Prediction of UGIB Event in NSAID Users: A Model Development

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The purpose of this study was to create a predicting tool for UGIB event in NSAID users. The patients of this case-control study were NSAID users who had received NSAIDs for at least 3 days and were gastroscoped. The patients with a history of gastrointestinal varices, gastrointestinal cancer, chronic renal failure, coagulopathy, or Mallory-Weiss tear were excluded. The data was collected between July 2001 and January 2002 by patient interviewing and medical record reviewing. One hundred and fifty four NSAID users were identified (89 in the UGIB group, 65 in the non-bleeding group).

Most patients were elderly (mean age $\pm$ SD: 60.9 $\pm$ 12.6 years). Age and the number of current NSAID users were significantly higher in UGIB patients than in non-bleeding patients ($p < 0.05$ and $p < 0.01$, respectively). The number of antiulceration drug users in non-bleeding patients was higher than in UGIB patients ($p < 0.01$).

An equation for prediction of UGIB probability in NSAID users was generated by using enter logistic regression. The best model of predicting the risk of UGIB event in NSAID users was logit (UGIB) = 0.33 + 2.09 Multiple NSAID use + 1.43 H. pylori infection + 0.34 Current NSAID use + 0.12 (Age x Sex) - 8.53 Sex - 2.41 Antiulceration drugs - 0.000048 Age. The model had 80.2% of the overall rate of correct classification. The positive and negative predictive values were 80.8% and 78.9% respectively. The probability of UGIB = $e^{logit(UGIB)}/1 + e^{logit(UGIB)}$. If the value of the probability of UGIB is more than 0.5, the patient has a high risk of UGIB.

Multiple NSAID use is the strongest factor that affects the probability of UGIB in NSAID users. H. pylori infection is another strong risk factor of NSAID-related UGIB. Antiulceration drug usage reduced the risk of UGIB in this group of patients. The developed model can be used as a guide for pharmacotherapeutic planning in clinical practices.

Keywords: *Nonsteroidal anti-inflammatory drugs, Upper gastrointestinal bleeding, Prediction*

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NSAIDs are commonly used for the treatment of musculoskeletal and arthritis syndromes. These medications are generally well tolerated, but their well known adverse effects are gastrointestinal (GI) problems including peptic ulcer and UGIB. Many studies have shown that NSAIDs increase the risk of peptic ulcer complication by 3-5 fold[1,2]. Mortality rate of NSAID-related GI bleeding is 6-7%[3,4]. Several studies revealed various risk factors for NSAID-induced UGIB. Established risk factors are older age, history of dyspepsia or peptic ulcer or GI complication, high dose of NSAIDs, multiple NSAID use and concomitant oral corticosteroids or anticoagulant therapy. Also, possible risk factors include cigarette smoking, alcohol consumption and *Helicobacter pylor* (*H. pylori*) infection[5-10].

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As Fries et al (1991) reported that GI-event risk per year on NSAIDs in rheumatoid arthritis was a predictor of GI incidence rates of hospitalization or death over the next 12 months[11]. Singh et al (1998) showed that the GI score anticipated incidence rates of serious NSAID-related GI event in rheumatoid arthritis and osteoarthritis patients[12]. To reduce the risk of bleeding in NSAID users, it would be beneficial to develop a tool for identification of patients at high risk of UGIB.

Material and Method

Patients with GI problems who participated in this case-control study were NSAID users taking NSAIDs (including aspirin) for at least 3 days and were gastroscoped at the gastroenterology unit in King Chulalongkorn Memorial Hospital. These GI problems included dyspepsia, melena or hematemesis. Patients with a history of gastrointestinal varices, cancer, chronic renal failure, coagulopathy, and Mallory-Weiss syndrome were excluded. One hundred and fifty four patients were classified into 2 groups. Eighty nine were in the UGIB group and sixty five in the non-bleeding group. Patients in the bleeding group were those who had melena, hematemesis, positive stool occult blood or anemia (decreased in the hematocrit level of 5% or more compared with one month before peptic ulcer bleeding) during 1 week before endoscopic examination.

