All bleedings following use of Ibuprofen in H pylori infected group were

located in the antrum part and dose or duration of Ibuprofen usage had no effect on the gastric bleeding anatomy (**Table.2**). Prevalence of H.pylori infection in Ibuprofen users with bleeding was 40%, this rate in non- user was 8% ( $P= 0.01$ ), and Mean  $\pm$  SD of age (year) in helicobacter infected vs. non- infected cases was higher significantly  $9\pm1$  vs.  $5.5\pm2$  ( $P= 0.04$ ), and haemoglobin following use of Ibuprofen was lower in H.pylori infected compared to non-infected  $8.3\pm1.3$  vs.  $12\pm0.5$  g/dl ( $P=0.0001$ ) (**Table.3**).

**Table-1:** Comparison of Ibuprofen user and non-user following GI bleeding episode

Ibuprofen	Age year	Gender (Female: Male)	H. pylori infection	Family History	Hemoglobin (g/dl)
User	$6\pm2$	30% : 70%	40%	10%	$10.5\pm2.1$
Non user	$6\pm3$	46% :54%	8%	7%	$11.9\pm1.2$
P- value	NS	NS	0.01	NS	0.08

NS: Non Specific; GL: Gastrointestinal; H. pylori: Helicobacter pylori.

**Table-2:** Comparison of the bleeding site, dose and duration of the Ibuprofen use and H. pylori infection

Site of Bleeding	Duration of drug use (day)	Dose of drug (mg/kg/day)	H. pylori infection
Antrum	$2\pm1$	$10\pm8$	4.7
Body	$1.6\pm1$	$6\pm2$	0.3
P-value	0.6	0.2	0.04

H. pylori: Helicobacter pylori.

**Table-3:** Comparison of H. pylori infection and non- infection

H. pylori	Hemoglobin (mg/dl)	Age (year)	Dose of Ibuprofen (mg/kg/day)	Duration of Ibuprofen Use (day)
Infection	$8.3\pm1.3$	$9\pm1$	$15\pm9$	$1.2\pm0.5$
Non infection	$12\pm0.5$	$5.5\pm2$	$5.4\pm2$	$2.3\pm1$
P- value	0.0001	0.04	0.1	0.06

H. pylori: Helicobacter pylori.

#### 4- DISCUSSION

The term "gastropathy", as the adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs) on the gastrointestinal tract, mainly refers to gastric ulcer and its complications without existence of any underlying GI disease or a previous ulcer (8). There is not a sole guideline about how to prescribe NSAIDs including Ibuprofen safely in patients, but it was shown that eradication of H. pylori infection alone in those with a past history of bleeding does not guarantee complete protection and therefore a proton pump inhibitor should also be given. The success of eradication therapy should always be confirmed, because of the risk of ulcer recurrence and bleeding in H. pylori-infected patients who require anti-inflammatory treatments (9, 10). The prevalence of H. pylori in patients with Peptic Ulcer Disease (PUD) ranges from 36% to 73%, depending on ethnicity, geographic factors, and socioeconomic factors (11). Prevalence of H. pylori, which is acquired within the first 5 years of life in children vary from 1.2% to 12.2% in developed countries up to 70% in some developing countries who get infection at age less than 20<sup>th</sup> month (12).

The interaction between H. pylori and NSAIDs in ulcer genesis has been visited by many studies and evidences show eradication of H. pylori may reduce the risk of ulcer and its complications but testing and treating H. pylori infection before prescribing NSAIDs is considered a complicated issue (13). Some studies suggest that eradication H. pylori should be considered but cannot guaranty prevention of GI bleeding after resuming NSAIDs and proton pump inhibitors should be given in prescription in selected cases (11). Prevalence of H. pylori in children who had upper GI bleeding following Ibuprofen usage was 40%, while in control group it was 8%, the average age of infection was 9 years; while it was

5.5 in children who were not infected. This shows that the higher the age, the higher risk for H. pylori and bleeding after Ibuprofen usage compared to younger ages. Contrary to our study, Usta et al. was showed that there was no connection between Helicobacter infection and Ibuprofen consumption (14). The other clinical finding in H. pylori infection is lower haemoglobin in infected patients by the speculative mechanisms that H. pylori colonisation in gastric mucosa may impair iron uptake and increase iron loss that potentially leads to Iron-deficiency anemia (IDA) (10). The other ignored factor is site of the ulcer because in a study showed in H. pylori infected patients ulcer size in antrum is larger than corpus part (15). This study was done in H. pylori infected adults and the authors found some factors like as age and smoking was in relation to ulcer size. However this truth can be addressed to ulcer size and H. pylori infection that results in more severe anemia in infected group needs more evaluation.

