**Reviewer’s Comments**

****

**Role of Non steroidal Anti-Inflammatory Drugs in acute upper GastroIntestinal Bleeding**

**Abstract**

**Background**:

Many patients presented to the causality with upper gastrointestinal bleeding, which is a serious condition associated with significant morbidity and mortality especially in elderly patients and those with coexisting medical diseases.

**Objectives:**

To assess the general use of NSAIDs and their relation to upper gastrointestinal bleeding.

**Methods:**

Cross sectional study on patients who were referred for endoscopy for upper gastrointestinal bleeding in Sulaimany Teaching Hospital during the period from January to December 2016. All of them had been exposed to full history taking regarding age, gender, smoking, alcohol and medication used in addition to thorough physical examination and upper gastrointestinal endoscopic examination with biopsy when indicated.

**Results:**

This study enrolled 100 patients with upper GIT bleeding and showed that 48% of those with upper GIT bleeding were using NSAIDs, with male to female ratio of approximately 2:1, and 37 patients (77.1%) of those who were taken NSAIDs, did not use PPI concomitantly The study also revealed that elderly patients taking NSAIDs were at higher risk of developing upper GIT bleeding.

**CONCLUSIONS:**

Elderly patients who were taken NSAIDs associated with significant upper GIT bleeding, and their uses were without prophylactic PPI cover in high risk individuals.

***Keywords***

***Introduction:***

 Approximately 50 non-steroidal anti-inflammatory drugs (NSAIDs) are in use throughout the world, the oldest and best known is aspirin. NSAIDs are popular because of their versatile effectiveness as analgesics, antipyretics, and (by definition) as anti-inflammatory agents (14). Aspirin is also widely used as an anti-thrombotic agent. Unfortunately, aspirin and most other NSAIDs can injure the gastric and duodenal mucosa, with considerable morbidity and mortality (14)

 UGI bleeding commonly presents with hematemesis (vomiting of blood or coffee-ground like material) and/or melena (black, tarry stools). A nasogastric tube lavage which yields blood or coffee-ground like material confirms this clinical diagnosis. However, lavage may not be positive if bleeding has ceased or arises beyond a closed pylorus.

 Gastroduodenal ulcer disease remains a common cause of UGI bleeding (1) There are four major risk factors for bleeding peptic ulcers (2, 3) Helicobacter pylori infection , nonsteroidal antiinflammatory drugs (NSAIDs) stress ,gastric acid .Reduction or elimination of these risk factors reduces ulcer recurrence and rebleeding rates(4,5,6,7 ) ,  NSAIDs are a common cause of gastrointestinal ulceration(8,9,10,11) . However, all patients with a prior history of bleeding ulcer disease are at increased risk for recurrent ulcer and complications (12, 13, and 14).

NSAIDs also have been implicated as an important factor for non-healing ulcers (15).

 Endoscopy is the preferred investigative procedure for upper gastrointestinal bleeding because of its accuracy, low rate of complications and potential for therapeutic intervention (16).

Pathology — Acute hemorrhagic and erosive gastropathy appears as multiple petechial hemorrhages and small red or black erosions on endoscopy (17, 18). Stress-related lesions (Curling's ulcers) usually appear in the fundus near the gastroesophageal junction and spread distally, but remain confined to the fundus and body (18). In contrast, gastropathy due to NSAIDs and alcohol involves the entire stomach from the start, although it may be most evident in the antrum (18)

The healthy gastric and duodenal mucosae constitutively use COX- to produce its mucosal protective PGs (18) Many NSAIDs block COX-1 and COX-2 more or less equally (i.e. are non-selective) and thus impair gastric PG production at low (<1µM) concentrations ,examples include aspirin, indomethacin, ibuprofen, and naproxen. Most drugs that spare COX-1 and selectively inhibit COX-2 have less suppressive effects on gastric PG synthesis, examples include celecoxib and etodolac. As a result, selective inhibitors of COX-2, and also COX–3 inhibitors such as acetaminophen, preserve PG-mediated GI mucosal protection (19, 20, and 21) .However, COX-2 selective inhibitors can lose their specificity for COX-2 at high doses and have the potential to also block COX-1 in the stomach and duodenum and cause damage. American College of Gastroenterology recommendations — A committee appointed by the American College of Gastroenterology has critically reviewed the data regarding the risk factors for NSAID toxicity, and identified the five most important variables that place patients at risk for NSAID-related gastrointestinal complications (22).

