Stress Ulcers and Organ Failure in Intubated Patients in Surgical Intensive Care Units

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This study compared prophylactic administration of either intragastric misoprostol (200 μg four times a day), a prostaglandin E_1 analog, or bolus intravenous cimetidine (300 mg every 6 hours) in preventing stress lesions and stress bleeding in 127 adult postoperative patients who required mechanical ventilation and also had developed hypotension or sepsis. Both drug treatments were equally effective in preventing the development of diffuse gastritis (>10 gastric hemorrhagic lesions) and in preventing upper gastrointestinal hemorrhage (UGIH). The combined data from both groups showed that for the 44 (35%) patients who died, death was significantly associated with the presence at study entry of renal failure (64% of 25 patients with renal failure died), hepatic failure (57% of 23 patients) or coagulopathy (62% of 29 patients) ($p < 0.02$ for each), and with the number of organ system failures at study entry (48% of 69 patients with multiple organ system failures died, $p < 0.001$). Death was also significantly associated with the presence of adult respiratory distress syndrome (ARDS) at study entry or the development of ARDS (63% of 24 patients with ARDS died, $p < 0.001$), and the development of UGIH (5% of 93 patients with known bleeding outcome died, $p < 0.05$). The number of stress lesions that developed was significantly associated with subsequent UGIH ($p < 0.001$). Additional organ system failure developed during the study in 31% of the 127 patients, as did diffuse gastritis in 20% of 111 patients who had a follow-up endoscopy. These results demonstrate that postoperative patients who require mechanical ventilation and have hypotension or sepsis are at significant risk for the development of stress gastric lesions and multiple organ system failure even when prophylaxis for stress ulcers is provided. Furthermore, the presence of ARDS, renal failure, hepatic failure, coagulopathy, and UGIH are significantly associated with death.

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HEMORRHAGE FROM STRESS-INDUCED gastric lesions (stress ulcers) was a significant problem in many critically ill surgical patients in the 1960s who had sepsis and evidence of organ failure.[1] Hemorrhage from stress ulcers has been defined as gut failure in the multiple organ failure syndrome[2] and continues to be associated with high mortality rates when it develops postoperatively.[1,2]

The development of postoperative pneumonia is also associated with high mortality rate.[3] The risk of death is significantly associated with pneumonia that develops during mechanical ventilation when evidence of other organ failure is present.[3] Studies[4,5] have recently suggested that prophylactic administration of agents designed to increase gastric pH to decrease the risk of hemorrhage from stress ulcers may increase the risk of the development of pneumonia in patients requiring mechanical ventilation. Only one of these studies showed a significant association between pneumonia and antacid administration; neither study was blinded. These reports have stimulated a reevaluation of prophylaxis of stress-induced bleeding, however. Currently, there is less consensus on what prophylactic treatment is indicated than at any time since Hastings and colleagues[6] demonstrated that antacids decreased the incidence of microscopic bleeding.

This report presents the results from 127 patients from 25 medical centers who were prospectively identified to be at high risk for the development of upper gastrointestinal hemorrhage (UGIH), using previously published criteria,[7] within 2 weeks of a surgical operation, and who also required mechanical ventilation. Although there have been many reports of various methods of preventing UGIH in intensive care unit (ICU) patient populations, few of these controlled studies have examined exclusively postoperative patients who have organ failure and other risk factors associated with bleeding at entry. Even fewer

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Accepted for publication October 11, 1991.

have endoscopically examined gastric mucosa to determine how the development of lesions related to the development of UGIH.

This report examines patients at the brink of the development of multiple system organ failure (MSOF). It also examines how the presence of MSOF influences the development of UGIH and the outcome and development of other complications, including pneumonia, by prospectively recording which other risk factors were present at entry.

Materials and Methods

This was a randomized, double-blind, double-dummy stress ulcer prophylaxis study performed at 25 medical centers in the United States. At each of these institutions, the protocol was approved by the Institutional Review Board. Written informed consent was obtained from the patient or surrogate before study entry. Patients were enrolled between July 1986 and January 1988. Adult men and nonpregnant women in an ICU who had undergone a surgical procedure requiring general anesthesia within 14 days before meeting the other entry criteria were considered eligible. Additionally, patients had to be intubated, require mechanical ventilation support, and experience an episode of either hypotension (systolic pressure < 90 mmHg or require medication to maintain blood pressure) or sepsis (positive blood cultures or clinical evidence of systemic infection) to be considered for enrollment.

