Review Articles

Effect of *Helicobacter Pylori* Infection and NSAIDs on the Risk of Peptic Ulcer Bleeding

Varocha Mahachai MD, FRCP(C), FACG*,
Alan BR Thomson MD, PhD, FRCP(C), FACG**, Ratha-korn Vilaichone MD, PhD***

** Department of Medicine, Faculty of Medicine, Chulalongkorn University*
*** Department of Medicine, University of Alberta, Edmonton, Canada*
**** Department of Medicine, Thammasat University Hospital, Pathumthani*

Peptic ulcer bleeding remains an important emergency situation with a high incidence and carries significant morbidity and mortality. Current evidence suggests that H. pylori and NSAIDs increase the risk of peptic ulcer bleeding and these two factors seem to act independently. Testing for, and cure of, H. pylori infection is recommended in patients prior to the initiation of NSAID therapy and in those who are currently receiving NSAIDs and have a history of peptic ulcer bleeding. For patients who present with peptic ulcer bleeding but require NSAIDs long-term, H. pylori eradication therapy should be considered, followed by continuous proton pump inhibitor prophylaxis to prevent re-bleeding, regardless of which kind of NSAID (nonselective NSAID /coxib) is being prescribed. The success of eradication should always be confirmed because of the risk of peptic ulcer recurrences and bleeding complication.

Keywords: *Helicobacter pylori , NSAIDs, Peptic ulcer bleeding*

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Peptic ulcer disease (PUD) a the worldwide health problem and bleeding is the most frequent complication which occurs in 20% of PUD patients [1]. Despite, improvements of endoscopic hemostatic techniques and acid suppressive drugs, peptic ulcer bleeding remains a life threatening condition that carries 10% mortality rate [2-4]. *Helicobacter pylori (H. pylori*) is gram negative bacterium and are estimated to colonize about 60% of the world population, with a higher rate in developing countries. Furthermore, this organism is a well established cause of PUD and nonvariceal upper gastrointestinal bleeding [5]. There is considerable evidence that eradication of the organism markedly alter the natural history, decreases the recurrence and reduces the complication of PUD [5-9]. New information on the relationship of *H. pylori* and upper gastrointestinal bleeding is now available.

The prevalence of *H. pylori* infection

H. pylori has been detected in more than 90% of patients with duodenal ulcer and approximately 75% of those with gastric ulcers [10]. However, the prevalence of *H. pylori* is lower in patients with complicated PUD. For example, the prevalence of *H. pylori* infection in peptic ulcer bleeding was present in 40-70% in a previous report [11] and 73% in Thai patients [6]. The lower prevalence of *H. pylori* detection in patients with bleeding peptic ulcer could be due to the varying sensitivity and specificity of the *H. pylori* diagnostic tests used in different studies. For example, the rapid urease test on the antral biopsy have been found to have a high false negative rate of *H. pylori* infection in bleeding ulcers [12,13]. Another explanation, in patients with a bleeding peptic ulcer may have factors other than *H. pylori* that are also important in the pathogenesis of the bleeding peptic ulcer. Nonsteroidal anti-inflammatory drugs (NSAIDs) is another important factor which has been found to be the most common cause of PUD in patients who had a negative test for *H. pylori* [14]. Furthermore, patient factors such as advanced age (>60years) and concurrent illness could also increase the bleeding complication and higher mortality rate [15-18].

Pathophysiology of *H. pylori* and NSAIDS in development of bleeding peptic ulcer

H. pylori infection produces important changes in the physiology of gastric acid production. Levels of the secretory hormone, gastrin, are increased in *H. pylori* infected patients. Release of gastrin from G-cells in the gastric mucosa is controlled by factors that include luminal pH and local somatostatin release

Correspondence to : Vilaichone R. 433 Ladphao 130 KlongJun, Bangkapi, Bangkok 10240, Thailand.

by nearby D-cells. Hypergastrinemia associated with *H. pylori* infection is thought to occur secondarily to the release of cytokines (TNF and IL-8) in response to infection and to diminish production of the inhibitory hormone, somatostatin. Infection with *H. pylori* has been associated with decreased levels of somatostatin, diminished somatostatin mRNA production, and fewer somatostatin-producing D-cells [19,20]. These imbalances in gastrin and somatostatin production can explain the observed effects of *H. pylori* on acid secretion. Clinically, patients with *H. pylori* infection have increased basal and maximal acid outputs that return to normal levels after the organism is eradicated, which suggests that infection is the cause of increased acid production [21].

Nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are widely prescribed and have been associated with gastric and duodenal ulcer disease. The inhibitory effects of NSAIDs on the production of prostaglandin in the stomach have been blamed for their ulcerogenic action. Use of NSAIDs predisposes the patient to the development of gastric and duodenal ulceration, although these drugs are more commonly associated with gastric ulcer. NSAIDs have the potential to induce and to exacerbate PUD, and these drugs have been reported to be an important risk factor for bleeding ulcers. Complications of ulcer disease caused by NSAIDs occur early in the course of NSAID therapy; NSAID-induced complications occur within the first month of therapy [22]. When use of NSAIDs is discontinued, NSAID-associated ulcers heal quickly.

