Management of Upper Gastrointestinal Bleeding due to NSAID Gastropathy that is Unresponsive to Ranitidine

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ABSTRACT

Non steroidal anti-inflammatory drugs (NSAIDS) are now commonly used in clinical practice. On the other hands, this drug could result severe complication such as bleeding and perforation. In such condition, proton pump inhibitor can be used to stop bleeding than H_2 antagonists.

We reported one cases of upper gastrointestinal bleeding due to NSAID gastropathy that was unresponsive to Ranitidine. The treatment was suitable to proton pump inhibitor that could overcome upper gastrointestinal bleeding.

Keywords: Upper GI bleeding, NSAID Gastropathy, Pantozole, Ranitidine.

INTRODUCTION

Hematemesis refers to black bloody vomiting from the upper gastrointestinal tract. Melena refers to black stool from the upper gastrointestinal tract. The upper gastrointestinal tract covers the part of the gastrointestinal tract proximal to the Treitz ligament, starting from the proximal jejunum, to the duodenum, gaster, and esophagus.[1,2]

Upper gastrointestinal tract bleeding or hematemesis-melena is an emergency in the field of internal medicine. Its prevalence in the United States and Europe is approximately 0.1% with a mortality rate of approximately 10%.[3] The mortality rate at Cipto Mangunkusumo Hospital according to a study from 1987-1988 is 26%.[2] The high mortality rate is very much influenced by the primary illness or condition resulting in bleeding.

In Western countries, 50% of upper gastrointestinal tract bleeding is caused by peptic ulcer.[3] In Indonesia, most bleeding is caused by rupture of esophageal varices or portal hypertension gastropathy due to liver cirrhosis.

Non Steroidal Anti-Inflammatory Drugs (NSAIDs) are now commonly used as a means of treatment. For example, the use of aspirin has developed immediately, since aside from acting as an analgetic antipyretic, it also functions as an anti-platelet aggregation agent. On the other hand, it could also result in gastrointestinal complaints of dyspepsia, ulcer, or even severe complications such as bleeding and perforation.[4] In the United States, the morbidity rate of nausea and dyspepsia related to NSAID use is approximately 50-60%, while 3-4% a year suffer from ulceration complicated by bleeding and perforation.[5]

Upper gastrointestinal tract abnormalities occur due to an imbalance of aggressive and defensive factors according to Shay's balance theory.[6]

NSAIDs could incur damage on the gastric mucosa by way of two mechanisms, the systemic and topical effects.[4,7]

In the systemic pathway, it causes damage through the inhibition of prostaglandin production, particularly

PGE1, PGE2 and PGI2. Prostaglandin inhibition reduces mucosal defense against aggressive factors in the gastric lumen.

NSAIDs also has a topical effect on gastric mucosa, since it acts as a weak acid, thus becoming non-ionized lipid soluble in acidic conditions, which allows it to passively diffuse through the epithelial membrane wall into the epithelial cell. The neutral pH conditions within the cell causes drug dissociation into the ionized non-lipid soluble form, which could no longer freely exit the cell, thus resulting in "ion trapping". A high drug concentration within the cell causes epithelial damage and facilitates re-diffusion of hydrogen ions.[4]

NSAID users may complain of dyspepsia, nausea, vomiting, epigastric pain, or even upper gastrointestinal tract bleeding. There is no correlation between symptoms and endoscopic findings.[4,8] An ulcer may still be detected by endoscopy in the absence of complaints, while according to data from the Division of Gastroenterology of the Faculty of Medicine of the University of Indonesia/Cipto Mangunkusumo Hospital, 30-40% of NSAID users were found without complaints even though NSAID gastropathy lesions have been found per endoscopy.[7]

In the case of NSAID gastropathy, examinations must be performed to ensure a definite diagnosis. Termination of NSAID use could prevent further complications and the mucosal lesion could heal rapidly using conventional medicine.