Exclusion criteria included psychiatric disorders requiring medication, upper gastrointestinal (UGI) malignancies, inflammatory bowel disease, active peptic ulcer disease, and burns. Also excluded were patients with recent central nervous system damage, head injury requiring neurosurgical intervention, or unstable spinal fractures. Patients who had had UGI surgery proximal to the ampulla of Vater within 30 days and patients not expected to survive at least 14 days also were excluded. Patients receiving nonsteroidal anti-inflammatory agents, anti-ulcer agents, or anti-neoplastic agents as well as those with known allergies to either of the study medications were not eligible.

Once informed consent had been obtained, but before randomization, patients underwent a screening endoscopy. The gastric and duodenal mucosae were graded according to the scoring system presented in Table 1. Patients with a score of 5 or more for either stomach or duodenum were considered ineligible for prophylaxis and were excluded from the study.

Patients who met eligibility criteria then were randomized to receive either active misoprostol 200 μg (G.D. Searle & Co., Skokie, IL), a new prostaglandin E_1 analog, mixed in 20 mL of water every 4 hours through their nasogastric (NG) tube and intravenous placebo every 6 hours, or placebo tablet mixed in water through the NG tube, and active intravenous cimetidine 300 mg (Smith Kline Beecham, Philadelphia, PA) every 6 hours. Patients were studied until one of three events occurred: (1) 2 weeks of ICU management were completed, (2) improvement allowing discharge from the ICU, or (3) the development of significant UGIH. Additionally, patients could be removed from the study if the investigator or the patient's personal physician thought it was in their best interest to do so.

TABLE 1. *Endoscopic Grading System for Gastroduodenal Mucosa*

Grade	Description
1	Normal mucosa or hyperemic changes
2	A single hemorrhagic lesion
3	2–5 hemorrhagic lesions
4	6–10 hemorrhagic lesions
5	Large areas of confluent hemorrhagic lesions
6	Erosions with white bases surrounded by erythematous edges
7	Ulcer craters

Significant UGIH was considered a sign of organ failure and was defined by any one of the following:

1. The occurrence of hematemesis, melena, or hematochezia.
2. The presence of bright red blood in the NG aspirate that did not immediately clear after lavage with 250 mL normal saline.
3. A drop in hemoglobin concentration over two consecutive measurements of at least 2 mg/dL with stools that had positive Hematest (Smith Kline Beckman, Sunnyvale, CA) results that were not attributable to other causes.

The development of UGIH was an endpoint for this study and therefore was not included in any calculations that involved numbers of organ system failures.

Patients meeting the above criteria for bleeding underwent an endoscopic evaluation within 12 hours and were removed from the study if a UGI bleeding source was confirmed. All patients still in the study at 72 hours underwent a follow-up endoscopy to determine whether the condition of the gastric or duodenal mucosa had changed. When possible, patients also underwent an endoscopy on exit from the study. If a patient underwent more than one follow-up endoscopy, the score that represented the most severe damage was used.

Patients were studied for the presence or development of other organ system failures as defined in Table 2. Complications were recorded prospectively using the risk criteria suggested by Zinner et al.[7] Recent publications[4,5] that have emphasized the potential relationship between stress ulcer prophylaxis and pulmonary problems stimulated us to retrospectively review data relevant to this issue as carefully as possible. All the investigators who

TABLE 2. *Definitions of Organ System Failures*

Organ	Definition
Pulmonary*	Mechanical ventilatory support
Renal	Serum creatinine value >3.0 mg/dL
Coagulopathy	Platelet count of <50,000/mm^3 or prothrombin time >30% higher than control level
Hepatic	Bilirubin value >5 mg/dL or transaminase value >3 times the upper limit of normal
Gastrointestinal†	A drop in hemoglobin value of ≥2 mg/dL, hematemesis, melena, hematochezia, or bright red blood via nasogastric tube
Cardiac	Congestive heart failure requiring therapy other than diuretics or digitalis, or myocardial infarction
Adult respiratory distress syndrome‡	Hypoxia that required ventilator support for >72 hr

* Required for study inclusion.
† This was an endpoint for the study and thus was not included in calculations of organ failure.
‡ Ongoing need for ventilatory support (see text) or reintubation for pulmonary problems was considered a new sign of organ failure.