Risk factors of UGIB in NSAID users were collected from July 2001 to January 2002 by patient interviewing and medical record reviewing. Risk factors were defined as age, a history of peptic ulcer, a history of GI complication, history of dyspeptic symptoms, multiple NSAID use, cigarette smoking, alcohol consumption, *H. pylori* infection, and combination usage of NSAIDs with either an oral corticosteroid or anticoagulant drug. A developed questionnaire and medication pictures or tablets were used in patient interviewing. *H. pylori* infection was confirmed by rapid urease test or serology test. Informed consent to study participation was obtained from each patient before enrollment.

Definitions used for data collection are as follows: (1) index date was defined as the day of endoscopic examination, (2) current NSAID user was a patient who was taking NSAIDs between 1 and 30 days before the index date, (3) past NSAID user was a patient who had been taking NSAIDs between 31 and 90 days before the index date, (4) multiple NSAID user was a patient who took more than one NSAIDs, (5) a regular NSAID user was a patient who took NSAIDs every day, (6) occasional NSAID user was a patient who took NSAIDs less than 3 days/week, (7) low dose of NSAID was defined as an aspirin dose of $\leq$ 325 mg/d, ibuprofen $\leq$ 1200 mg/d, diclofenac $\leq$ 75 mg/d, indomethacin $\leq$ 100 mg/d, naproxen $\leq$ 750 mg/d, ketoprofen $\leq$ 100 mg/d, piroxicam $\leq$ 20 mg/d, mefenamic acid $\leq$ 1000 mg/d, sulindac $\leq$ 200 mg/d, and nabumetone $\leq$ 1000 mg/d, and (8) alcohol consumption was defined as alcohol drinking at least one unit per week. One unit was defined as equivalent to 45 ml of liquor, 120 ml of wine, or 360 ml of beer.

Demographic data were analyzed by using the independence t-test and χ^2-test. A predicting model of GI bleeding in NSAID users was generated by using enters logistic regression.

Results

Of 154 patients who were eligible to participate in the present study, seventy one were male and 83 were female. The mean age ($\pm$ SD) of these patients was 60.9 ($\pm$ 12.6) years. Forty five percent of the UGIB patients experienced the dyspeptic symptom before the bleeding. The characteristics of NSAID user were current user (88.3%), single user (79.3%), regular user (68.8%) and low dose NSAID user (90.2%). Diclofenac was the most common drug used (33.3%) followed by aspirin (30.9%) and indomethacin (18.2%). Only 27.3% of these patients concomitantly took oral corticosteroid or warfarin. Seventy-eight patients had *H. pylori* infection. Only 16 and 22 patients took alcohol and smoked cigarettes, respectively. Most of the patients who consumed alcohol or smoked cigarettes were male. Twenty six percent of the NSAID users had received antiulceration drugs (H_2-blockers or proton pump inhibitors) for at least 1 week before the bleeding events. The incidence of gastric ulcer was higher than those of duodenal ulcer (46.8% and 22.1%, respectively). Most gastric ulcers were found at the antrum (83.1%).

The demographic data of 154 patients is shown in Table 1. History of UGIB was higher in the UGIB group (6.7%) when compared with the non-bleeding group (4.6%). Three patients in the non-bleeding group had a history of ulcer. None of the patients in the UGIB group had a history of ulcer. The number of combination usage of NSAIDs and warfarin was lower in the non-bleeding patients (one patient) than in the patients with UGIB (four patients). The number of patients who smoked cigarettes was not different between the two groups

(p > 0.05). The number of patients who consumed alcohol (≥ 5 U/week) in the UGIB group was higher than those in the non-bleeding patients (10 and 3 patients, respectively).