Interaction of H. pylori and NSAIDs in bleeding peptic ulcer

Since both *H. pylori* and the use of NSAIDs are the most common cause of peptic ulceration, whether the presence of *H. pylori* infection would affect the risk of ulcers in patients taking NSAIDs is important for both theoretical and practical reasons. The results have been so conflicting that there is no consensus on the management of patients requiring NSAIDs who are infected with *H. pylori*. The controversy is largely due to the variable study design and marked heterogeneity of the study population. However, current evidence suggests that *H. pylori* and NSAIDs increased risk of peptic ulcer bleeding and these two factors seem to act independently [23,24]. The authors' recent study showed that *H. pylori* and NSAIDs increase the risk of peptic ulcer bleeding (OR = 3.7, 95%CI = 1.20-11.16 and OR = 3.1, 95%CI = 1.53-6.12 respectively) and they act independently [6] confirm the previous observations as summarized in Table 1. Furthermore, recent evidence suggests that *H. pylori* contribute to ulcer bleeding associated with low-dose aspirin. Among *H. pylori*-positive patients with a history of ulcer bleeding who are taking low-dose aspirin, the eradication of *H. pylori* has been shown to be comparable to omeprazole in preventing recurrent bleeding [25].

Table 1. Result of multivariable model for prediction of UGIB event in Thai population

Variables	Odd ratio(OR)	95% CI	p-value
Current NSAIDs use	A3.7	1.20-11.16	<0.05
H. pylori infection	3.1	1.53-6.12	<0.01
NSAIDs & *H. pylori*	2.9	1.45-5.75	<0.01

From the reference No.6

Diagnostic tests for *H. pylori* infection in peptic ulcer bleeding

H. pylori diagnostic tests divide into those requiring endoscopy to obtain biopsies of the gastric mucosa and those not requiring endoscopy. Endoscopic tests include gastric mucosal culture, histology and biopsy-rapid urease test (biopsy-RUT). Non-biopsy based tests include serology analysis and urea breath test (UBT). Gastric mucoasal culture remains the gold standard for detecting *H. pylori* and is particularly useful for patients in whom eradication therapy has failed and antimicrobial resistant need to be determined. Although, culture considers the gold standard for diagnosis of *H. pylori* infection, culture is not usually yield on for diagnosis of *H. pylori* infection because the organism is fastidious and the sensitivity of culture often is lower than that of the other tests. Histology is usually related to observer error, sampling error, the density of the organism and the staining methods. However, to the experienced pathologist, hematoxilin and eosin stain is adequate for routine clinical purposes. Three (author's standard) or five biopsy specimens (two antral, two corpus and one incisura) as suggested by the Sydney system (revised version) correctly separate infected mucosa from uninfected mucosa. Biopsy-RUT at the antrum is generally considered the initial endoscopic test of choice. The biopsy-RUT is based on the urease producing, urea in the tests is hydrolyzed, releasing ammonia and raising the pH. A color change caused by the pH indicator in the tests denotes a positive result. A false negative biopsy-RUT is common in *H. pylori* associated bleeding peptic ulcers [1] and blood in the stomach is thought to interfere with the biopsy-

RUT, the underlying mechanism remains unknown. The authors' previous study found that exposure of gastric biopsy specimens to their own blood for four hours significantly decreased the sensitivity of the biopsy rapid urease test for *H. pylori* detection [26].

Serologic testing is a useful noninvasive testing strategy for *H. pylori* infection. It appears to be similar to any other bacterial infections (i.e. after approximately 14 days, IgM is present, and by 21 days, IgG is detectable). IgM declines over the next 3 months, thus, patients with chronic *H. pylori* infection usually have no IgM but always have IgG. The three main formats for the serologic kits are ELISA, immunochromatography and Western blotting. The test is not usually to diagnose infection with the bacterium because the result may indicate a prior rather than a current infection. The UBT is a non-invasive and non-endoscopic test that also employs the potent urease test of the bacterium. Patients are required to drink a solution of urea labeled with carbon 13 or 14. Breath samples are collected before and after 30 minutes after the administration of the labeled urea solution. The sensitivity and specificity of this test are good in peptic ulcer bleeding (sensitivity of 93% and specificity of 87.5%) [27]. *H. pylori* antigen-based stool assay (HpSA) has proven to be accurate in diagnosing *H. pylori* infection in dyspeptic patients. However, HpSA gave a high number of false positive results in bleeding peptic ulcers, probably because of blood constituents cross reaction in the enzyme immunoassay [28]. Comparative of the invasive and non-invasive test of *H. pylori* detection in bleeding peptic ulcers is summarized in Table 2. Since none of the above tests are perfect and the analysis of C13 level requires an expensive mass spectrometer, it is wised to do two diagnostic tests (biopsy RUT and histology) during emergency endoscope in stable patients. If negative, serology is suggested to confirm the absence of *H. pylori*. If positive serology, repeat bioysies or UBT should be done to confirm current *H. pylori infection*.

