Since their introduction, H₂-receptor blockers have been used extensively in neurosurgical patients to prevent development of stress-related gastroduodenal (GD) lesions. The efficacy of cimetidine in preventing occult and overt GD bleeding has only been proven in a prospective double-blind randomized manner in patients with severe head injury. Eight Whether H₂-receptor blockers are also useful in the prophylaxis of GD lesions in patients with nontraumatic neurological disease is not known, as the pathophysiological mechanisms of stress ulcer formation may be different in these cases.

The authors conclude that ranitidine is useful in preventing postoperative GD complications in high-risk neurosurgical patients.

**KEY WORDS** • gastrointestinal hemorrhage • stress ulceration • ranitidine

**Prospective double-blind placebo-controlled randomized trial on the use of ranitidine in preventing postoperative gastroduodenal complications in high-risk neurosurgical patients**


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To determine the efficacy of ranitidine in preventing clinically acute overt gastroduodenal (GD) complications (bleeding and/or perforation) after neurosurgery, 101 patients with nontraumatic cerebral disease considered at high risk of developing postoperative GD complications were randomized in a standard double-blind manner to receive either ranitidine (50 mg every 6 hours) or placebo medication preoperatively. Postoperative serial GD endoscopy was used to document the occurrence of complications: an overt symptomatic complication was defined as bleeding requiring blood transfusion and/or surgery.

Fifty-two patients received ranitidine and 49 received a placebo preoperatively; 30 developed overt GD bleeding; nine of these received ranitidine and 21 received a placebo. Ranitidine significantly reduced the incidence of bleeding (p < 0.05). Multivariate logistic regression analysis revealed three factors of independent significance in predicting overt GD bleeding: use of a placebo drug, a gastric pH of less than 4, and a high daily volume of gastric output.

The authors conclude that ranitidine is useful in preventing postoperative GD complications in high-risk neurosurgical patients.

**Clinical Material and Methods**

Between July, 1988 and December, 1989, 131 consecutive patients suffering from nontraumatic neurosurgical lesions with two or more risk factors underwent operations in our unit. Of these patients, 101 were entered into the study. The remaining patients were excluded for the following reasons: 1) failure to obtain consent (four patients); 2) presence of GD bleeding before neurosurgery (10 patients); 3) past history of chronic GD diseases or chronic ulcers, identified at endoscopy (nine patients); and 4) concomitant major medical illnesses such as heart, lung, kidney, hematological, and liver problems (seven patients). Table 1 shows the demographic data of the 101 patients.

The protocol used in our study was approved by the
Ethics Committee of the Faculty of Medicine, The University of Hong Kong. Written consent was obtained from the patients or their next-of-kin.

**Management Protocol**

All 101 patients underwent emergency neurosurgery, after which all were managed according to a standard regimen that included artificial ventilation with muscle paralysis using pancuronium and sedation with midazolam. All individuals had continuous monitoring of arterial blood pressure, arterial oxygen saturation (maintained above 95%), and end-tidal carbon dioxide concentration (kept between 3.5 and 4.5 kPa).

**Endoscopic Examination.** Endoscopic examination of the GD tract up to the second part of the duodenum was performed in all patients within 12 hours of surgery. Additional bolus doses of sedative and analgesic medications were given during endoscopy. A nasogastric tube was passed into the stomach after endoscopy; its position was confirmed by radiological means, and it was connected to a bag for free drainage. Aspiration from the tube was performed at 6-hour intervals and a pH paper was used to measure the pH of the gastric content. The total volume of daily gastric output was recorded.

A follow-up endoscopy was performed for the following clinical indications: 1) development of overt upper GD bleeding in the form of coffee-ground and/or fresh-blood aspirate from the nasogastric tube; 2) passage of melena; 3) unexplained fall in hemoglobin concentration; 4) hypovolemic shock; and 5) abdominal pain when consciousness was regained.

The endpoint of the study was the development of symptomatic GD lesions defined as GD bleeding requiring blood transfusions and/or surgery for acute perforated ulcers. These lesions were confirmed either endoscopically or during abdominal surgery; lesions observed on endoscopy that were chronic or near the region of the nasogastric tube were excluded.

**Management of Medication.** Before surgery, all patients were randomized in a standard double-blind manner to receive either ranitidine (50 mg) or placebo medication (normal saline) identical in appearance and volume. The medications were administered intravenously every 6 hours and were started on call to the operating theater and continued into the postoperative period. Twice daily doses of oral ranitidine (150 mg) or placebo were commenced when patients were considered ready for enteral feeding. Concomitant medications included dexamethasone, 4 mg every 6 hours, and a single dose of ceftriaxone (1 g), which was given intravenously as prophylaxis with the first dose of ranitidine or placebo. Subsequent antibiotic medications were administered only for treatment of culture-proven infections. Those patients who required anticonvulsant therapy or prophylaxis received phenytoin (100 mg every 8 hours).