Our data show affected patient with upper GI bleeding due to H pylori infection involve antrum part and patients had lower haemoglobin level. Our study shows that bleeding following Ibuprofen is unpredictable and occurs early from the first up to third day with the lowest permitted usual doses any had history of peptic ulcer disease other than vague complaints hard to diagnose clinically at the first visit. These findings are not compatible with findings of other studies that show that following prescription of Ibuprofen, upper GI bleeding is infrequent, and is usually associated with long-term use they believe of all the NSAIDs, Ibuprofen appears to have one of the best GI tolerability profiles (16).

##### 4-1. Limitations of the study

This limited study shows that bleeding following use of Ibuprofen can occur at any age from age one in first day of

treatment with lower standard dose while Ibuprofen related bleeding associated with H. pylori infection occur in average age 9 year-old mostly in antrum and lower haemoglobin level indicated a pre-existing iron deficiency anemia and probably a more complicated bleeding.

## 5- CONCLUSION

This study show that, in spite of the fact that H pylori prevalence in children with upper GI bleeding following NSAIDs prescription is higher than control cases, bleeding following Ibuprofen in children has a complex matter not completely related to H. pylori infection.

**6- CONFLICT OF INTEREST:** None.

## 7- REFERENCES

1. Rotondano G. Epidemiology and diagnosis of acute nonvariceal upper gastrointestinal bleeding. *Gastroenterol Clin North Am.* 2014;43(4):643-63.
2. Hirofumi M, Osamu S, Tsuyoshi K, Yumiko N, Kanho R, Ichinosuke H. The pathophysiology of non-steroidal anti-inflammatory drug (NSAID)-induced mucosal injuries in stomach and small intestine. *J Clin Biochem Nutr.* 2011;42(2):107-11.
3. Bjarnason I. Ibuprofen and gastrointestinal safety: a dose-duration-dependent phenomenon. *J R Soc Med.* 2007;48:11-4.
4. Sabrina C, Massimo M, Arrigo B, Paolo G, Salvatore O, Giovanni DN, et al. Italian survey on non-steroidal anti-inflammatory drugs and gastrointestinal bleeding in children. *World J Gastroenterol.* 2016;22(5):1877-83.
5. Musa D. Peptic ulcer disease and non-steroidal anti-inflammatory drugs. *Aust Prescr.* 2017;40(3):91-3.
6. Tielleman T, Bujanda D, Cryer B. Epidemiology and Risk Factors for Upper Gastrointestinal Bleeding. *Gastrointest Endosc Clin N Am.* 2015;25(3):415-28.
7. Gimiga N, Olaru C, Diaconescu S, Miron I, Burlea M. Upper gastrointestinal bleeding in children from a hospital center of Northeast Romania. *Minerva Pediatr.* 2016;68(3):189-95.
8. McCarthy D. Ulcers, Helicobacter pylori infection, platelets and gastrointestinal complications of non-steroidal anti-inflammatory drugs: what are the connections? *Eur J Surg Suppl.* 2002 (587):89-99.
9. Chaussade S, Abitbol V. Role of Helicobacter pylori in drug-induced gastrointestinal bleeding. *Presse Med.* 2003;22; 32(37 Pt 2):60-3. (French).
10. Hunt RH, Bazzoli F. Review article: should NSAID/low-dose aspirin takers be tested routinely for H. pylori infection and treated if positive? Implications for primary risk of ulcer and ulcer relapse after initial healing. *Aliment Pharmacol Ther.* 2004;19(1):9-16.
11. Alarcón T, JoséMartínez-Gómez M, Urruzuno P. Helicobacter pylori in pediatrics. *Helicobacter.* 2013;18(1):52-7.
12. Shaman R, Niranga MD, Hithanadura JdS. Helicobacter Pylori Infection in Children. *Saudi J Gastroenterol.* 2009;15(2):86-94.
13. Sung JJ. Should we eradicate Helicobacter pylori in non-steroidal anti-inflammatory drug users? *Aliment Pharmacol Ther.* 2004;20(2):65-70.
14. Usta M, Urganci N. Upper Gastrointestinal Bleeding in Children: The Role of Helicobacter pylori Infection and Non-steroidal Anti-inflammatory Drug Use. *West Indian Med J.* 2015;64(2):113-6.
15. Helena M, Montserrat F, Maria E, Mercé R, Carme L, Jorge CE, et al. Helicobacter pylori infection as a cause of iron deficiency anaemia of unknown origin. *World J Gastroenterol.* 2013;19(26):4166-71.
16. Arkkila PE, Kokkola A, Seppälä K, Sipponen P. Size of the peptic ulcer in Helicobacter pylori-positive patients: association with the clinical and histological characteristics. *Scand J Gastroenterol.* 2007;42(6):695-701.