TABLE 3. *Clinical Characteristics of Patient Populations on Admission*

Characteristics	Misoprostol (n = 63)	Cimetidine (n = 64)
Age (mean ± SD)	60.2 ± 15.2	59.9 ± 17.5
Sex (M/F)	39/24	40/24
White/nonwhite	51/12	46/18
Risk factors at entry		
Hypotension	52	53
Sepsis	47	48
Coagulopathy	15	14
Renal failure	13	12
Hepatic failure	11	12
Cardiac failure	9	13
Adult respiratory distress syndrome	6	8
No. of gastric lesions		
None	15	19
1–5 hemorrhagic lesions	24	30
6–10 hemorrhagic lesions	23	13
Unknown	1	2
No. of duodenal lesions		
None	60	61
1–5 hemorrhagic lesions	1	0
Unknown	2	3

submitted data to this study made a distinction between patients requiring short-term postoperative ventilatory support and those who had additional complicating conditions such as pneumonia or adult respiratory distress syndrome (ARDS). Bronchial culture data, however, were not routinely collected and, therefore, diagnostic criteria for pneumonia were inconsistently available. We therefore chose to classify as ARDS cases those patients who developed both of the following features:

1. They were labeled by their investigator as having either pneumonia or ARDS; and
2. They required either initial ventilatory support for more than 3 days or required reintubation.

Statistical Analysis

Clinical characteristics of the two treatment groups were compared by means of Student's two-sample t test (age), Pearson's chi-square test (sex, race, and risk factors at entry) and Kruskal-Wallis test (number of lesions on admission). The Kruskal-Wallis test was used also to test for association between UGIH and gastric lesion scores, and between organ system failures on entry and death. All statistical testing was two-sided at the 5% level of significance.

Results

One hundred twenty-seven patients meeting all entry criteria were randomized to receive either misoprostol (n = 63) or cimetidine (n = 64). The groups were clinically equivalent at entry (Table 3). The mean time between surgery and first dose of study medication was 4 days for each group (range, less than 1 day to 16 days). Outcome data comparing the patients receiving misoprostol with those receiving cimetidine demonstrated no statistically significant differences in final gastric endoscopy scores ($p = 0.764$), the development of UGIH ($p = 0.179$), the development of additional organ system failure ($p = 0.073$), or death ($p = 0.292$) (Table 4).

Therefore, because the two treatment groups were not shown to differ in any of the entry or outcome variables indicated above, data from the two groups were combined to determine the association, if any, between the development of stress lesions and the development of UGIH, additional organ system failures, and death.

Forty-four of the 127 patients died (35% mortality rate). All but two of these patients had organ failure in at least two systems at the time of death. Twenty-nine patients

TABLE 4. *Examination of Outcome Criteria by Treatment Group*

Outcome Criteria	Misoprostol (N = 63)	Cimetidine (N = 64)	Test Statistic	p
Final gastric score*			0.090†	0.764
1 (n = 24)	11/56 (20%)	13/55 (24%)		
2–4 (n = 65)	34/56 (61%)	31/55 (56%)		
>4 (n = 22)	11/56 (20%)	11/55 (20%)		
Met UGIH criteria (n = 10)	7/63 (11%)	3/64 (5%)	1.806‡	0.179
Additional organ system failure (n = 39)	24/63 (38%)	15/64 (23%)	3.206‡	0.073
Died (n = 44)	19/63 (30%)	25/64 (39%)	1.112‡	0.292

* Patients who did not undergo a second endoscopy were excluded.
† From Kruskal-Wallis test.
‡ From Pearson's chi square test.
UGIH, upper gastrointestinal tract hemorrhage.

died within 14 days of the first dose of study medication, and the other 15 died more than 20 days after the first dose. The time between surgery and the first dose (approximately 4 days) did not affect survival ($X^2 = 0.541$, $p = 0.462$).