1. Prior history of an adverse GI event (ulcer, hemorrhage) increases risk four to fivefold .
2. Age >60 increases risk five- to sixfold .
3. High dosage of a NSAID increases risk 10-fold .
4. Concurrent use of glucocorticoids increases risk four to fivefold.
5. Concurrent use of anticoagulants increases risk 10- to 15-fold .

 Patients with several risk factors are at highest risk for NSAID-induced GI toxicity (up to 9 percent after six months) (23,24) , Assessment of these risk factors is recommended for identifying patients who should be considered for prophylaxis if it is felt that an NSAID must be given.

**Aim of the study:**

1. To determine the overall causes of upper GIT bleeding.
2. To determine the frequency of NSAIDs induced upper GIT bleeding.
3. To assess local practice in using prophylaxis against NSAIDs induced upper GIT bleeding.

**Patients and methods:**

 This study is a cross sectional study. One hundred patients with upper GIT bleeding had been included in this study. They were randomly selected from those who were referred for GIT centre at Sulaimany Teaching Hospital during the period from January to December 2016. All of them had been exposed to full history taking regarding age, gender, smoking, alcohol intake and medication used, in addition to thorough physical examination and upper gastrointestinal endoscopy with biopsy when indicated.

 We excluded those patients with history of upper GIT bleeding with no endoscopic evidence of bleeding.

All of the collected data had been analyzed using Microsoft Excel and Statistical Package for Social Sciences (SPSS) software. The data had been tabulated in form of frequency distribution tables and graphs. Student’s t-test and Chi-square test had been used for testing the level of significant association or difference between different quantitative and qualitative groups, respectively. A value of less than 0.05 had been selected as the P value required to determine the significant association or difference.

 **Results:**

 This study enrolled 100 patients with upper GIT bleeding. The sample included 66 male (66% of the sample) and 34 female patients (34% of the sample). The mean age of the patients was 49.33$\pm $ 14.9 year old (range: 20-80year old). The mean age of male patients was 50.26$\pm $ 13.7 year old (range: 23-80year old) and the mean age of the female patients was 47.5$\pm $17.1 year old (range 20-70 year old). Twenty nine patients (29% of the sample) were 60 years or older. 49 male patients were younger than 60 years (74.3% of male patients) compared to 22 females patients (64.7% of female patients) were within the same age group.

Table- 1 shows age and gender distribution of the sample.

|  |  |  |  |
| --- | --- | --- | --- |
| Age group | Male | Female  | M:F ratio |
| No.  | % | No.  | % |
| 20- 39 year old | 17 | 25.8% | 12 | 35.3% | 1.4:1 |
| 40-59 year old | 32 | 48.5% | 10 | 29.4% | 3.2:1 |
| $\geq $60 | 17 | 25.8% | 12 | 35.3% | 1.4:1 |
| total | 66 | 100.0% | 34 | 100.0% | 1.9:1 |

Table - 2: patient’s distribution according to their age and history of NSAID use

|  |  |  |
| --- | --- | --- |
| Age group | Use NSAIDs | Not use NSAIDs |
| No. | % | No. | % |
| 20-39 year- old | 9 | 31.0% | 20 | 69.0% |
| 40-59year old | 15 | 35.7% | 27 | 64.3% |
| ≥60 year old | 24 | 82.8% | 5 | 17.2% |
| Total(n=100) | 48 | 48.0% | 52 | 52.2% |
| mean± SD | 53.63± 16.5 | 45.37±12.2 |
| Statistical analysis | Calculated t = 2.84, p value = 0.01 |

 it can be seen clearly from table -2 that total number of patients taken NSAIDs were 48, with mean± SD 53.63± 16.5, and total number of patients who did not taken NSAIDs are52 with mean± SD 45.37±12.2 which represent statically significant association between NSAIDs and upper GIT bleeding with calculated t =2.84 and p value 0.01, it can also be seen that 82.8% of those aged above 60 year old were taken NSAIDs.

Graph 1: frequency of gastrointestinal irritant agents.

It can be seen clearly from the graph 1 that approximately half of those with upper GIT bleeding were taking NSAID, while steroids 3% of the sample, alcohol 3% and 16 % of patients were smokers.

 Graph 2: frequency of different NSAIDs usage

 Graph 2: demonstrate aspirin is the most frequently used drugs among the NSAID which represent 64.4%, while the selective NSAID usage is only 6.25% from the total usage of NSAID. It had been shown that there was a significant association between the use of NSAIDs in all of their types and the development of upper GIT bleeding (*X*2 = 5.6, p value = 0.001). On the other hand no statistically significant association had been observed between use of COX-2 inhibitors and the development of upper GIT bleeding (X2 = 1.43, p value > 0.05).

