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Review Article

UPPER GASTROINTESTINAL BLEEDING AFTER OPEN HEART SURGERY IN CHILDREN: A REVIEW

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ABSTRACT

Non-variceal upper GI bleeding is a serious complication in ICU after open heart surgery. This article discusses the risk factors attributed to development of stress ulcer and prophylactic implements that applied in ICU to prevent mucosal damage. We try to review a number of articles that searched this complication.
Our goal is to determine the most effective prophylactic measure and recommend the use of PPI in our ICU protocol.

INTRODUCTION

Definition

Upper gastrointestinal bleeding UGIB is an infrequent but potentially life-threatening complication after open heart surgery [1]. Stress induced mucosal damage or stress ulcer is the main cause of UGIB in infants and young children, while in older children the duodenal ulcer, esophagitis and varices can be attributed to the causation [2].

The stress ulcers are multiple superficial mucosal erosions seen in proximal stomach and may develop virtually in all patients who have severe unremitting stressful insult [3]. However, few patients have clinically significant gastrointestinal GI bleeding in the intensive care unit ICU. Stress ulcer was described, for first time, in 1969 as focal erosions in the gastric fundus were reported during post-mortem examinations in 7 (4.7%) out of 150 critically ill patients. Endoscopic studies reported that 74 – 100% of critically ill patients have mucosal lesions or subepithelial hemorrhage within first 24 hours of ICU admission [4,5].

Pathogenesis

The underlying mechanism of the ulceration is a complex pathology mediated by multifactorial neurohumoral changes; however, all investigators mention that reduced mucosal blood flow and mucosal ischemia is the basic ulcer pathology [6-8].

In general, there are three independent risk factors for clinically significant upper GI bleeding, these are: respiratory failure necessitates mechanical ventilation for more than 48 hours, coagulopathy and pediatric risk of mortality (e.g. sepsis, organ failure, anticoagulation and antiplatelet, burn, neurologic injury, high-dose of corticosteroid and prolong ICU stay) [9,10]. However concerning open cardiac surgery procedures, many factors play a role in development of stress ulcer. These include: prolonged cardiopulmonary bypass time, aortic cross-clamp time, non-pulsatile flow and inflammatory state activation of humoral amplification cascade (complement, fibrinolysis, coagulation and bradykinin-kallikreinin), anticoagulation and hypothermia, need for blood transfusion, re-exploration after postoperative bleeding and hypotention [1,10-15], in addition to high dose of vasoconstrictor inotropes.

These lesions develop within 72 hours up to 10 days of ICU admission in most of the patients. Geissler *et al* [16] reported that gastrointestinal complications are occurring at a mean of 9.3 ± 5.9 days after cardiac surgery in nearly 60% of patients after a primarily uneventful postoperative course. Other investigator claimed that time elapsed after surgery may play a role in ulcer pathogenesis and its severity delineating in two peaks: multiple gastric and /or duodenal ulcerations developed on 5th day, while large and deep duodenal ulcer elaborated on 21st day [15].

The occurrence of overt GI bleeding denotes hematemesis, melena or bloody gastrointestinal aspirate, while clinically

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significant bleeding is an overt bleeding in association with hemodynamic compromise or need for blood transfusion (Cook DJ *et al*, 1994, Cook DJ *et al*, 1994). The overt bleeding comprises only 20 – 25% while asymptomatic bleeding may reach 80 %. It is important to emphasize that variceal bleeding is not included.

Lacroix *et al* (1992) reported 4 patients (0.4%) with clinically significant upper GI bleeding among 984 children admitted to the ICU, while (Choibou *et al*, 1998) reported incidence of 1.6%. Generally, the incidence of upper GI bleeding in pediatrics is similar to that in high-risk adult patients (Behrens R *et al*, 1994). However, higher incidence ranging from 5.5 – 51.8 % has been reported in various studies, mechanical ventilation is attributed to higher figure (Ombeva OM *et al*, 2013).

Management

The algorithm of non-surgical management of acute upper GI bleeding is shown in Figure (1), which is focused on profound acid suppression (Kim J).

The intensivist applies Rockall scale as a prognostic tool to predict the risk of re-bleeding and mortality for the adult patients presented with upper GI bleeding using both clinical and endoscopic criteria, see Table (1) (Kim J). We put this scale here to gain more informative description about this problem.

However, a corresponding scale for pediatric age group has not established yet. The prophylactic medications are directed to suppress or neutralize gastric secretion. Specific regimens designed to enhance gastroduodenal mucosal resistance or promote epithelial regeneration, which may be efficacious. See Table (2) and (3).

Evidence-based standard of care pediatric dosages for these medications are not well established. Dosages listed are taken from Pediatric Lexi Drug Online Formulary. They do not necessarily apply to neonates or infants younger than 3 months of age. Higher doses may be used by individual pediatric gastroenterologist based on peer-reviewed published case series and personal experiences. Ranitidine and famotidine dosages may be adjusted downward for patients who have renal impairment.