Of the 127 patients, 10 (8%) met criteria for UGIH secondary to stress lesions, from 3 to 14 days after the first dose of study medication. None of the patients who developed UGIH had less than 10 stress lesions (combined gastric and duodenal lesions) when they hemorrhaged, and all but one of these patients had a preponderance of lesions in the stomach (Table 5). Four of the patients who went on to bleed were initially without lesions (score of 1) or showed healing (decreased their gastric score by at least one grade) at the 72-hour endoscopy. All four of these patients developed multiple new lesions at subsequent endoscopies. One additional patient had UGIH 9 days after the last dose of study medication.

Twenty-two of 111 patients (20%) who had a follow-up endoscopy demonstrated more than 10 gastric lesions (lesion score greater than 4) on repeat examination (Table 5). This was considered clinically significant evidence of diffuse gastritis. There were 36 patients with 6 to 10 gastric lesions at entry, which was the maximum number of lesions allowed (Table 3). When these patients were re-endoscoped, 13 (36%) demonstrated fewer lesions (*i.e.*, decreased their gastric score), eight (22%) showed no change, 11 (31%) developed more lesions (*i.e.*, increased their gastric score), and four (11%) could not be re-endoscoped (two of these patients had died). When patients were stratified by the results of their worst gastric endoscopic score (Table 5), the risk of developing significant UGIH was strongly associated with the number of gastric stress lesions developed ($p < 0.001$).

Five of the ten patients who met the criteria for UGIH died, but death was not temporally related to the hemorrhage (mean interval between bleeding and death, 9.6 ± 5.0 days). When bleeding status at the time of study termination was reviewed for the 127 patients, there was not a significant association between known UGIH and death (5 of 127; $p = 0.288$). There were 34 patients, however, who did not undergo a final endoscopic evaluation at the time of study withdrawal ($n = 10$) or at the time of death ($n = 24$), although they may have had a 72-hour endoscopy. These 34 patients could not be evaluated for UGIH because endoscopic confirmation of a bleeding source was required. None of these 34 patients, however, showed any of the three clinical signs of bleeding. Therefore, they were classified as having an unknown bleeding outcome. In the group of 24 patients who died before a second endoscopic examination could be performed, two patients had extensive UGI tract ulcerations and blood present at autopsy. When the remaining 93 patients who had an endoscopy at study termination were examined, there was a significant association observed between UGIH and death (5 of 93; $p < 0.05$). There were significantly ($p < 0.001$) more patients with an unknown bleeding outcome in the group who died (24 of 44, 55%) when compared with the group who did not die (10 of 83, 12%). Therefore, it is possible that the significant association for known UGIH and death for the 93 patients who had an endoscopy at study termination would be nonsignificant if the bleeding outcomes of a large fraction of the 24 patients who died with unknown bleeding outcome were known to be negative.

Patients who had a prior history of UGIH or peptic ulcer disease were not excluded from this study as long as their initial endoscopic examination did not demonstrate mucosal damage more severe than 10 gastric or duodenal lesions. Six patients had a history of outpatient ulcer treatment, one patient had a history of a UGIH, and one patient had a history of bloody NG drainage. Four of these eight patients died (nonsignificant association with death, $X^2 = 0.889$, $p = 0.346$). One of the patients who died also met criteria for UGIH during study participation.

Sixty-nine patients (54%) in this study had MSOF at entry (Table 6). The presence of renal failure ($n = 25$), coagulopathy ($n = 29$), or hepatic failure ($n = 23$) at entry were each significantly associated with death, (64%, $p < 0.001$; 62%, $p < 0.001$; and 57%, $p < 0.02$, respectively). Additionally, the number of organ system failures at entry was significantly associated with death ($p < 0.001$).

Thirty-nine patients (31%) in this study developed 57 additional organ system failures not present at study entry. The development of either hepatic (14 of 104 patients at risk) or renal (22 of 102 patients at risk) failure was usually fatal (71% and 59%, respectively). The development of coagulopathy was less common (7 of 98 patients at risk) and associated with a 43% mortality rate. Eight of the

TABLE 5. *Relationship Between UGIH and Gastric Lesions*

Highest Gastric Score at Follow-up Endoscopy	Met Criteria for UGIH: Yes (n = 10)*	Met Criteria for UGIH: No (n = 101)
1	0	20
2	0	12
3	1†	42
4	1	13
5	3	2
6	4	7
7	1†	5

Chi square (Kruskal-Wallis) = 14.840
$p < 0.001$

* Follow-up endoscopy for these patients was when UGIH occurred.
† Duodenal mucosal score of 7.
UGIH, upper gastrointestinal tract hemorrhage.