Table 2. Comparative of the invasive and non-invasive test of *H. pylori* detection in bleeding peptic ulcers

Diagnostic tests	Sensitivity	Specificity
Biopsy RUT	47.5%	100%
Culture	48.0%	91.0%
Histology	82.6%	81.8%
UBT	93.0%	87.5%
Serology	86.4%	77.7%
HpSA	96.6%	33.3%

From references No.1 and 27

Table 3. *H. pylori* eradication reduces the rate of peptic ulcer rebleeding: long term F/U

Studies	Duration of F/U	Rebleeding rate		p-value
		HP eradication	PPI or H2RA only	
Jasperson et al [31]	1 year	0%(0/29)	27.0%(6/22)	<0.01
Macri et al[32]	4 years	0%(0/21)	81.8%(9/11)	<0.002
Sung et al[33]	6 weeks	0%(0/126)	7.2%(9/124)	<0.05

In unstable patients, UBT or endoscopy (biopsy RUT and histology) should be performed later. PPI should be stopped at least 1 week before testing.

Long term outcome for patients with bleeding peptic ulcer

Before the recognition of the role of *H. pylori* in the pathogenesis of the PUD, approximately 30% of patients with bleeding duodenal ulcer and 20% of patients with bleeding gastric ulcer have repeat bleeding in 2 to 3 years after the first episode [29,30]. A numbers of studies have demonstrated that eradication of *H. pylori* reduces the rebleeding significantly more than those with persistent *H. pylori* infection as summarized in Table 3.

In summary, all patients with peptic ulcer bleeding should be tested for *H. pylori* infection, regardless of the use of NSAIDs. Because invasive tests are less sensitive in peptic ulcer bleeding patients, negative tests in patients with no other risk factors should be confirmed by UBT. Eradication therapy with a proton pump inhibitor or ranitidine bismuth citrate-based triple therapy should be given to all *H. pylori*-positive patients. After eradication therapy, acid-suppressant therapy is advised to heal the ulcer. The success of eradication should always be confirmed because of the risk of recurrence of peptic ulcer disease and bleeding in *H. pylori*-infected patients.

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ผลของการติดเชื้อ เฮลิโคแบคเตอร์ ไพโลไร ร่วมกับ ยากลุ่มต้านการอักเสบที่ไม่ใช่สเตียรอยด์ และโอกาสการตกเลือดจากแผลเปปติก

วโรชา มหาชัย, Alan BR Thomson, รัฐกร วิไลชนม์

ในปัจุบันแผลเปปติกยังเป็นปัญหาสำคัญของประชากรทั่วโลกรวมทั้งประเทศไทย ซึ่งแม้ว่าจะมีการพัฒนาการรักษาผู้ป่วยกลุ่มนี้โดยการส่องกล้องกระเพาะอาหาร และยาลดกรดที่มีประสิทธิภาพมากขึ้น ผู้ป่วยกลุ่มนี้ยังมีอัตราการเสียชีวิตถึง 10% การติดเชื้อ เฮลิโคแบคเตอร์ ไพโลไร พบว่าเป็นสาเหตุหนึ่งที่สำคัญของการเกิดแผลเปปติกและการตกเลือดจากแผลเปปติก จากการศึกษาพบว่าการกำจัดการติดเชื้อชนิดนี้สามารถทำให้แผลเปปติกหายขาดได้รวมถึงสามารถลดภาวะแทรกซ้อนจากแผลเปปติก เช่นการตกเลือดในกระเพาะอาหารได้ นอกจากนี้การศึกษาเพิ่มเติมพบว่าการติดเชื้อ เฮลิโคแบคเตอร์ ไพโลไร ร่วมกับการใช้ยากลุ่ม NSAIDs เป็นสาเหตุสำคัญของการเกิดภาวะนี้ ซึ่งผู้ป่วยที่ใช้ยากลุ่ม NSAIDs ทุกคนควรได้รับการตรวจการติดเชื้อเฮลิโคแบคเตอร์ ไพโลไร ในกรณีที่พบการติดเชื้อควรได้รับการกำจัดเชื้อ และได้รับยาในกลุ่มลดกรดเพื่อรักษาแผลต่อประมาณ 6-8 สัปดาห์ และควรมีการตรวจยืนยันว่าสามารถกำจัดเชื้อ เฮลิโคแบคเตอร์ ไพโลไร ได้สำเร็จเพื่อป้องกันการกลับเป็นซ้ำของแผลเปปติก