TABLE- 3: patient’s distribution according to their history of NSAIDs and PPI use.

|  |  |
| --- | --- |
|  | Use NSAIDs |
| No. | % |
| Use PPI | 11 | 22.9% |
| Did not use PPI | 37 | 77.1% |
| Total | 48 | 100% |

We can see from table 3 that the majority of patients who use NSAIDs (77.1%) do not use PPI concomitantly, compared to (22.9%) who were using PPI.

Table 4: Patients’ distribution according to the endoscopic finding and their history of NSAIDs use

|  |  |  |
| --- | --- | --- |
|   | use NSAIDs | Did not use NSAIDs |
| No. | % | No. | % |
|  Duodenal ulcer | 18 | 34.6% | 34 | 65.3% |
|  Erosive gastritis | 13 | 61.9% | 8 | 38.1% |
| Gastric ulcer | 10 | 76.9% | 3 | 23.1% |
| Oesophagitis | 3 | 60% | 2 | 40% |
| Oesophageal varices | 1 | 33.3% | 2 | 66.7% |
| Gastric malignancy | 2 | 66.7% | 1 | 33.3% |
| Mallory Weiss syndrome | 0 | 0% | 2 | 100% |
| Gastric arteriovenous malformation | 1 | 100% | 0 | 0% |

 **Discussion:**

Acute upper GIT bleeding is a common emergency with important implications for health care costs worldwide. Negative outcomes include rebleeding and death, and many of the deaths are associated with decompensation of coexisting medical condition precipitated by acute bleeding events (25). In a study from one large health maintenance organization, the annual incidence of hospitalization for acute upper GIT bleeding was 102 per 100 000; the incidence was twice as common in males as in females and increased with age (26). Similar findings were observed in this study which indicated that overall male to female ratio in all age groups was 1.9:1. Furthermore, this phenomenon of higher frequency of upper GIT bleeding was most prominent and evident among those whose age ranged between 40 and 59 year-old with a frequency of upper GIT bleeding among male patients 3 times its frequency among female patients. The M: F ratio showed some decline among those aging 60 years or older, with M: F ratio of about 1.4:1. Examining the data collected from this study showed that in this age group, female patients were more frequently using NSAIDs drugs for different reasons and with the possible taking of drugs with more toxic effects on the gastrointestinal tract. In addition, many other studies showed that the impact of NSAIDs on the risk of upper GIT bleeding was greater in women than in men (27, 28, and 29).

Age had been considered as one of five most important risk factors for gastroduodenal toxicity from NSAIDs according to the committee appointed by the American College of Gastroenterology (30). Similarly, this study showed that elderly patients taking NSAIDs were at higher risk of developing upper GIT bleeding, as 24 out of 29 patients with an age of 60 years or older (82.8%) were taking NSAIDs, In contrast, only 9 out of 29 patients (31%) whose age was 20-39 year-old were taking NSAIDs indicating that the effect of other risk factors for upper GIT bleeding had stronger effect in comparison to the effect of NSAIDs on the frequency of upper GIT bleeding among young patients.

Regarding the history of NSAIDs use including the use of aspirin in all of its recommended doses, many studies with different designs reached the conclusion of considering the use of NSAIDs as a major risk factor in the development of upper GIT bleeding which is the main cause of morbidity and mortality related to NSAIDs use(31,32) In the United States cohort of rheumatoid arthritis patients alone, it has been estimated that GI toxicity related to NSAIDs use accounts for at least 2600 deaths annually(33). This study had shown that 48% of those with upper GIT bleeding were using NSAIDs, making the use of NSAIDs the most frequent risk factors for developing upper GI bleeding in the sample enrolled in this study. Lim et al (2005) indicated that over 25% of those with significant upper GIT bleeding were using NSAIDs including COX2 inhibitors (31). The relatively higher frequency of NSAIDs use among patients enrolled in our study (48% in our study versus 25% in Lim’s study) can be attributed to the current trends in our community where drugs are available without proper prescription by an authorized physician; this makes a lot of NSAIDs as an over the shelf medicine with more frequent use as an analgesic.