**Management of Complications.** Computerized tomography scans were performed before surgery and repeated whenever clinically indicated to document any postoperative neurological complication.

All patients were observed for development of complications possibly related to use of the medications. Tracheal aspirates were taken for culture daily. In awake patients, sputum, whenever present, was also sent for culture. Chest radiograms were obtained every day in all individuals while they were receiving ventilatory support, twice weekly when they had been weaned off the ventilators, and whenever clinically indicated. The criteria for diagnosis of chest infections were radiographic evidence of pulmonary changes with or without a temperature rise to higher than 39°C or positive cultures from tracheal aspirates or sputum.

Cultures from other body fluids were taken whenever clinically indicated. Systemic sepsis was diagnosed only with positive cultures from body fluids; central nervous system sepsis was diagnosed when cultures from either cerebrospinal fluid or brain tissue were positive.

**Classification of Outcomes**

**Gastrointestinal Outcomes.** Patients were classified into three groups according to the clinical behaviors of their

### TABLE 1

<table>
<thead>
<tr>
<th>Factor</th>
<th>Ranitidine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>demographic data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>women</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>men</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>mean age (range)</td>
<td>61 (17–84)</td>
<td>61 (32–89)</td>
</tr>
<tr>
<td>median no. of risk factors (range)</td>
<td>2 (2–5)</td>
<td>2 (2–5)</td>
</tr>
<tr>
<td>median preop GCS (range)*</td>
<td>6 (3–8)</td>
<td>6 (3–8)</td>
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<tr>
<td>pathology</td>
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<td></td>
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<tr>
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<td>33</td>
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<tr>
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<td>14</td>
<td>15</td>
</tr>
<tr>
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</tr>
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<td>3</td>
</tr>
<tr>
<td>lesion location</td>
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<tr>
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<td>24</td>
</tr>
<tr>
<td>basal ganglia &amp; suprassellar</td>
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<td>14</td>
</tr>
<tr>
<td>posterior fossa</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>operation†</td>
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<td></td>
</tr>
<tr>
<td>shunt/ventriculostomy</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
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<td>26</td>
</tr>
<tr>
<td>posterior fossa exploration</td>
<td>8</td>
<td>7</td>
</tr>
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</table>

* GCS = Glasgow Coma Scale.
† Patients may have undergone more than one operation.

### TABLE 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ranitidine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>normal (no lesion)</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>asymptomatic (lesion, no bleeding)</td>
<td>30</td>
<td>24</td>
</tr>
<tr>
<td>symptomatic (lesion, bleeding)</td>
<td>9</td>
<td>21</td>
</tr>
<tr>
<td>total</td>
<td>49</td>
<td>52</td>
</tr>
</tbody>
</table>

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lesions and endoscopic findings: 1) normal (without GD lesions); 2) asymptomatic (presence of endoscopically documented acute GD lesions but no evidence of bleeding); and 3) symptomatic from the GD lesions (presence of endoscopic stigmata of recent hemorrhage, requiring blood transfusion and/or surgery to stop bleeding, or treatment of peritonitis as a result of perforation of acute GD tract ulcers).

Neurological Outcome. At 6 months after surgery patients’ final outcomes were classified according to the modified Glasgow Outcome Scale into 1) good recovery or moderate disability; and 2) severe disability, vegetative state, or death. Final outcomes were also assessed by an independent observer to ascertain whether they were a direct result of the GD lesions.

Statistical Analysis

The sample size, estimated from our previous retrospective study, showed that there was a 25% incidence of symptomatic GD lesions in high-risk cases undergoing surgery. Review of the literature showed that, in other critically ill patients, H$_2$-receptor blocker antagonists could reduce the incidence of clinically overt bleeding to approximately 5%. For nine patients would be required in each arm of the trial with a power of 0.8 and a 0.95 significance level by two-tailed test. Chi-square and Student’s t-tests were used for statistical analysis. The histories of individuals who developed symptomatic GD lesions were analyzed by univariate logistic regression analysis and the Mann-Whitney U-test to identify significant risk factors for prediction of symptomatic GD lesions. Multivariate logistic regression analysis was then used to identify risk factors that were of independent significance in predicting symptomatic GD lesions. Significance was taken at the 5% level.

Results

Patient Characteristics

Forty-nine patients received ranitidine and 52 received placebo medication. The nature and location of diseases, types of operation, number of preoperative risk factors, and demographic data were comparable in the two groups (Table 1).

