A Review of Stress Ulcer Prophylaxis in the Neurosurgical Intensive Care Unit

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Abstract*

STRESS ULCERS OCCUR frequently in intensive care unit patients who have intracranial disease. After major physiological stress, endoscopic evidence of mucosal lesions of the gastrointestinal tract appears within 24 hours of injury; 17% of these erosions progress to clinically significant bleeding. Gastrointestinal hemorrhage has been associated with mortality rates of up to 50% (102, 105, 120, 122). Harvey Cushing reported 11 cases of either GI ulceration, perforation, or hemorrhagic erosion in his postoperative brain tumor patients (24). Subsequently, all GI lesions associated with intracranial disease have borne his name: Cushing's ulcers.
Studies with their focus on neurosurgical patients suggest that stress ulcer prophylaxis is warranted \((1, 5, 11, 13, 33, 34, 41, 43, 45, 47, 55, 56, 58, 66, 68, 71, 73, 99, 112, 128, 130, 142, 143, 145, 148)\). This type of preventive therapy has traditionally been directed toward neutralization of GI luminal acid; several studies have pointed toward a hypersecretion of gastric acid as the source of ulcerations \((5, 24, 36, 55, 93, 143)\). Recent debate concerning the risk of nosocomial pneumonia associated with acid-neutralizing therapy has led to the evaluation of sucralfate in stress ulceration because it does not affect gastric pH \((30, 32, 57)\).

The literature dealing with stress ulcer prophylaxis is vast and conflicting. This review will describe the pathophysiology of stress-related mucosal lesions, define some of the risk factors for bleeding, and summarize the studies concerning stress ulceration in neurosurgical patients. It also seeks to evaluate the efficacy of prophylactic therapy in neurosurgical patients as well as address related issues, such as enteral nutrition, corticosteroid therapy, and nosocomial pneumonia.

**PATHOPHYSIOLOGY**

The pathogenesis of stress ulcers is not completely understood, but studies have indicated that the origin may be multifactorial. There is probably an imbalance between protective and destructive factors. Major destructive factors include acid, pepsin, and bile. Protective factors include adequate mucosal blood flow, the mucus-bicarbonate layer, epithelial cell renewal, and prostaglandins, all part of a normally functioning GI mucosal barrier \((88, 144)\).

**Destructive factors**

The presence of luminal acid is essential for the development stress ulcerations \((62, 63, 85, 89)\). An overproduction of gastric acid is more likely to occur in patients with intracranial disease. Acid and pepsin hypersecretion peak by 3 to 5 days after central nervous system (CNS) injury \((55, 74)\). Several proteolytic enzymes within pepsin may add to the destruction of GI mucosa already damaged by excess acid. The reflux of bile salts, which is commonly found in critically ill patients, is thought to disrupt the gastric mucosal barrier and enhance mucosal injury \((15, 88, 114, 125, 126)\).

**Protective factors**

The first-line defense against GI injury is the thin layer of mucus that is adherent to the superficial mucosa. This gel-like substance is composed of bicarbonate, which depends on normal gastric acid secretion, and a glycoprotein matrix, which serves as a physical barrier to the influx of pepsin and hydrogen ions. This mucous layer can be disrupted by ischemic insults to the underlying mucosa, the result being a change in mucosal...
permeability. Subsequently, an unrestricted influx of hydrogen ions is permitted, which can lead to direct destruction of the gastric mucosa (16, 42). Other factors that can lead to the breakdown of the mucus glycoproteins are fasting states and corticosteroid use (115).

A variety of stressors can cause a reduction in gastric mucosal blood flow, with resultant mucosal ischemia. This leads to a depletion of mucosal adenosine triphosphate energy stores, which disrupts the production of the alkaline mucus layer. This permits the damaging back-diffusion of hydrogen ions. The severity of mucosal injury has been correlated with the magnitude of ischemia and intramural acidosis (37). The buildup of free radical by-products of anaerobic metabolism can promote lipid peroxidation and membrane damage within the mucosal cells (98, 110).

Mucosal protection is also provided by the ability of the surface epithelial cells of the gastric mucosa to quickly replenish normal cell turnover. During periods of stress, the gastric mucosa has a decreased rate of cellular proliferation and deoxyribonucleic acid synthesis. Fasting also decreases ribonucleic acid and protein synthesis in the gastric epithelium. Nutritional support or the use of trophic agents, such as pentagastrin, growth hormone, and epidermal growth factor, may provide the catalysts for mucosal repair and regrowth (134).

