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Stress Ulcer Prophylaxis

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EDITORIAL

Stress ulcer is a broad spectrum of the pathologic condition of the acute, erosive, inflammatory change on the upper gastrointestinal tract (UGIT) which is associated with critical illness. Stress ulcer is also called stress-related mucosal damage (SRMD) [1] Stress ulcer can cause profound upper gastrointestinal bleeding (UGIB) which result in death, thus now stress ulcer prophylaxis (SUP) become the standard care in the intensive care unit (ICU) [2]. The author tried to retrace the historical concept regarding stress ulcer.

Some Patients Died from UGIB, Not Their Own Admission Diseases Such as Burn

At 1842, Curling reported 8 patients who died from UGIB during hospital stay ranged from few days to nearly one month. They initially admitted with a major burn. Upper GI tract ulceration (especially in the duodenum) was found at postmortem examination [3]. At 1867, Billroth reported a fatal peptic hemorrhage after a thyroid operation [4]. Till, 1950, similar autopsy reports were followed continuously [5] [6].

Stress Ulcer Was Named and it Was Fatal

At 1950, Hans Selye used the term “stress ulcer” at first and this term became popular [7]. Although the cause of a stress ulcer was not clear, the association between adrenocortical axis adaptation against stress and UGIT ulcer was suggested by H.Selye. At 1966, Fogelman reported 88 cases with stress ulcer, and the mortality was 58% (51/88) [surgery (n = 30), mortality 53%, trauma (n = 20), mortality 45%, and miscellaneous (n = 38), mortality 68%)]. Until then, the surgical approach was regarded as the primary treatment considering that most stress ulcers were single site ulcers [8].

Incidence is 5% and an Important Cause is Increased Acid Secretion

At 1969, Skillman collected the data of 150 consecutive ICU patients, wherein 8 patients (5.3%) experienced the massive hemorrhage because of the acute multiple gastric ulcers [9]. In addition, gastric secretory studies indicated that increased acid secretion may be an important cause for the stress ulcer evolution. Followed studies also showed the similar results with excessive gastrin stimulation of parietal cells [10-12].

Pharmacologic Prophylactic Acid Suppression for Stress Ulcer was Effective

At 1978, Hastings and Skillman performed a randomized controlled trial (RCT) whether neutralization of gastric acid by the use of H2 receptor blocker or antacid drugs prevent stress ulcer or not. Significant UGIB was 4% (2/51) among the intervention group while it was 25% (12/49) among the control group ($p < 0.005$) [13].

Pharmacologic Prophylactic Acid Suppression for Stress Ulcer was Harmful

However, because gastric acidity is a defensive mechanism to pathogenic organisms, acid-suppressive treatment may be associated with increased pathologic colonization in the UGIT. This implies the increased chance for the nosocomial infection. Especially, hospital-acquired pneumonia (HAP) and C.difficile infection have become the major concerns. Gastric acid is an important defense against the acquisition of C.difficile spores. Herzig reported that acid-suppressive medication is associated with HAP occurrence [4.9% in 32,922 acid-suppression group vs. 2.0% in 30,956 no acid–suppression group, propensity-matched odd ratio (OR) of 1.3 (1.1-1.4)] [14]. Adjusted OR (AOR) of proton-pump inhibitors (PPI) group (n = 25,374) was 1.3 (1.1-1.4), while that of H2 receptor antagonists group (n = 5,686) was 1.2 (0.98-1.4) [14]. Cunningham et al. reported that PPI is associated with C.difficile-associated diarrhea [OR 2.5 (1.5-4.2)] [15]. Dial et al. reported that PPI is associated with C.difficile diarrhea [AOR 2.1 (1.2-3.5)], but not H2 blocker [AOR 1.1 (0.4-3.4)] [16].

It is Time for Weighing the Benefit-Risk-Cost for Prophylactic Acid Suppression for Stress Ulcer

5 RCTs regarding PPI vs. placebo showed no significant difference in UGIB, VAP, C.difficile diarrhea incidence [17-21]. To evaluate this issue further, the Reevaluating the Inhibition of Stress Erosions (REVISE) study was begun and recently the pilot result was published [22]. For clinically important UGIB, the incidence was 6.1% in PPI group (n = 49) vs. 4.8% in placebo group (n = 42). It was 20.4% in PPI group vs .14.3% in placebo group for ventilator-associated pneumonia and 2.0% in PPI group vs. 2.4% in placebo group for prevalent C.difficile infection. Hospital mortality was 34.7% in PPI group vs. 31.0% in placebo group. The length of ICU stay was 12 days in PPI group vs. 8.5 days in the placebo group. Although there were no significant differences for outcomes in the pilot study, we guess that the increased morbidity owing to acid suppression therapy will translate to increased mortality (difference of 3.4%).

Enteral Nutrition - Other Option for Stress Ulcer Prophylaxis?

Pharmacologic stress ulcer prophylaxis seems ineffective or even harmful when combined with enteral nutrition. Among enteral nutrition patients, H2 blocker was associated with increased HAP occurrence [AOR 2.81(1.20-6.56)] and increased mortality [AOR 1.89 (1.04-3.44)], while it was not associated with UGIB [AOR 1.26(0.43-3.70)] [23]. Considering that, pharmacologic stress ulcer prophylaxis should be held when patients resume enteral nutrition. Furthermore, Cook, et al. revealed that enteral nutrition is independently associated with lowering the incidence of clinically important UGIB [AOR 0.30 (0.13-0.67)] along with the H2 blocker (ranitidine) [AOR 0.39 (0.17-0.83)] [24]. Raff, et al. compared early enteral nutrition to the H2 blocker (cimetidine) and antacid among burn patients who did not need mechanical ventilation. While UGIB occurred in 9.1% (21/232) in H2 blocker and antacid group, only 3.4% (9/264) experienced UGIB in enteral nutrition group [25]. Further extensive researches are needed regarding this issue, but aforementioned results imply that enteral nutrition may have a potential role in preventing a stress ulcer by itself. If the REVISE study fails to show the benefit of PPI prophylaxis, enteral nutrition may be the other option to be tested for successful prophylaxis against a stress ulcer.

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