The investigators put these points forward regarding comparison between H2RA and PPI [8,24]:

- The anti-secretory effect of ranitidine is progressively decreased with continuous intravenous infusion over time and intragastric pH monitoring demonstrates that 70% of patients have pH more than 4 in the first 24 hours while the percent decreased to 26% in third day of the infusion. In contrast, continuous infusion of PPI maintained the intragastric pH over 4 in all patients for more than 72 hours.

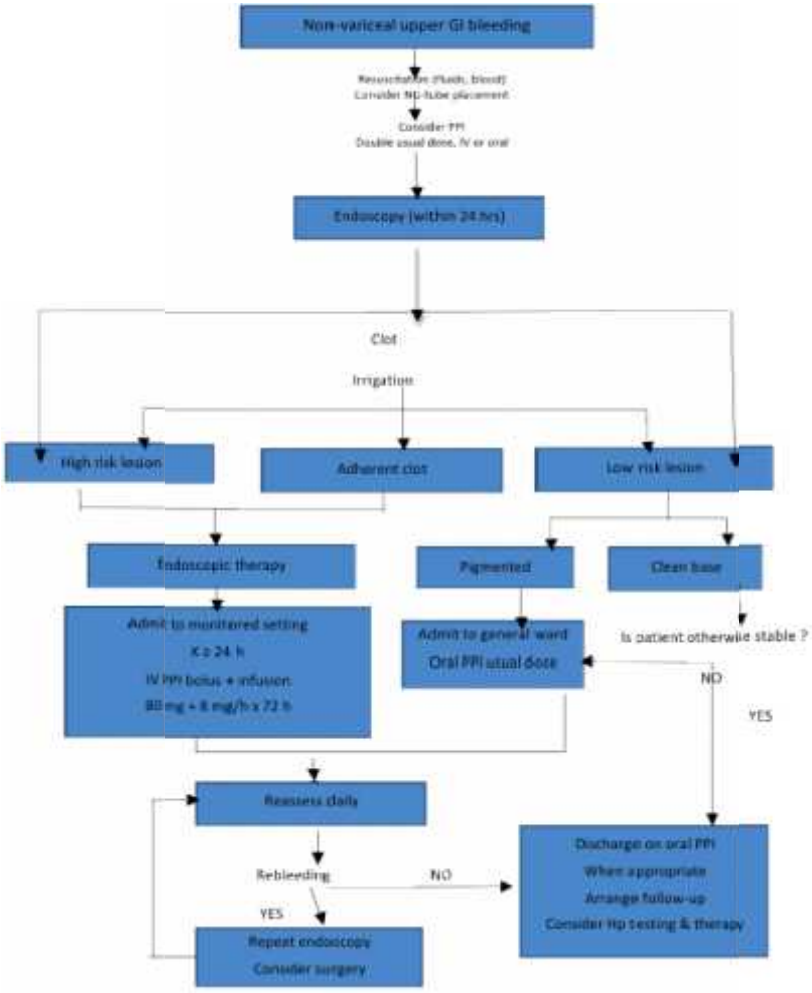

Figure 1 Algorithm for non-surgical management of non-variceal upper GI bleeding (Gralnek IM *et al*, 2008).

Table 1 Rockall scale for assessment of upper GI re-bleeding (Gralnek IM *et al*, 2008)

The score ranges from 0 -11, with higher score indicates higher risk. ≤ 2 low risk, 3 -7 moderate risk, ≥ 8 high risk.

Table 2 Medications used in stress ulcer prophylaxis.

Drug	Mechanism of action	Advantage	Disadvantage
Oral adhesive protection (Sucralfate)	Forming physical barrier	More effective than palcebo	Impairs absorption of enteral feeding and co-administered oral medicine. Risk of bezoar formation.
Histamine-2 receptor antagonists (H2RA)	Inhibits competitively histamine-2 receptors of gastric parietal cells	Significantly reduces clinically significant bleeding than placebo.	Tachyprophylaxis.
Proton pump inhibitors (PPI)	H/K ATPase inhibition of gastric parietal cells.	No tolerance. More effective than H2RA.	? Nosocomial pneumonia.