Prostaglandins have a variety of actions within the gastric mucosa that may contribute to mucosal protection. These include the stimulation of mucus and bicarbonate secretion by gastric and duodenal mucosa, as well as increasing the gastric mucosal blood flow. Prostaglandins also protect the mucosa from agents, such as aspirin, alcohol, and nonsteroidal anti-inflammatory agents. High concentrations of prostaglandin E₂ and prostaglandin I₂ are normally present in the gastric mucosa. The role of exogenously administering prostaglandins for the prevention of stress-related mucosal damage in the clinical setting has yet to be determined (88).

In summary, the following sequence of events can occur among trauma patients. It begins with an initial episode of hypotension that induces GI mucosal ischemia. Energy stores in the form of adenosine triphosphate are rapidly depleted, hampering the neutralization of back-diffusing hydrogen ions and disrupting the production of the alkaline mucus layer. The formation of mucosal erosions and frank hemorrhage can then occur as a result of this breakdown of the gastric mucosal barrier (15, 16, 42, 49, 62, 64, 84, 126, 127).

**CLINICAL RISK FACTORS**

A number of risk factors that may influence the development of GI bleeding in critically ill patients have been reported. In addition to CNS lesions, these include the following: burns of > 25% body surface area, respiratory failure, hypotension, sepsis, jaundice, peritonitis, coagulopathy, renal failure, and hepatic failure (19, 24, 26, 49, 78-80, 88, 107, 120, 126, 150). The accumulation of risk factors seems to increase the risk of bleeding (13, 16, 42, 49, 62, 64, 84, 126, 127).
Stress ulcer bleeding in patients with head trauma correlates with the severity of injury, regardless of the presence of other risk factors (56).

Brain injury

A neurogenic basis for stress ulcerations was first proposed by Carl Rokitansky in 1841. Premortem ulcerations of the GI system were found in newborns with intracranial tumors, in children and adults with CNS disease, and in patients in cachectic states. Harvey Cushing further elaborated on the subject in his classic work of 1932. He reported 11 cases of either GI ulceration, perforation, or hemorrhagic erosion in postoperative tumor patients. He thought that these lesions arose from the actions of the parasympathetic centers of the hypothalamus with their connections to vagal nuclei in the medulla. Lesions occurring anywhere along this pathway would interrupt normal inhibitory mechanisms, causing unopposed parasympathetic stimulation. This led to abnormal amounts of acid secretion and, consequently, to gastric erosions. Responsible insults included traumatic injuries, infectious diseases (especially of the basal brain), and tumors with an emphasis on cerebellar lesions (24). Cushing's hypothesis was corroborated by laboratory experiments that sought to destroy or stimulate various hypothalamic areas (3, 24, 36). French et al. (38) further demonstrated that an imbalance of autonomic function, originating in the hypothalamus, predisposed patients to gastrointestinal ulcerations. Norton et al. (92) showed that in vitro, direct pressure stimulation of the vagal nuclei resulted in gastric acid hypersecretion. Lewis (73) wrote of the increased frequency of gastroduodenal ulceration and hemorrhage in her review of childhood intracranial diseases. She also postulated that the pathological basis was vagal hyperactivity. The success of vagotomy and pyloroplasty in preventing the recurrence of bleeding or ulceration supported her theory.