Proton pump inhibitors permanently bind to H^+, K^+ ATPase enzymes or proton-pumps, thus inhibiting acid secretion. These drugs inhibit 90% of acid production within 24 hours. A cure rate of over 90% is achieved after 4 weeks of use for duodenal ulcer and 8 weeks for gastric ulcer.[8,9]

Short-term treatment using proton-pump inhibitors is safe. Chronic use causes increased serum gastrin levels associated with gastric enterochromaffin cell hyperplasia in humans and gastric carcinoid tumor in rats. However, experience with patients who received PPI treatment for over 5 years has not demonstrated toxicity.[8,9]

A study demonstrated a higher cure rate from all sorts of ulcer with the administration of proton-pump inhibitors (72%) compared to H_2 antagonists (52%).[10]

CASE ILLUSTRATION

A male 58 year-old was admitted to the hospital with a chief complaint of brownish vomiting since the previous day.

Two weeks prior to admission the patient had undergone cataract surgery for his left eye, and was diagnosed with retinal bleeding due to central retinal vein occlusion, and had received 1 x 10 tablets of prednisone, 2 x 80 mg of aspilets, and 3 x 1 tablet of trental. After taking the drugs for 10 days, the patient complained of epigastric pain, heartburn, and nausea.

Since 2 days prior to admission the patient complained of excreting loose tar black stools 6 times a day amounting to approximately 2 glasses/day.

Since 1 day prior to admission, the patient got black bloody vomiting 3 times a day, approximately 2 tablespoons each time, containing food. The patient also complained of generalized weakness, dizziness and paleness.

The patient denied any history of fever, transfusion, intake of rheumatic drugs, painkillers, or traditional herbs. The patient has also smoked 1 pack of cigarettes per day for 35 years.

The patient also denied any history of jaundice, diabetes, heart disease, or previous black vomit and stools. The patient has a history of hypertension since 2 years prior to admission, taking an uncertain type of drug and visited the Public Health Center irregularly.

The patient denied of family history of hypertension, diabetes, and heart disease.

Physical examination during admission revealed the patient to be moderately ill, fully conscious, weak, with a blood pressure of 140/90 mmHg, a pulse rate of 100x/minute, body temperature of 36.70 °C, and a respiratory rate of 20x/minute. No abnormality was found in the head. The patient's conjunctiva were pale, sclera not jaundiced; ear, nose, and throat normal. The patient's jugular venous pressure was 5 – 2 cmH_2O. Heart examination revealed a normal size, normal first and second heart sounds, without murmur or gallop. Lung examination revealed a sonor percussion sound, vesicular breath sound, no rales or wheezing. Abdominal examination revealed an undistended abdomen, no epigastric tenderness, no ascites, while the liver and spleen were not palpable and bowel sounds normal. The patient's extremities were warm and not edematous. There were no liver cirrhosis stigmata such as spider nevi, ascites, caput medusa, splenomegaly, collateral vein, and palmar erythema. Rectal touche revealed normal anal sphincter tone, while the ampulla was not collapsed, there was no mass, and black feces were found on the gloves.

Laboratory results were as follows: hemoglobin level 9.7 g/dl, white blood cell count 29.500 / ul, red blood cell count 3,05 million / ul, hematocryte level 27 vol %, platelet

count 369,000 / ul. Ureum level was 131 mg/dl, and creatinine level 1.3 mg/dl. Cito blood sugar was 129 mg/dl. Sodium level was 130 mEq, potassium level 4.3 mEq. Urinalysis revealed a urinary pH of 6, with no presence of protein, glucose, ketone, blood, or bilirubin. Urinary white blood cell was 2 – 4 /large microscopic view, while urinary red blood cell was 1 – 2/large microscopic view. There was no cylinder, crystals, or bacteria in urinary sedimentation.

Electrocardiography demonstrated sinus rhythm, a QRS rate of 100 times/minute, normal axis, without right or left ventricular hypertrophy and no ST changes or T wave.

Chest x-ray demonstrated a cardiothoracic ratio of <50%, no infiltrates, and aortal elongation.