This study indicated that different types of NSAIDs had different frequency of usage in patients with upper GIT bleeding, with aspirin as the most frequently used drug (64.6% of the sample). Other NSAIDs were observed much less frequently including ibuprofen, diclofenac (Voltarin®), indomethacin (Indocid®) and meloxicam ( mobic®), which had been used by 16.7%, 12.8%, 8.3% and 6.25% of patients, respectively. On reviewing the results of similar studies , the risk of gastrointestinal complications was highest with indomethacin and putting ibuprofen at the bottom of the list(34). Another potentially important finding that can be derived from this study is that cox2 inhibitors are the least frequent risk factor for upper GI bleeding in our sample (6.25% of the sample). This finding is similar to the finding of two large trials that studied the effect of cox2 inhibitors to reduce the gastrointestinal complications. The first trial is the CLASS study which involved 8059 patients and found that over the initial six months of therapy, cox2 inhibitors were associated with significantly fewer symptomatic ulcers and ulcer complications than ibuprofen or diclofenac (35). A second trial (the SUCCESS-I study) included a total of 13, 274 patients with osteoarthritis from 39 countries and found that there was a reduction in gastrointestinal complications only in patients not taking concomitant aspirin i.e. cox2 inhibitors only (36).

The cornerstone in approaching the problem of NSAIDs induced gastrointestinal toxicity is the primary prevention of such a catastrophic adverse effect aiming to reduce the associated high mortality and morbidity (32). Proton pump inhibitors (PPIs) are useful for the prevention of NSAIDs induced ulcers (37-40). In an illustrative study, the combined incidence of gastric and duodenal ulcers detected endoscopically was reduced in patients who were also treated with 20 mg omeprazole per day (3.6% versus 16.5% with placebo at 6 months) (40). Unfortunately, our study only 11 out of 48 patients using NSAIDs (22.9%) were taking PPIs for the prevention of NSAIDs induced GIT bleeding. This means that the remaining 37 patients (77.1%) had been deprived from the protecting effect of PPIs use despite their history of NSAIDs intake.

This study revealed that NSAIDs use was more frequently associated with gastric mucosal injury. Twenty three out of 34 patients (67.6%), diagnosed endoscopically as having a gastric mucosal injury in the form of either erosive gastritis (13 patients) or gastric ulcer (10 patients), were using NSAIDs. This higher frequency of gastric mucosal injury in association with NSAIDs use in comparison to less frequent injuries to other parts of GI tract, can be related to the fact that gastric mucosa, not the duodenal or esophageal mucosa, is dependent on COX-1 (which would be inhibited by NSAIDs) to generate mucosal-protective prostaglandins. This protective mechanism can be inhibited by a very low dose of aspirin or other NSAIDs. Cryer et al found that aspirin doses as low as 10 mg/day can inhibit gastric prostaglandin generation considerably and can damage the stomach (41). In contrast, some studies showed that aspirin doses as low as 325 mg/day every other day increase the risk of duodenal ulcer (42). Although the risk of gastric mucosal injury is increased with increasing dose of NSAIDs depending on the finding of several epidemiological and placebo controlled studies (43-45), but lower doses of NSAIDs are required to initiate gastric mucosal injury compared to the high doses required for creating the same degree of injury in the mucosa of other parts of GIT.

 **CONCLUSIONS:**

Elderly patients who were taken NSAIDs associated with significant upper GIT bleeding, and their uses were without prophylactic PPI cover in high risk individuals.

**Recommendation:**

1. We have to increase public and physician awareness of NSAIDs side effects ,and limit its usage whenever possible
2. To cover NDAIDs usage with prophylactic PPI in high risk groups