Clinical and autopsy studies have indicated the probable existence of Cushing's ulcers in neurosurgical patients. An autopsy review of patients dying of CNS diseases revealed an incidence of hemorrhagic ulcers (12.5%) that was double that found in patients succumbing to non-neurological diseases (58). Gastric hypersecretion of pepsin and acid does occur in neurosurgical patients (11-13, 42, 112). Severe head injury and Glasgow Coma Scale scores of < 9 can lead to gastric acid hypersecretion and hemorrhage rates exceeding 17% (5, 45, 47, 50, 55, 56, 68, 87, 93, 143). Bleeding may be more likely to occur during the first 2 weeks of hospitalization (11, 68). Other relevant risk factors include the following: syndrome of inappropriate secretion of antidiuretic hormone, respiratory failure, age of >60 years, CNS infection, gastric pH value of <4, and hypotension (11-13, 50). As the number of risk factors increases, the cumulative risk of bleeding also rises significantly (13, 87). High mortality rates can occur with GI complications; up to one-third of patients can succumb as a direct result (13). Herein lies the basis for the use of prophylactic measures in neurosurgical patients. Conflicting reports on the efficacy of various preventative medications have emerged, however (11, 13, 47, 68, 87, 112).
GI bleeding may also occur in ischemic stroke patients and may be exacerbated by the use of antithrombotic drugs. The frequency of significant GI hemorrhage is low and does not usually contribute to increased morbidity or mortality in the majority of patients (27, 76, 146). A reduction (from 65 to 6%) in the frequency of bleeding in patients with a Glasgow Coma Scale score of <=10 has been reported in those who received prophylactic cimetidine (76).

**Spinal cord injury**

The incidence of GI ulceration or hemorrhage in spinal cord injury has ranged from 2 to 20% (34, 43, 65, 66, 142). A neurogenic basis for this association, involving a persistence of vagal activity in the absence of sympathetic outflow, has been espoused by many (1, 65, 66, 71, 130, 142). Those patients with cervical cord injuries seem especially prone to developing GI complications, compared with lesions at other levels (65, 71, 130, 142). Again, bleeding usually occurs during the acute phase of injury (within the first 4 wk) and peaks at 4 to 10 days postinjury (43, 71, 142). Other authors have not reported this increase in GI complications with spinal cord injuries; they implicate a multifactorial pathogenesis (33, 66, 71). Similarly, the appropriate prophylactic agent to use in this setting is unknown (148).

**Animal experiments**

Recent experiments have refocused attention on the influence of the brain on gastric pathophysiology. Animal restraint and cold-stress models have been developed that accurately reproduce gastric ulcers (41). Bilateral lesions of the amygdala have ameliorated the degree of stress-induced gastric lesions; bilateral hippocampal lesions can aggravate these types of injuries (51). The CNS effects of various neuropeptides on gastric acid secretion have also been studied. Thyroid-releasing hormone receptors are abundant near the preganglionic neurons of the vagus nerve of the dorsal motor nucleus. An intracisternal injection of thyroid-releasing hormone can cause the hypersecretion of gastric acid, and antibodies to thyroid-releasing hormone receptors can attenuate this gastric response (133). Corticotropin-releasing factor may be a protective component of the stress response because its release in the hypothalamus will decrease gastric acid secretion and increase duodenal bicarbonate production (46). The gastric protective effects, neurotensin, beta-endorphin, and neuropeptide Y, also seem to be mediated by adrenergic systems using dopamine and norepinephrine (52, 60, 70, 97).

**STRESS ULCER PROPHYLAXIS THERAPY**

The optimal method for the prophylaxis of GI complications for neurosurgical patients is a subject of debate. Which one of the available agents is best? What dosing schedules are optimal for maximum benefit? What are
the side effects of these therapies? Most studies on the efficacy of prophylaxis have involved surgical and medical ICU patients. Cautious extrapolation of these results to the neurosurgical population may be appropriate.

**Antacids**

Antacids have been the mainstay of preventive therapy. As previously discussed, gastric acid plays an integral role in the formation of ulcers during stressful conditions. Raising the intragastric pH to 3.5 has been shown to decrease the incidence of bleeding (12, 48). Attaining levels above 4.5 inactivates pepsin, and pH values of 5 and higher neutralize 99.9% of the acid (8). Antacids elevate pH quickly for a sustained period of time. Magnesium hydroxide is more effective in achieving this goal than aluminum or aluminum-magnesium mixtures (91). Increases in dosing and frequency are needed in many cases to produce pH elevation in critically ill patients. However, when these compounds are given in large doses, side effects may result. These include diarrhea or constipation, electrolyte abnormalities, hypophosphatemia (secondary to their phosphate-binding properties), and metabolic alkalosis (91). The primary route of excretion for magnesium and aluminum may also be compromised in renal failure. Aluminum encephalopathy does not result from increased antacid intake (138).