Table 2 summarizes the result of enter logistic regression analysis using all risk factors. The best model of predicted risk of bleeding event in NSAID users was logit (UGIB) = 0.33 + 2.09 Multiple NSAID use + 1.43 *H. pylori* infection + 0.34 Current NSAID use + 0.12 (Age x Sex) - 8.53 Sex - 2.41 Antiulceration drugs - 0.000048 Age. The probability of UGIB = $e^{logit\ (UGIB)}/1+e^{logit\ (UGIB)}$. If the value of the probability of UGIB is more than 0.5, the patient has a high risk of UGIB. Value of parameters in the equation was defined as follows. For sex, male is 0 and female is 1. For pattern of NSAID use, current NSAID use is 1, past NSAID use is 0, multiple NSAID use is 1, and single NSAID use is 0. For *H. pylori* infection, infection of *H. pylori* is 1 and non-*H. pylori* infection is 0. For antiulceration drug use, antiulceration drug use is 1 and no antiulceration drug use is 0.

The authors found that multiple NSAID use and *H. pylori* infection are two major risk factors of UGIB event in NSAID users. Antiulceration drugs usage reduce the risk of bleeding. From the best model, Table 3 was then developed to ease of practical use. For example, there was a 68 year old woman who was taking diclofenac every day without antiulceration

Table 1. The demographic data of bleeding and non-bleeding patients

Characteristic data	Bleeding group (percentage)	Non-bleeding group (percentage)	p-value
Age (year)	62.7±13.3	58.6±11.1	<0.05
Sex			
Male	52.8	36.9	0.05
Underlying disease			
Dyspeptic symptoms	27.0	23.1	0.58
Cardiovascular disease	16.9	35.4	0.11
Bone and joint disease	16.9	20.2	0.62
Diabetes Mellitus	15.7	15.4	0.95
Pattern of NSAID use			
- Current use	94.4	80.0	<0.01
Past use	5.6	20.0	
- Single NSAID use	75.4	84.3	0.24
Multiple NSAID use	24.6	15.7	
- Regular use	73.0	63.1	0.19
Occasional use	27.0	36.9	
Concomitant corticosteroids therapy	30.3	18.5	0.09
H. pylori			0.12
Positive	61.6	48.1	
Negative	38.4	51.9	
Antiulceration drugs	13.5	43.1	<0.01

Table 2. Results of fitting a multivariable model

Risk factors	Coefficient	Standard error	Odd ratio	95%CI	p-value
Age	-0.000048	0.03	1.00	0.94-1.06	0.99
Sex	-8.53	2.91	0.0002	0.00-0.06	<0.01
Current NSAID use	0.34	0.89	1.41	0.25-8.04	0.69
Multiple NSAID use	2.09	0.75	8.06	1.86-34.86	<0.01
H. pylori infection	1.43	0.54	4.18	1.45-11.99	<0.01
Antiulceration drugs	-2.41	0.59	0.09	0.03-0.29	<0.01
Age X sex	0.12	0.04	1.12	1.03-1.23	<0.01
Constant	0.33	1.97	-	-	0.86

-2 log likelihood = 99.9, Overall percent correct = 80.2%
Positive predictive value = 80.8%, Negative predictive value = 78.9%

drugs usage. She also had *H. pylori* infection. Her probability of UGIB could be easily estimated. Risk factors of UGIB in this patient were current NSAID use and *H. pylori* infection. Current NSAID use and *H. pylori* infection can be found in the seventh row of the first column on the left-hand side of Table 3. Since this woman was 68 years old, the probability of UGIB in this patient was 0.65-0.84, which can be found in the seventh row of the fifth column of Table 3.

Discussion

The aim of the present study was to generate the predicting tool for UGIB event in NSAID users. The presented study population was NSAID use with GI problems. Most of the presented patients were elderly (mean age $\pm$ SD = 60.9 $\pm$ 12.6 years) and there were more females than males (F:M = 1.2:1). This finding is expected as it is known that NSAIDs are generally used in the elderly and women[13]. NSAID use was the cause of GI bleeding in all patients in the bleeding group. Results of the present study also support findings from previous reports that risks of UGIB among various NSAIDs are not different[1,2,5,7,14,15], the elderly are at greater risk of UGIB[7,9,10], and the incidence of UGIB in NSAID users who have a history of dyspepsia and GI bleeding is high[7,15]. However, the number of patients with a history of ulcer was higher in the non-bleeding group than in the bleeding group of the present study.