TABLE 6. *Association Between Organ System Failures and Death*

No. of Organ System Failures at Entry*	Died (n = 44)	Survived (n = 83)
1	11†	47
2	16	29
3	12	6
4	5	1

Chi square (Kruskal-Wallis) = 18.08
$p < 0.001$

* Failures in addition to mechanical ventilatory support and hypotension or sepsis.
† Had both hypotension and sepsis at entry.

thirty-two patients who did not have sepsis at entry developed sepsis during the study, and five (63%) of these patients died.

Fourteen patients were classified as having ARDS at the time of study entry. Six of these patients (43%) died. Ten other patients developed ARDS during study participation, and nine of these (90%) died. Of the 103 patients who did not have ARDS, only 29 (28%) died. Therefore, the presence of ARDS was significantly associated with death ($X^2 = 15.87$, 2 *df*, $p < 0.001$).

Discussion

This report examined postoperative patients who required ventilatory support and experienced an episode of either hypotension or sepsis, to assess the associations among the development of UGIH, diffuse gastritis, organ system failure, and death. Overall, only 8% of these patients developed UGIH, and this was significantly associated with the number of gastric lesions they developed. Of the 111 patients who underwent at least one follow-up endoscopy, 22 (20%) developed diffuse gastritis, and eight of these patients (36%) had a UGIH (Table 5). No patients required surgical intervention. This implies that although stress lesions are common in critically ill patients, hemorrhage requiring surgical treatment is rare when prophylaxis regimens are used.

Very few studies of critically ill patients have included multiple endoscopic evaluations. This is the first study to demonstrate that UGIH can develop in patients after interim endoscopy (72 hours after the initiation of prophylaxis) has shown that the gastric mucosa is either free of lesions or improving (*i.e.*, the number of lesions has decreased). The interpretation of this information must be made in light of the entry criteria for the study, which by design excluded patients who had already developed lesions or bleeding. This also may mean that studies that claim to identify patients not in need of prophylaxis on the basis of short-term evaluation may miss some patients who continue to be at risk.

The observed bleeding rate of 8% falls within the range of previously published reports examining patients given prophylaxis,[4–8] although few studies have examined a similar patient population. The expected rate of bleeding in groups receiving placebo in other studies ranges from 5% to 21%.[1,2,8] Despite the absence of overt gastrointestinal hemorrhage on entry to the study and the administration of prophylaxis, 41% of these patients (45 of 111) increased their gastric mucosal scores by at least one grade. Although there are some groups of patients in whom prophylaxis has legitimately been questioned,[9] patients with MSOF clearly needed prophylaxis to prevent gastrointestinal hemorrhage and the expensive evaluation and acute treatment such hemorrhage initiates.

This study confirms previous work identifying the stomach as a primary target organ in stress.[8,10,11] Only five patients had duodenal lesions on entry, and three of the four who had a second endoscopy improved (the other patient's status did not change). Of the two patients with late developing duodenal ulcers, one also had a gastric ulcer that was bleeding and a history of ulcer disease. The other patient had gastric erosions that were bleeding.

Published rates of pneumonia in ICU patients requiring mechanical ventilation have ranged from 10% to 34%.[4,5] Although ventilator dependence was an admission criterion for this study, ARDS was observed in 24 (19%) of the patients, 14 at admission and 10 who developed ARDS during the study (9% of the patients at risk). This rate is lower than prior reports[4,5] of pneumonia rates of up to 35% in patients receiving agents that raise pH; this may be because other studies included patients regardless of expected survival, whereas this study excluded patients who were not expected to survive at least 14 days. Additionally, this study did not prospectively collect information relevant to changes in each patient's pulmonary status and therefore had to rely on the reporting of the development of pneumonia or ARDS as an adverse event. In these patients, when a worsening of pulmonary status was reported, it was significant; 9 of the 10 patients whose pulmonary status worsened, died.