Clinical studies have confirmed the superiority of titrated antacid therapy over untreated control groups in preventing the GI complications in critically ill patients. McAlhany et al. (81) effectively neutralized gastric acid and reduced the incidence of hemorrhage and perforation in patients with burns of > 35% body surface area. Hastings et al. (48) demonstrated that antacid titration of gastric pH values above 3.5 could effectively reduce the incidence of clinical GI bleeding. Meta-analyses of many different clinical studies have also borne out the efficacy of antacid therapy (21, 67, 122, 141).

**Histamine receptor antagonists**

Histamine receptor antagonists (cimetidine, ranitidine, and famotidine) have also been used as prophylactic agents against GI bleeding. The reversible inhibition of parietal cell histamine Type 2 receptors reduces acid secretion. Stimulation of acid production by pentagastrin, pepsin, and food are all suppressed by H₂ blockade in a dose-related fashion (113). The effects of bolus dosing in the case of cimetidine or ranitidine are demonstrable within 30 minutes and keep pH elevated for 3 to 4 hours (95). Continuous infusion regimens are more likely to abolish the peaks and troughs of gastric pH that are seen with intermittent dosing schedules. This achieves a more precise degree of pH control, avoiding the potentially adverse effects of gastric alkalinity (23, 40). Renal excretion is the primary route of elimination of these agents, although hepatic dysfunction may also alter the pharmacokinetics of these drugs (95).
A number of studies have documented the ability of histamine antagonists to decrease GI bleeding in critical care patients, compared with placebo or untreated groups (13, 21, 67, 72, 102, 122). Whether these agents are more effective than antacids for prophylaxis is controversial. H$_2$ blockers are at least equal to the preventive action of antacids (67, 106, 122, 141). With an increased severity of illness and risk factors, antacids seem to hold a slight advantage but these studies were performed mainly with intermittent dosing regimens of H$_2$ blockers (80, 107, 141, 149). It has been shown that continuous infusion protocols control pH better, and when used in such a fashion, they can be superior to control treatments, antacids, or intermittent H$_2$ blockade (23, 59, 75, 78, 90, 101, 109, 117, 123, 136).

Reports of neurosurgical patients are few. In a recent study, CNS injury predicted the poor control of gastric pH in patients receiving continuous infusion ranitidine (41). Rapp et al. (108) reported a failure of continuous infusion ranitidine (6.25-18.75 mg/hr) in maintaining gastric pH > 4 in 12 ICU patients with head injuries. We recently evaluated the effectiveness of continuous infusion cimetidine (50-150 mg/hr) in controlling intragastric pH in 12 patients with head injuries. We found results similar to the above studies (unpublished data).

CNS toxicity with cimetidine occurs in a dose-related fashion in less than 3% of patients (61, 119). Liver and/or renal dysfunction and advanced age are risk factors for the development of this complication. Both cimetidine and ranitidine cross the blood-brain barrier. Serum trough levels of >1.25 µg/ml may be associated with the milder CNS side effects of restlessness, confusion, disorientation, agitation, and visual hallucinations. Levels of >2.0 µg/ml may infrequently produce muscular twitching, seizures, unresponsiveness, and apnea. A reduction in dose or use of other agents in patients with these risk factors avoids unwanted changes in mental status (28, 61, 119, 138).

Other major side effects of H$_2$ antagonists include the inhibition of the cytochrome P$_{450}$ enzyme system, interference with antibiotic activity, hypotension, and thrombocytopenia. Altered hepatic metabolism occurs mainly with cimetidine (138). Important drugs that are affected include theophylline, phenytoin, and warfarin; this necessitates the appropriate monitoring of their use. Rapid bolus administration may cause hypotension, which can be avoided with slower infusion rates (54, 95). Unexplained thrombocytopenia has been reported with the concurrent use of cimetidine and phenytoin (147). We have also observed 12 cases (unpublished data).

Sucralfate

Sucralfate consists of a complex of sucrose, sulfates, and aluminum hydroxide. Its protective effect is exerted through its mucosal strengthening action. Sucralfate binds to normal and defective gastric mucosa, increasing the viscosity and mucin content of the gastric mucus, as well as its hydrophobic characteristics (129).
Experimentally, it has been shown to increase mucosal blood flow in a dose-dependent manner (14). A myriad of other beneficial effects have been reported also, including inhibition of peptic digestion, stimulation of prostaglandin, protection of the mucosal proliferative zone, and facilitation of mucosal regeneration and healing. Bactericidal properties and phosphate binding properties have also been described (139). These all make sucralfate an attractive choice for use in the prevention of Cushing's ulcers.