The best model for prediction of UGIB episode is overall percent correction of 80.2. Major risk factors in the model are multiple NSAID use and *H. pylori* infection. This is consistent with a previous finding that concomitant use of more than one NSAID more than doubled the risk of bleeding[7,15]. Also, NSAID users with *H. pylori* infection increase the risk of UGIB[16,17]. In contrast, several reports have shown that both *H. pylori* infection and NSAID use do not increase the risk of bleeding[18,19]. Antiulceration drug usage reduced the risk of GI bleeding. The result from

Table 3. The probability of UGIB event in NSAID users

Risk factors	Male	Female, age (years)			
		<50	50-59	60-69	>70
No all factors	0.58	<0.09	0.09-0.22	0.48	>0.51
Current NSAID use only	0.66	<0.11	0.12-0.29	0.31-0.56 (67)*	>0.59
Multiple NSAID use only	0.92	<0.41	0.44-0.69 (53)*	0.72-0.88	>0.89
H. pylori infection only	0.85	<0.27	0.29-0.54 (58)*	0.57-0.79	>0.81
Antiulceration use only	0.11	<0.01	0.01-0.02	0.03-0.08	0.08-<0.5
Current and multiple NSAID use	0.94	<0.49	0.53-0.76	0.78-0.91	>0.92
Current NSAID use and *H. pylori* infection	0.89	<0.34	0.37-0.63 (55)*	0.65-0.84	>0.86
Current NSAID use and antiulceration use	0.15	<0.01	0.01-0.03	0.04-0.10	>0.10 (88)*
Multiple NSAID use and *H. pylori* infection	0.98	<0.74 (40)*	0.77-0.90	0.91-0.97	>0.97
Multiple NSAID use and antiulceration use	0.50	<0.05	0.06-0.17	0.18-0.40	>0.43 (73)*
H. pylori infection and antiulceration use	0.34	<0.03	0.03-0.09	0.11-0.26	>0.28 (79)*
Current and multiple NSAID use and *H. pylori* infection	0.98	<0.47-0.82 (37)*	0.82-0.93	0.94-0.98	>0.98
Current and multiple NSAID use and antiulceration use	0.58	<0.08	0.09-0.22	0.25-0.48	>0.51
Current NSAID use and *H. pylori* infection and antiulceration use	0.81	<0.04	0.05-0.13	0.14-0.33	>0.35 (76)*
Multiple NSAID use and *H. pylori* infection and antiulceration use	0.81	<0.21	0.23-0.46	0.49-0.74 (61)*	>0.76
Having all factors	0.86	<0.27	0.29-0.55 (58)*	0.58-0.79	>0.82

* = The number in parenthesis is patient's age that the probability of UGIB event is greater than 0.5

enter logistic regression showed that concomitant corticosteroid therapy, history of dyspeptic symptoms and cigarette smoking were not risk factors of GI bleeding. The history of ulcer and bleeding, alcohol consumption, and concomitant warfarin therapy were not included in the model because only a small number of patients had these factors. Accordingly, further research is crucial to further study in a larger sample size and to validate the model.

To use the developed tool in other populations, one should consider some limitations of this tool such as (1) NSAID users in the present study were at higher risk of peptic ulcer than in the general population. It is possible that the NSAID user with a low risk of peptic ulcer has a smaller probability of GI bleeding. (2) The risk of GI bleeding may be lower in men who did not drink alcohol and smoke cigarettes. (3) The probability of a UGIB event can be different in a patient who had other risk factors such as a history of ulcer or bleeding and concomitant corticosteroids or warfarin therapy.