**Reference:**

1. Longstreth, GF. Epidemiology of hospitalization for acute upper gastrointestinal hemorrhage: A population-based study. Am J Gastroenterol 1995; 90:206.
2. Hunt RH, Malfertheiner, P, Yeomans, ND, et al. Critical issues in the pathophysiology and management of peptic ulcer disease. Eur J Gastroenterol Hepatol 1995; 7:685.
3. Hallas, J, Lauritsen, J, Villadsen, HD, et al. Nonsteroidal anti-inflammatory drugs and upper gastrointestinal bleeding, identifying high-risk groups by excess risk estimates. Scand J Gastroenterol 1995; 30:438.
4. Graham, DY, Hepps, KS, Ramirez, FC, et al. Treatment of Helicobacter pylori reduces the rate of rebleeding in peptic ulcer disease. Scand J Gastroenterol 1993; 28:939.
5. Tytgat, GN. Peptic ulcer and Helicobacter pylori: Eradication and relapse. Scand J Gastroenterol Suppl 1995; 210:70.
6. Rokkas, T, Karameris, A, Mavrogeorgis, A, et al. Eradication of Helicobacter pylori reduces the possibility of rebleeding in peptic ulcer disease. Gastrointest Endosc 1995; 41:1.
7. Bayerdorffer, E, Neubauer, A, Rudolph, B, et al. Regression of primary gastric lymphoma of mucosa-associated lymphoid tissue type after cure of Helicobacter pylori infection. MALT Lymphoma Study Group. Lancet 1995; 345:1591.
8. Scheiman, JM. NSAID-induced peptic ulcer disease: A critical review of pathogenesis and management. Dig Dis 1994; 12:210.
9. Bretagne, JF, Raoul, JL. Management of nonsteroidal anti-inflammatory drug-induced upper gastrointestinal bleeding and perforation. Dig Dis 1995; 13 Suppl 1:89.
10. Bjorkman, DJ, Kimmey, MB. Nonsteroidal anti-inflammatory drugs and gastrointestinal disease: Pathophysiology, treatment and prevention. Dig Dis 1995; 13:119.
11. Lanas, A, Perez-Aisa, MA, Feu, F, et al. A nationwide study of mortality associated with hospital admission due to severe gastrointestinal events and those associated with nonsteroidal antiinflammatory drug use. Am J Gastroenterol 2005; 100:1685.
12. Hansen, JM, Hallas, J, Lauritsen, JM, et al. Non-steroidal anti-inflammatory drugs and ulcer complications: A risk factor analysis for clinical decision-making. Scand J Gastroenterol 1996; 31:126.
13. Koch, M, Dezi, A, Ferrario, F, et al. Prevention of nonsteroidal anti-inflammatory drug-induced gastrointestinal mucosal injury. A meta-analysis of randomized controlled clinical trials. Arch Intern Med 1996; 156:2321.
14. Smalley, WE, Ray, WA, Daugherty, JR, et al. Nonsteroidal anti-inflammatory drugs and the incidence of hospitalizations for peptic ulcer disease in elderly persons. Am J Epidemiol 1995; 141:539.
15. Lanas, AI, Remacha, B, Esteva, F, et al. Risk factors associated with refractory peptic ulcers. Gastroenterology 1995; 109:1124.

16 .Sperber AD, Fich A, Eidelman L, et al. Open access endoscopy for hospitalized patients. Am J Gastroenterol 1997;92:1823-6.