Recently, Eddleston et al. (32) compared the frequency of acute stress ulceration in 60 ICU patients treated with either sucralfate (1 gm every 6 h) or ranitidine (50 mg intravenously every 6 h). At admission, the frequency of gastric lesions was 13.5%. After 4 days of therapy, the rate had increased to 18% in patients receiving sucralfate and 36% in patients receiving ranitidine. This study included 19 patients with CNS injuries. The investigators recommended the adoption of sucralfate for routine prophylaxis against stress-related gastric mucosal damage (32). In two meta-analyses, sucralfate was found to be as effective as antacids, but significantly more efficacious than H₂ antagonists, in the prevention of clinical bleeding (140, 141).

No major adverse effects of sucralfate have been reported, but aluminum retention in patients with renal failure may occur. This has not been causally linked with aluminum encephalopathy, however (139). Simply dissolving the sucralfate tablet in water before administration eliminates the potential for sorbitol accumulation with slurry formulations. Decreased bioavailability has been reported with a concurrent oral administration of a number of drugs (e.g., quinolone and tetracycline antibiotics, theophylline compounds, phenytoin, antacids, digoxin, and amitriptyline). No perceived reduction in the absorption of these medications is seen if they are given at least 2 hours before sucralfate. The interaction with histamine antagonists does not seem to be clinically significant (82).

RELATED ISSUES

Enteral nutrition

It has been suggested that enteral nutrition plays a role in protection from stress ulceration. The exact mechanism is unclear, but two explanations have been postulated. Dilutional alkalinization may occur when the feeding tube is located within the stomach. Secondly, the maintenance of an adequate nutritional state provides a positive nitrogen balance, which is important for normal reparative functions of the gastric mucosa. A fasting state can result in the disruption of gastric protective factors. The evidence in the literature is somewhat conflicting. Kuric et al. (66) retrospectively showed that enteral nutrition was associated with a significantly lower incidence of ulceration in patients with spinal cord injuries. Cannon et al. (9) did not report any differences in GI bleeding in patients who received enteral alimentation. A potential concern of gastric flora colonizing the trachea and causing nosocomial pneumonia has been raised (104). Further study is
necessary to establish the significance of enteral nutrition as a protective factor against stress-induced GI hemorrhage.

**Steroids**

Steroids may exert their deleterious effects on the GI tract by the gastric inhibition of mucus secretion, epithelial proliferation, and prostaglandin biosynthesis (4, 25, 29). Currently, steroid use in the neurosurgical ICU is limited mainly to patients with brain tumors or spinal cord injuries. The results of three meta-analyses revealed a very low incidence of steroid-induced GI complications (17, 18, 86). The consensus states that the duration of steroid therapy of > 3 weeks and dosing regimens of > 400 to 1000 mg/day of prednisone (or 10 mg, 4 times a day, of dexamethasone) increase the incidence of toxic effects (17, 86, 121, 145). Even high doses of up to 100 mg/day of intravenously administered Decadron for short periods of time (<3 weeks) have minimal side effects (6, 7, 44, 94, 96, 99, 128).

Marshall et al. (77) reported an increased risk for GI complications in patients with a history of peptic ulcer disease who undergo steroid therapy. Other conditions, such as renal or hepatic dysfunction and hypoalbuminemia (possibly associated with inadequate nutrition) may cause increased amounts of unbound steroid with potentially adverse effects (29, 145). The concurrent use of steroids and ulcerogenic medications, such as aspirin or nonsteroidal anti-inflammatory agents, may increase the risk for the development of ulcers (10, 22, 29, 39). Patients with connective tissue disorders, especially rheumatoid arthritis, often fall into this category. Ulcers that develop because of steroid therapy are no more likely to perforate or hemorrhage than controls (135). Decreasing the dosage or discontinuing the steroid dose should reverse symptoms when they occur. Patients receiving chronic steroid therapy should receive GI prophylaxis. Those receiving short-term steroid therapy probably do not need preventive measures unless risk factors are present.