The patient was asked to fast, and the following treatment was procured: a nasogastric tube was inserted, and spooling with ice water was conducted every six hours and if two spoolings revealed no blood, the nasogastric tube may be removed and the patient may gradually receive gastric diet I. The patient was also scheduled for enema in the mornings and afternoons, and was given 2 x 1 vial of ranitidine injection and 4 x 1 tablespoon of sucralfate per nasogastric tube. Transfusion was administered according to the results of complete blood check. In addition, 500 cc of NaCl 0.9 % was administered every 8 hours due to mild hyponatremia.

On the second day of care, the patient still had approximately 250 cc of black feces, and 100 cc of bleeding was obtained from the nasogastric tube. There was a hemoglobin level reduction from 9.7 to 9.1, and even though the patient had received 200 cc of packed red cells, the patient received 400 cc more. Liver function test results and CHE were within normal limits. Protein evaluation revealed mild hypoalbuminemia, while cholesterol and triglyceride levels were within normal levels.

On the third day, there was still 100 cc of bleeding from the nasogastric tube and 200 cc of black feces.

On the fifth day, the hemoglobin level had increased to 12.3 from 8.5 g% after 500 cc of packed red cell transfusion. Endoscopy revealed ulcerative esophagitis suspected to be due to gastroesophageal reflux disease, moderate erosive gastritis, and duodenal ulcer. The gastroenterology division recommended the administration of 2 x 10 mg of rabeprazole, 3 x 5 mg of cisapride, 4 x 1 tablespoons of sucralphate solution, and the termination of ranitidine. The patient was to undergo endoscopic evaluation after four weeks of treatment.

On the seventh day, results of hepatitis serology testing were obtained as follows: negative HbsAg, and negative anti-HCV IgM. The patient also underwent IgG anti-Helicobacter pylory testing with negative results. The opthalmology department was consulted, and recommended the administration of 3 x 1 tablet of trental and 4 x 2 drops of cendoxitrol for the left eye. Funduscopy revealed good condition of the right ocular fundi, while the left is a bit cloudy, with a round papil with weakly defined borders, as well as bleeding and fibrosis of the retina. Ureum and creatinine tests were repeated, demonstrating an improvement where the ureum level dropped from 131 to 21, and the creatinine level fell from 1.3 to 0.9, resulting in an increase in calculated CCT from 54 to 80. Repeat electrolyte also demonstrated an improvement with a sodium level increase from 130 to 145.

On the eleventh day, the patient no longer suffered from black stools and vomiting, and the patient was released and required to come for regular visits to the out-patient clinics from the gastroenterology, renal hypertension, hematology, and opthalmology departments. The patient was scheduled for a hepatic ultrasound during his visits.

On the fourth week, an endoscopic examination was performed as evaluation, revelaing improvements of the condition of the upper digestive tract and a remaining scar in the duodenum.

Anatomic pathology evaluation of the tissue obtained from the antrum of the gastric mucosa concluded that the patient had a non-active, non-atrophic chronic gastritis with negative helicobacter pylori.

DISCUSSION

The patient is a fifty-nine year-old male who suffered from hematemesis melena, with a history of ten days of aspilet and prednisone use due to occlusion of his left central retinal vein. Literature mentions that non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin play an important role in causing damage of the gastrointestinal mucosa. An endoscopic survey revealed a high prevalence rate of gastric and duodenal ulcer in NSAID users of 22% and 3.5% respectively. A case control study demonstrated that the risks of ulcer, bleeding, or gastrointestinal perforation increases 3 to 5 times in NSAID users.[8] This patient took 2 aspilets daily for 10 days, each containing 81 mg of acetyl salicilate acid.