1. Sloan, JM. Acute haemorrhage gastritis and acute infective gastritis, gastritis caused by physical agents and corrosives, uraemic gastritis. In: Gastrointestinal and oesophageal pathology, Whitehead, R (Ed), Churchill Livingstone, Edinburgh 1989. p.385.
2. Sloan, JM. Acute haemorrhage gastritis and acute infective gastritis, gastritis caused by physical agents and corrosives, uraemic gastritis. In: Gastrointestinal and oesophageal pathology, Whitehead, R (Ed), Churchill Livingstone, Edinburgh 1989. p.385.
3. Cryer, B, Feldman, M. Cyclooxygenase-1 and cyclooxygenase-2 selectivity of widely used nonsteroidal anti-inflammatory drugs. Am J Med 1998; 104:413.
4. Jick, H. Effects of aspirin and acetaminophen in gastrointestinal hemorrhage. Arch Intern Med 1981; 141:316.
5. Blot, WJ, McLaughlin, JK. Over the counter non-steroidal anti-inflammatory drugs and risk of gastrointestinal bleeding. J Epidemiol Biostat 2000; 5:137.
6. Lanza, FL, Codispoti, JR, Nelson, EB. An endoscopic comparison of gastroduodenal injury with over-the-counter doses of ketoprofen and acetaminophen. Am J Gastroenterol 1998; 93:1051.
7. Lanza, FL. A guideline for the treatment and prevention of NSAID-induced ulcers. Members of the Ad Hoc Committee on Practice Parameters of the American College of Gastroenterology. Am J Gastroenterol 1998; 93:2037.
8. Silverstein, FE, Graham, DY, Senior, JR, et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. Ann Intern Med 1995; 123:214.
9. Simon, LS, Hatoum, TH, Bittman, RM, et al. Risk factors for serious nonsteroidal-induced gastrointestinal complications: Regression analysis of the MUCOSA trial. Fam Med 1996; 28:202.
10. Lim CH, vani D, Shah SG, Everett SM, Rembacken Bj . the outcome of suspected upper gastrointestinal bleeding with 24-hour access to upper gastrointestinal undoscopy: a prospective cohort study. Endoscopy2006 ;38:581-5.
11. Longstreth, GF. Epidemiology of hospitalization for acute upper gastrointestinal hemorrhage: A population-based study. Am J Gastroenterol 1995; 90:206.
12. Garcia Rodrigues LA. Jick H . risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. Lancet 1994;343:769-772
13. Hallas J,Lauritsen L Falsgard Villadsen H Gram LF . non-steroidal anti-inflammatory drugs and uppergastrointestinal bleeding , identifying high risk groups by excess risk estimated . scandJ Gasterenterol 1995;30:438-444
14. Perez –gutthann S,Garcia R odrriguez LA ,Raiford DS. Individual non-steroidal anti-inflammatory drugs and other risk factors for upper gastrointestinal bleeding and perforation . epidemiology . 1997;8:18-24
15. Lanza, FL. A guideline for the treatment and prevention of NSAID-induced ulcers. Members of the Ad Hoc Committee on Practice Parameters of the American College of Gastroenterology. Am J Gastroenterol 1998; 93:2037.
16. C H Lim, RV Healtley . prospective study of acute gastrointestinal bleeding attributable to anti-inflammatory drug ingestion in the Yorkshire region of the United Kingdom .Postgraduate medical journal 2005;81:252-254.
17. Wallace, JL. Nonsteroidal anti-inflammatory drugs and gastroenteropathy: The second hundred years. Gastroenterology 1997; 112:1000.
18. Gabriel, SE, Jaaklimainen, L, Bombadier, C. Risk for serious gastrointestinal complications related to use of nonsteroidal antiinflammatory drugs: A meta-analysis. Ann Intern Med 1991; 115:787.
19. Richy, F, Bruyere, O, Ethgen, O, et al. Time dependent risk of gastrointestinal complications induced by non-steroidal anti-inflammatory drug use: a consensus statement using a meta-analytic approach. Ann Rheum Dis 2004; 63:759.
20. Silverstein, FE, Faich, G, Goldstein, JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: A randomized controlled trial. JAMA 2000; 284:1247.
21. Singh, G, Fort, JG, Goldstsein, JL, et al. Celecoxib versus naproxen and diclofenac in osteoarthritis patients: SUCCESS-I study. Am J Med 2006; 119:255.
22. Graham, DY, Agrawal, NM, Campbell, DR, et al. Ulcer prevention in long-term users of nonsteroidal anti-inflammatory drugs: Results of a double-blind, randomized, multicenter, active- and placebo-controlled study of misoprostol vs lansoprazole. Arch Intern Med 2002; 162:169
23. Lai, KC, Lam, SK, Chu, KM, et al. Lansoprazole for the prevention of recurrences of ulcer complications from long-term low-dose aspirin use. N Engl J Med 2002; 346:2033.
24. Ekstrom, P, Carling, L, Wetterhus, S, et al. Prevention of peptic ulcer and dyspeptic symptoms with omeprazole in patients receiving continuous non-steroidal anti-inflammatory drug therapy. A Nordic multicentre study. Scand J Gastroenterol 1996; 31:753.
25. Hooper, L, Brown, TJ, Elliott, R, et al. The effectiveness of five strategies for the prevention of gastrointestinal toxicity induced by non-steroidal anti-inflammatory drugs: systematic review. BMJ 2004; 329:948.
26. Raskin, JB, White, RH, Jackson, JE, et al. Misoprostol dosage in the prevention of nonsteroidal anti-inflammatory drug-induced gastric and duodenal ulcers: A comparison of three regimens. Ann Intern Med 1995; 123:344.
27. Cullen, D, Bardhan, KD, Eisner, M, et al. Primary gastroduodenal prophylaxis with omeprazole for non-steroidal anti-inflammatory drug users. Aliment Pharmacol Ther 1998; 12:135.
28. Richy, F, Bruyere, O, Ethgen, O, et al. Time dependent risk of gastrointestinal complications induced by non-steroidal anti-inflammatory drug use: a consensus statement using a meta-analytic approach. Ann Rheum Dis 2004; 63:759.
29. Graham, DY, Agrawal, NM, Campbell, DR, et al. Ulcer prevention in long-term users of nonsteroidal anti-inflammatory drugs: Results of a double-blind, randomized, multicenter, active- and placebo-controlled study of misoprostol vs lansoprazole. Arch Intern Med 2002; 162:169.
30. Lai, KC, Lam, SK, Chu, KM, et al. Lansoprazole for the prevention of recurrences of ulcer complications from long-term low-dose aspirin use. N Engl J Med 2002; 346:2033.