**Nosocomial pneumonia**

A body of evidence has accumulated concerning the increased incidence of nosocomial pneumonia with the use of pH-altering stress ulcer prophylaxis. Bacteria originating in the oropharynx and stomach may play important roles (111, 118). When the pH of gastric secretions is kept consistently above 4.0, bacterial colonization of the stomach contents rises in a logarithmic manner (2, 20, 31, 53). The concentrations of bacteria may increase by up to 10,000 times, with up to 30% of these pathogens later colonizing the respiratory tract. Radioactively labeled technetium studies have demonstrated that 40% of intubated patients aspirate gastric contents despite their heads being elevated. This confirms previous reports of aspiration despite inflated endotracheal tube cuffs (131). Colonization of the respiratory tract develops into pneumonia in up to 60% with gram negative and
20% with gram positive organisms. The exact mechanism in the development of nosocomial pneumonia is still unclear (111, 137).

Comparative studies of the rates of nosocomial pneumonia, using the three preventive drug regimens, yield conflicting results. One confounding variable may be the lack of universal criteria for diagnosing nosocomial pneumonia. Several clinical studies have shown an increased risk for pneumonia with pH-alkalinizing therapies (30, 32, 57). Driks et al. (30) suggested that sucralfate decreased the incidence of pneumonia when compared with antacids but not to H₂ blockers. Two separate meta-analyses have also shown lower rates of pneumonia with sucralfate (21, 141). Individual studies have not confirmed this benefit (35, 78, 103). Fabian et al. (35) did not report a direct association between pH alkalinization and pneumonia, but a multivariate analysis revealed the following: Glasgow Coma Score, Injury Severity Score, spinal cord injury, shock, and head injury as risk factors for pneumonia development. The association of pneumonia with pH-altering therapy has not been firmly established. Further large-scale trials will be necessary before a definitive answer is found.

Gastric monitoring

The standard methods for assessing the efficacy of GI prophylaxis include sampling for intragastric pH and detecting for the presence of occult bleeding. These parameters may be intrinsically flawed. Layne et al. (69) found that acid adversely affected the sensitivity of Gastroccult (Smith Kline, San Jose, CA) results and required neutralization before interpretation. Commercial antacids may help neutralize gastric acid, but they interfered significantly with the detection of blood. Rosenthal et al. (116) confirmed that a dark-blue result on Gastroccult testing was the only accurate predictor of blood in low pH conditions (116). The Hematest and Bililabstix (Bayer Corp., Elkhart, IN) were too sensitive because only a few red blood cells were enough for a positive result. Meiners et al. (83) found gastric luminal pH samples overestimated the mucosal pH when obtained during an antacid administration. Measurements of luminal and mucosal pH taken during parenteral cimetidine therapy correlated well, however. Based on these reports, monitoring for clinical bleeding seems to be a more effective parameter than the detection of occult bleeding, which may be too sensitive or may be altered by antacid therapy. Indicator paper should continue to be used for measurements of pH but interpreted cautiously when used concurrently with antacid therapy (83).

Surgery

When prophylaxis has failed and GI bleeding occurs, there are a series of steps that may be instituted in an attempt to control the hemorrhage. Iced saline lavage is commonly used as a first step, controlling 80% of bleeding episodes (74). Other reviews have also reported that bleeding stops spontaneously with these conservative measures in the majority of cases (100, 132). Some reports have espoused the use of titrated
antacids to keep gastric pH greater than 7.0 in these critically ill patients. Intravenously administered vasopressin should probably only be used as a temporizing measure because of its damaging ischemic effects on the gastric mucosa (125). Pharmacological therapy has otherwise been ineffective in stopping the hemorrhage (100). Arteriographic embolization is hazardous, with gastric and splenic necrosis being potential side effects (125).

Endoscopic intervention has been evaluated in the management of acute GI bleeding. In a recent review of this type of therapy, several facts have emerged. No statistically significant benefits with regard to outcome were garnered. Lesions were usually not amenable to thermal coagulation. Its unproven cost-effectiveness, a 3 to 5% complication rate, and better results when intervention was delayed until rebleeding occurs make this intervention controversial. Some valid reasons for endoscopy do exist, however. Hemodynamically significant rapid bleeding demands urgent endoscopy for the identification of active bleeding sources. These lesions and any nonbleeding vessels or clots originating from ulcer craters that are visualized should undergo thermal intervention, leaving other lesions alone until rebleeding occurs. Age of > 60 years, major associated diseases, inpatients with GI hemorrhage, and rebleeding episodes are included in the National Institutes of Health criteria for endoscopic hemostatic intervention (100, 132).