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การพัฒนาสมการทำนายโอกาสเกิดเลือดออกจากทางเดินอาหารส่วนต้นในผู้ใช้ยาต้านการอักเสบที่ไม่ใช่สเตียรอยด์

มยุรี ตั้งเกียรติกำจาย, สมฤทัย วัชราวิวัฒน์, วโรชา มหาชัย

วัตถุประสงค์ของการศึกษาคือเพื่อสร้างสมการทำนายโอกาสเกิด UGIB ในผู้ใช้ NSAIDs การศึกษานี้เป็นการศึกษาวิจัยเชิงวิเคราะห์แบบย้อนหลัง (case-control study) โดยมีเกณฑ์การคัดเลือกผู้ป่วยเข้าการศึกษาคือ ผู้ใช้ NSAIDs มาอย่างน้อย 3 วัน และได้รับการส่องตรวจด้วยกล้อง เกณฑ์การคัดผู้ป่วยออกจากการศึกษาคือ ผู้ป่วยที่มีประวัติหลอดเลือดขอดในหลอดอาหารและกระเพาะอาหาร มะเร็งในทางเดินอาหาร โรคไตวายเรื้อรัง และโรคเลือด ผู้วิจัยเก็บข้อมูลตั้งแต่ กรกฎาคม พ.ศ. 2544 ถึง มกราคม พ.ศ. 2545 โดยการสัมภาษณ์ผู้ป่วย และเก็บข้อมูลจากเวชระเบียน พบว่าผู้ป่วยที่ใช้ NSAIDs ทั้งหมด 154 คน ในจำนวนนี้มีผู้ป่วยที่เกิด UGIB จำนวน 89 คน และผู้ป่วยที่ไม่เกิด UGIB จำนวน 65 คน

ผู้ป่วยส่วนใหญ่ที่ใช้ NSAIDs เป็นผู้สูงอายุ มีอายุเฉลี่ย $\pm$SD เท่ากับ 60.9$\pm$12.6 ปี และพบว่าผู้ป่วยที่เกิด UGIB มีอายุสูงกว่าและมีการใช้ NSAIDs ในปัจจุบันมากกว่าผู้ป่วยที่ไม่เกิด UGIB อย่างมีนัยสำคัญทางสถิติ ($p < 0.05$, $p < 0.01$ ตามลำดับ) ผู้ป่วยที่ไม่เกิด UGIB มีการใช้ยารักษาแผลในทางเดินอาหารมากกว่าผู้ป่วยที่เกิด UGIB อย่างมีนัยสำคัญทางสถิติ ($p < 0.01$)

การสร้างสมการทำนายโอกาสเกิด UGIB ในผู้ใช้ NSAIDs ทำโดยการวิเคราะห์ความถดถอยโลจิสติควิธี enter สมการทำนายที่ดีที่สุดคือ logit (UGIB) = 0.33 + 2.09 การใช้ NSAIDs หลายชนิดร่วมกัน + 1.43 การติดเชื้อ H. pylori +0.34 การใช้ NSAIDs ในปัจจุบัน + 0.12 (อายุ X เพศ) - 8.53 เพศ - 2.41 การใช้ยารักษาแผลในทางเดินอาหาร - 0.000048 อายุ สมการมีการทำนายถูกต้องเท่ากับร้อยละ 80.2 ค่าการพยากรณ์ในทางบวกเท่ากับร้อยละ 80.8 ค่าการพยากรณ์ในทางลบเท่ากับร้อยละ 78.9 โอกาสเกิด UGIB = $e^{logit(UGIB)}/1+e^{logit(UGIB)}$ ถ้าค่าโอกาสเกิด UGIB มากกว่า 0.5 แสดงว่าผู้ใช้ NSAIDs มีโอกาสเกิด UGIB

ปัจจัยเสี่ยงที่เพิ่มโอกาสเกิด UGIB ในผู้ใช้ NSAIDs มากที่สุดคือ การใช้ NSAIDs ร่วมกันหลายชนิด รองลงมาคือการ ติดเชื้อ H. pylori ยารักษาแผลในทางเดินอาหารจะลดโอกาสเกิด UGIB ดังนั้นสมการนี้อาจนำมาใช้เป็นแนวทางประกอบการวางแผนการรักษาผู้ป่วยด้วยยาต่อไป