Finally, gastric pH was not measured in our patients, which makes it impossible to know how effective these treatments were in raising gastric pH and whether patient values correlated with either the development of UGIH or pneumonia. The dose of cimetidine used in this study does not routinely keep pH above 4 in critically ill patients.[11] The dose of misoprostol used in these patients kept mean gastric pH above 4 in a prior group of 141 surgical ICU patients, but intubation and sepsis or hypotension were not required for inclusion in that study.[12] Sepsis has been correlated with lower gastric pH values and a high incidence of UGIH in other studies.[1,11] It is therefore possible that the lower rate of pulmonary problems seen in this study was due to prophylaxis regimens

that did not routinely raise gastric pH above some critical value where pneumonia is more likely to occur.

The science of outcome prediction in the critically ill patient is relatively new and still inexact. Techniques for stratification often have been poorly applied or simply not used at all. Even when stratification criteria such as the APACHE II score have been used to study outcome,[5] the inclusion of many different types of patients (*i.e.*, medical and surgical admissions) does not allow outcome prediction because equations are disease specific.[13] This study examined a relatively homogenous group concentrating on postoperative patients without head injuries who were thought to be on the brink of the development of MSOF. In the patients in this study, the risk for the development of hemorrhage was similar to the risk for the development of ARDS. Any additional organ failure can push this type of patient over the brink.

Thirty-five per cent (35%) of the study population died, with all but two patients having MSOF. Death was significantly associated with the total number of organ system failures at entry and especially with the presence of hepatic failure, renal failure, or coagulopathy. Multiple system organ failure has become the most common cause of both prolonged stays and deaths in surgical ICUs in the last decade.[14,15] Techniques to better support organ function are desperately needed to reverse this trend. It seems essential to try to prevent stress lesions in patients with MSOF because even with prophylaxis, 41% of these patients develop more lesions, and lesion number correlates with the risk of UGIH.

Acknowledgments

This study represents the work of the following participating physicians: David Adams, M.D., Medical University of South Carolina, Charleston, South Carolina; Nanakram Agarwal, M.D., Our Lady of Mercy Center, Bronx, New York; Samuel Appavu, M.D., Cook County Hospital, Chicago, Illinois; Macram Ayoub, M.D., Medical Center of Central George, Macon, Georgia; Christopher J. Barde, M.D., VA Medical Center, Dayton, Ohio; James E. Barone, M.D., St. Francis Medical Center, Trenton, New Jersey; Edgar J. Caldwell, M.D., Maine Medical Center, Portland, Maine; Michael S. Dahn, M.D., VA Medical Center, Detroit, Michigan; Ralph J. Doerr, M.D., Buffalo General Hospital, Buffalo, New York; John Ferrara, M.D., University of South Alabama, Mobile, Alabama; David Figg, M.D., Butterworth Hospital, Grand Rapids, Michigan; Robert J. Goulet, Jr., M.D., Indiana University Medical Center, Indianapolis, Indiana; David H. Harshaw, M.D., Brackenridge Hospital, Austin, Texas; Eddie Hoover, M.D., Meharry Medical Center, Nashville, Tennessee; Young Song Kim, M.D., 6196 Eagle Crest Drive, Huntington Beach, California; Gerald Larson, M.D., Humana Hospital-University, Louisville, Kentucky; Thomas McGarrity, M.D., Hershey Medical Center, Hershey, Pennsylvania; Frank Mitchell, M.D., University Hospital, Columbia, Missouri; Frederick Moore, M.D., Denver General Hospital, Denver, Colorado; L. Beaty Pemberton, M.D., Truman Medical Center, Kansas City, Missouri; Eric Rypins, M.D., VA Medical Center, Long Beach, California; William Schumer, M.D., M.S., Chicago Medical School, North Chicago, Illinois; Marc Jerome Shapiro, M.D., St. Louis University Medical Center, St. Louis, Missouri; Steven Steinberg, M.D., Buffalo VA Medical Center, Buffalo, New York; Thomas Vargish, M.D., University of Chicago, Chicago, Illinois.

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