When all measures have failed, surgical intervention is indicated. The majority of opinions favors vagotomy with pyloroplasty and ligation of bleeding points (74, 88, 125). Partial gastrectomy with its increased mortality risk is used only if there is diffuse bleeding or other associated critical illnesses (74, 88).

CONCLUSION:

A central theory linking the brain and upper GI tract emerges from a review of the available literature. Intracranial diseases, especially those that have a significant impact on the diencephalon and brain stem, may cause a disinhibition of the medullary vagal system. This leads to the hypersecretion of gastric acid and pepsin. Simultaneously, stress-induced alterations in neuropeptide levels within the brain may also indirectly affect GI functioning. At the mucosal level, these dual actions may cause an imbalance between destructive and protective mechanisms, ultimately leading to erosions and hemorrhage.

Several clinically relevant risk factors for the formation of stress-related mucosal damage have been reported. Diencephalic and brain stem injuries are more likely to be associated with the presence of erosions or ulcerations in the GI tract. These insults may result from severe head injuries (Glasgow Coma Scale score of < 9), infection, tumors, or hemorrhagic events. Cervical spinal cord injuries may also be a predisposing factor along with others such as hypotension, ventilator dependence, renal or hepatic dysfunction, and thrombocytopenia. An additive effect is seen with an increasing number of risk factors.
Antacids, $H_2$ antagonists, and sucralfate are all effective prophylactic agents for stress-related mucosal damage in the medical/surgical ICU. Antacids given in doses titrated to intragastric pH values have been proven to be superior to placebos, yet their administration is time-consuming. Continuous infusion cimetidine is superior to intermittent $H_2$ blockade, antacids, and sucralfate in the control of gastric pH, but it is ineffective in the context of severe CNS injury. The incidence of pneumonia seems to increase with the use of pH-altering therapy. Hence, the bactericidal properties and subsequent role in the prevention of nosocomial pneumonia, as well as its proven superiority to $H_2$ blockers, make the use of sucralfate very attractive.

Routine prophylaxis with steroid use is not warranted except when certain risk factors are present: a prior history of peptic ulcer disease, concurrent use with aspirin or nonsteroidal anti-inflammatory drugs, renal or hepatic dysfunction, and malnourished states. Only patients who were administered steroids for > 3 weeks and daily doses of dexamethasone (> 40 mg/d) seem to be at increased risk for GI side effects.

Stress ulcer prevention plays an important role in the aggressive critical care of neurosurgical patients. Certain inferences from studies conducted in medical and surgical ICUs are applicable. The proven superiority of sucralfate and titrated antacids to $H_2$ blockers in the prevention of GI erosions and hemorrhage exists. Titrated infusion of $H_2$ blockers has been used unsuccessfully in the manipulation of gastric pH in head-injured patients. Whereas antacid use has certain drawbacks, sucralfate may be able to diminish the incidence of nosocomial pneumonia. In theory, these data would support the initial use of sucralfate in neurosurgical patients. Surveillance for overt clinical bleeding rather than occult hemorrhage seems to be a more efficient use of resources, with prompt endoscopic evaluation of clinical bleeding. At this point, either the further stepwise addition of antacids and $H_2$ blockers or aggressive surgical intervention should reduce the consequences of this type of GI hemorrhage.

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COMMENTS

Gastrointestinal stress ulcerations are of special importance to neurosurgical patients, who are particularly prone to this complication. In this exhaustive review, Lu et al. detail the salient pathogenic features of stress ulcers and review the various therapies available for prophylaxis. As the authors point out, the incidence of gastrointestinal bleeding can be reduced (but not eliminated) by careful attention to these treatment parameters.