Risk factors for complications due to NSAID use include age of over 60 years, history of ulcer, toxic NSAID use, high doses of NSAID, simultaneous use of

anticoagulants or steroids, extent of NSAID use, female sex, rheumatism or cardiovascular disease, helicobacter pylori infection, smoking, and alcoholism. In this patient, the risk factors were smoking and simultaneous use of NSAID and steroid.[11]

The differential diagnosis for hematemesis melena in this patient is esophageal varices rupture due to hepatic cirrhosis. However, no cirrhotic stigmata was clinically found, and laboratory examination demonstrated a liver function within normal limits, and negative hepatitis serology, while hepatic ultrasound did not reveal signs of liver cirrhosis and endoscopic evaluation did not reveal esophageal varices. Another possibility is the Mallory Weiss syndrome, usually preceded by severe vomiting, causing a tear in the lower esophageal sphincter.[2] This condition was not found in this patient.

Endoscopic findings of the distal esophagus demonstrated hyperemic ulceration due to ulcerative esophagitis. Such destruction may be due to the consumption of certain drugs, one of which is NSAID (the condition is called pill esophagitis). Such esophageal abnormality may cause hematemesis even though the bleeding that ensues is rarely massive.[12]

The patient took a low dose of aspirin for ten days before suffering from upper gastrointestinal bleeding preceded by complaints of dyspepsia and heartburn. Literature states that within few minutes, NSAID consumption is followed by ultra-structural damage of surface epithelial cells of the gaster. Endoscopy would reveal bleeding and erosion of the gastroduodenal epithelium for several hours following NSAID consumption. Most complications due to NSAID use occur within one month of drug consumption.[4]

Histopathological examination from tissue taken from the antrum during endoscopy revealed chronic non-active non-atrophic gastritis, which resembles reactive gastritis due to bile reflux. This is in line with literature that mentions that findings of NSAID gastropathy resemble bile reflux gastritis, where there is foveolate hyperplasia, vascular ectasia, and increased smooth muscle cell fibers.[8]

Histopathological and serological evaluation for helicobacter pylori was performed to determine risk factors for NSAID complications and to determine the etiology of duodenal ulcer in this patient. The examinations did not reveal helicobacter pylori infection. Thus, the patient did not receive eradication treatment.

The first form of treatment in this patient is the management of hematemesis melena while maintaining adequate circulation. A nasogastric tube was inserted to detect upper gastrointestinal bleeding, monitor activity or the severity of bleeding, administer medications, perform gastric lavage, and predict prognosis. An intravenous line was also inserted for preparation for transfusion as well as fluid resuscitation using crystalloid in case of shock.

In addition, drugs were administered to deal with gastric abnormality due to reduced prostaglandin production as well as to reduce gastric acidity, which could aggravate damage of the gastric mucosa.

Sucralphate was also administered. A study demonstrates that sucralphate is able to reduce damage of the digestive tract mucosa due to NSAIDs. However, a larger study by Agrawal et al demonstrated no significant benefit in the use of sucralphate for the prevention of ulcer in NSAID use.[4] Nevertheless, in cases like these where gastrointestinal tract bleeding has occured, sucralphate may be administered to increase defence of the upper gastrointestinal tract.[2]

The patient initially receives ranitidine, but on the fifth day, due to continued bleeding treatment was switched to proton-pump inhibitor. A study demonstrated that proton-pump inhibitors produced a higher average healing rate from various types of ulcers (72%) compared to H_2 antagonists (52%).[10]

The patient also received a pro-kinetic drug, which is good for patients with esophageal abnormality. Endoscopy revealed ulcerative esophagitis, though to be due to NSAID consumption aggravated by esophageal reflux. A study demonstrated that the use of prokinetic agents produced better results compared to placebo in treating esophageal reflux.[12]

H. pylori eradication was not performed in this patient, since there was no proof of H. pylori infection in serological and histopathological examination. In addition, other literature mention that the benefits of H. pylori eradication in NSAID gastropathy is still unclear.[13]

After 4 weeks of treatment with sucralphate, prokinetic agents, and PPI, the patient was re-evaluated by endoscopy, revealing improvements in the upper gastrointestinal tract.

This case was presented to remind us on the need to protect the digestive tract when administering NSAID and the presence of risk factors such as old age, combination with corticosteroids, etc, to avoid side effects that could produce dangerous complications such as gastrointestinal bleeding due to NSAID gastropathy.

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