- By disturbing pH gastric barrier and its bactericidal action, this will lead to development of infections particularly ventilator-related and *Clostridium difficile* infection.
- The risk of nosocomial infection will be increased by1.89 fold in those patients taking PPI versus those who have stopped using PPI, although open heart surgery may be a confounding factor in this association.
- The issue of stomach colonization may particularly be relevant for enterally fed patients, as enteral feeding per se may be a risk for nosocomial infections [8].
- The PPI are effective in adequately suppressing gastric acid secretions, regardless of *Helicobacter pylori* infection status.
- Risk of GI bleeding will be lower in patients receiving PPI compare to group of no prophylaxis or those patients using H2RA.
- Higher rate of active gastrointestinal ulceration in H2RA in opposite to PPI (21.4 %vs 4.3%) following cardiac surgery.
- The evidence for H_2RA in preventing GI bleeding shows no clear benefit with no clinical outcome.
- Gastric ulceration is a common gastrointestinal complication in spite of regular H_2RA use.
- H_2RA may augment the immune system and reduce stress following cardiac surgery but PPI appear to be the superior agent for prophylaxis against gastrointestinal bleed in patients undergoing cardiac surgery.

Table 3 Drugs doses used in upper GI bleeding prophylaxis [23].

Indication	Category of Drug	Dosage
Active Bleeding		
Intravenous Inhibitors of Gastric Acid Secretion		
Ranitidine	Histamine $_2$ Antagonist	Continuous infusion, 1 mg/kg followed by infusion of 2-4 mg/kg per day. Bolus infusion, 3-5 mg/kg per day divided every 8 hours.
Pantoprazole	Proton pump inhibitor	Children <40kg: 0.5-1 mg/kg per day IV once daily Children >40kg: 20-40 mg once daily (maximum, 40mg/day)
Intravenous Vasoactive Agents		
Octreotide	Somatostatin analog	1mcg/kg bolus (maximum, 50 mcg) followed by 1 mcg/kg per hour May increase infusion rate every 8 hours to 4 mcg/kg per hour (maximum, 250 mcg per 8 hours) When bleeding is controlled, taper 50% every 12 hours. May stop when reaches 25% of starting dose.
Vasopressin	Antidiuretic hormone	0.002-0.005 units/kg/minute every 12 hours, then taper over 24-48 hours (maximum, 0.2 units/minute)
Prevention of Rebleeding		
Oral Inhibitors of Gastric Acid Secretion		
Ranitidine	Histamine$_2$ antagonist	2-3 mg/kg per dose twice or three times a day (maximum, 300 mg/day).
Famotidine	Histamine$_2$ antagonist	0.5 mg/kg per dose twice daily (maximum, 40 mg per day).
Lansoprazole	Proton pump inhibitor	1-1.5 mg/kg per day once to twice daily (maximum, 30 mg twice daily).
Omeprazole	Proton pump inhibitors	1-1.5 mg/kg per day once to twice daily (maximum, 20 mg twice daily)
Oral adhesive Protection of Ulcerated Mucosa		
Sucralfate	Local adhesive paste	40-80 mg/kg per day in 4 divided doses (maximum, 1000 mg/dose in 4 divided doses).
Oral Prevention of Variceal Rebleeding		
Propranolol	Reduced mesenteric blood flow (beta-adrenergic blocker).	1 mg/kg per day in 2-4 divided doses. May increase every 3-7 days to maximum of 8 mg/kg per day to achieve a 25% reduction from baseline pulse rate

Octreotide, a somatostatin analog, is standardly used to reduce the risk of bleeding from esophageal varices [25].
Antacid should not be used in ulcer prophylaxis [26].

Early enteral feeding, within first 24 hours, was proved to be the only independent protective factor associated with gastrointestinal bleeding. Those patients who have been subjected to early enteral feeding have lower rate of bleeding and it was effective in preventing stress ulcer bleeding [26,27]. Liquid nutrient buffers gastric acid by alkaline pH of the food, increases mucosal blood flow and enhances secretion of cyto-protective prostaglandins and mucus [28]. In addition, postpyloric delivery may still prevent development of stress ulcerations. So, routine drug prophylaxis should not be used in patients with enteral feeding [26].

When the diagnosis of stress gastric ulcer is made, an intensive medical program in accordance with severity of bleeding is begun. A nasogastric tube is used to serve as a monitoring device to assess the degree of continuing hemorrhage. The medical therapy includes intravenous PPI, red blood cells and fresh frozen plasma transfusion is initiated although these supportive treatments are not always efficient in stress ulcer treatment. Endoscopic therapies are generally recommended as the first-line treatment for upper GI bleeding as it has been shown to reduce recurrent bleeding, need for surgery and mortality rate [29]. Hemoclips, injection of adrenaline or sclerosant and thermo-coagulation are the most commonly used procedures of endoscopic hemostasis for control of GI bleeding. In case of severe re-bleeding or failure of medical and endoscopic treatment, angiography and transcatheter embolization provides a non-operative modality of treatment, keeping in mind procedural age limit [30,31]. Otherwise the patients should be referred to surgical exploration which is seldom required for bleeding gastritis. Interference in form of gastrectomy, total or subtotal, is an effective procedure when hemorrhage is severe. It has the advantage of ablation of all or most of the bleeding sites; however, it attends significant morbidity and mortality [6,22].

This review article highlights the usage of PPI prophylaxis against stress ulcer.

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