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Lu et al. provide a valuable review of the pathophysiology of stress ulceration and an initial approximation of treatment schemes. As the authors clearly stress, these schemes have centered on the neutralization of hypersecretion of gastric acid. Sucralfate, H2 antagonist (especially when given as an infusion), and antacids all are effective at least in some studies in the prevention of gastrointestinal hemorrhage.
Unfortunately, the only prospective, randomized, double-blind study of which I am aware in neurosurgical patients is that by Chan et al. (1). To truly provide relevant information in our neurosurgical patients, these are the subjects that must be studied. The pathophysiology, as suggested by the authors, is indeed different. Clearly, common factors still exist, such as gastric ischemia. The historical use of dehydration therapy in the context of neurosurgical traumatic and nontraumatic disease has probably contributed to hypoperfusion of the gastric mucosa as well as of the brain itself. Maintenance of adequate tissue perfusion of all organs could be expected to improve the overall medical status of the patients, including gastrointestinal integrity.

I do have a question about the recommendation for ice saline lavage. Most gastroenterologists seem to have abandoned this technique as potentially contributing to further ischemia of the gastric mucosa. Similarly, our more current gastroenterological input to this problem has suggested that lavage of the stomach actually dislodges clots and may well contribute to bleeding. I notice that their Reference 74 dates back to 1971.

Also, the aggressive use of interventional radiology, both for the identification of bleeding points and embolization, is somewhat abbreviated and under-represented in this review. If expert interventional radiology is available, good results in terms of hemorrhage control can be achieved quickly and safely in a large number of patients. Similarly, although intravenously administered vasopressin is mentioned in the article, the potential for directed, intra-arterial vasopressin infusion in the control of hemorrhage is not mentioned but may be useful.

Endoscopy is more useful than the authors imply in that it can clearly help in identifying the patient with generalized erosive gastritis and those who are bleeding from erosions actually induced by nasogastric tubes (the majority of patients in some studies) and in actually making a diagnosis of gastrointestinal hemorrhage in patients who are hemodynamically unstable or who have progressive anemia as the result of an unsuspected duodenal ulcer, without regurgitation of blood into the gastric contents.

It is also worthwhile to emphasize again that the use of steroids per se in the majority of patients is not associated with an increased risk of gastrointestinal hemorrhage and does not justify the addition of other drugs, which, in fact, do have their own complications. Because each of the treatment modalities has its own side effects or difficulties, it indeed would be worthwhile to pursue randomized, prospective studies of effective prophylaxis in identified groups of patients at high risk who have neurosurgical diseases.

The assumption that these patients are similar to the general surgical and general medical intensive care unit population is perhaps the best that we can make at the moment but is probably not going to prove the case for the majority of our patients. Given the economic considerations of prolonged stay in the intensive care unit
and mortality and morbidity brought about by hypotension as the result of bleeding, etc., these studies would be very worthwhile to pursue.

Michael J. Rosner

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This is a thoughtful and well-prepared review of stress ulcer prophylaxis. The reader will be especially served by reviewing the conclusions in which the clinical risk factors for stress-related mucosal damage and the advantages and disadvantages of various prophylactic agents are well reviewed. Particularly instructive is the conclusion regarding the concurrent use of routine prophylaxis with steroids; the authors conclude that this is warranted only when other risk factors are present or when patients have been receiving steroids for a long time or in a high-dose regimen.

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The authors provide a comprehensive review of the issue of stress ulcer prophylaxis in critically ill neurosurgical patients. Diencephalic and brain stem injuries with subsequent disinhibition of the medullary vagal system predisposing to gastric hypersecretion is not a new concept. With modern validation of this principle, the wealth of epidemiological information cited by the authors provides compelling evidence that neurosurgeons should offer routine prophylaxis in the majority of intensive care unit patients. The authors also make a substantial argument that agents such as sucralfate may provide optimal protection without increasing the risk of nosocomial pneumonia.

Their comment about the use of routine gastrointestinal prophylaxis in patients receiving steroids, however, is controversial. The authors state that unless risk factors are present, such as a prior history of ulcer disease, concurrent use of aspirin, renal or hepatic disease, or malnourished states, patients do not require prophylaxis unless steroid use is prolonged or the doses are extremely high. This recommendation goes against practice patterns in the majority of areas with which I am familiar.
It seems to me that some form of prophylaxis during steroid therapy provides a reasonably low risk and potentially cost-effective strategy when contrasted with the severity of potential gastrointestinal hemorrhage. Nevertheless, this review should provide a ready resource to practitioners as they consider which agents to employ in various clinical circumstances.

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