Patients received between two and eight endoscopic examinations of the GD tract (median two). No complications attributable to this procedure were encountered. None of the patients developed perforation of the GD tract. The incidences of GD bleeding in the two groups of patients are shown in Table 2. Patients with normal or asymptomatic lesions did not require blood transfusion. Patients with symptomatic lesions required blood transfusions of between 1 and 10 U (median 4). One patient in the placebo group required abdominal surgery to stop GD bleeding. When individuals who developed symptomatic GD bleeding were compared to those who were asymptomatic or had no GD lesions, it was observed that ranitidine significantly decreased the incidence of overt GD bleeding when compared with placebo medication (chi-square test = 5.86, p < 0.05).

Chest Complication and Adverse Effects of Drug

Eighteen patients in the ranitidine and 11 in the placebo groups developed chest infections. This was statistically similar to the 31 and 41 patients who did not develop chest complications in the ranitidine and placebo groups, respectively (chi-square test = 2.28, p > 0.05). No adverse effects directly attributed to the use of ranitidine or placebo were noted.

Outcomes in the Ranitidine and Placebo Groups

Nineteen patients in the ranitidine and 15 in the placebo groups had good recovery or moderate disability (chi-square test = 0.71, p > 0.05). Only one patient in the placebo group died as a direct result of GD bleeding.

Risk Factors for Development of Symptomatic GD Lesions

Tables 3 and 4 show the results of univariate logistic regression analysis to identify risk factors that were significant in predicting symptomatic GD lesions. Multivariate analysis revealed three factors of independent significance: use of placebo medication, a gastric pH less than 4, and daily volume of gastric output (Table 5). Use of ranitidine significantly decreased the risk of overt GD hemorrhage in the logistic equation.

Discussion

Stress ulceration is a well-known complication of neurosurgery. A previous study revealed an overall incidence of 6.8% in neurosurgical patients with nontraumatic pathology. Although this complication is relatively uncommon, it is frequent enough so that most neurosurgeons must occasionally deal with it. Previous research on
Cushing's ulcers was conducted mainly on patients with head injury, in whom hypergastrinemia and gastric hyperacidity had been demonstrated and H₂-receptor blocker had been proven to be useful in preventing such complications.\textsuperscript{7,8,11,13}

\textbf{Study Results}

The results of these studies, however, contrasted with those conducted on other critically ill patients, in whom hyperacidity and hypergastrinemia were often not encountered.\textsuperscript{1,6,16,19,20} These observations led to the speculation that stress ulceration complications in neurological patients may have a different pathogenesis. This, however, has only been demonstrated in severely head injured patients in whom trauma alone, which can cause stress ulcerations, is an additional complicating factor.\textsuperscript{19,20} Whether patients with nontraumatic neurosurgical pathology will behave similarly to patients with severe traumatic brain injury remains speculative. This study demonstrated that H₂-receptor blocker is useful in the prophylaxis of stress ulceration in postoperative neurological patients with nontraumatic lesions who were considered to be at high risk of developing such complications.

Studies of other critically ill patients have shown that drug prophylaxis reduces the incidence of GD bleeding; however, symptomatic and occult bleeding are often analyzed together and the study population is heterogeneous.\textsuperscript{12,15,16,19-21,23} This research was conducted in a homogeneous patient population with standard management protocol, although only clinically overt bleeding was considered; our results are in accord with these past studies.

\textbf{Incidence of Nosocomial Pneumonia}

With the extensive use of H₂-receptor blockers and antacids in critically ill patients, the incidence of nosocomial pneumonia increased significantly.\textsuperscript{5,18,24} This has been attributed to the alkalization of gastric contents, which may predispose to gastric colonization by gram-negative organisms with their retrograde migration and aspiration into the respiratory tract leading to pneumonia, especially in mechanically ventilated patients.\textsuperscript{9} Although several studies report a higher incidence of nosocomial pneumonia in patients receiving antacids or H₂-receptor blockers than in those receiving cytoprotective agents, which do not reduce gastric pH, this may not be a universal finding;\textsuperscript{4,17,24} however, our results concurred with these studies. Routine use of preoperative prophylactic antibiotic drugs might have accounted for our findings, but only a single dose was given and at an early stage. The contribution of the use of antibiotic drugs to the reduction in the incidence of chest complications could not be sustained.

\textbf{Analysis of Factors}

Apart from the use of a placebo drug, multivariate analysis has identified two other factors in predicting symptomatic GD hemorrhage. We concur with Watts and Clark,\textsuperscript{25} who reported that a small number of comatose patients who developed GD bleeding had a greater volume of gastric secretions. Reduction in gastric pH has also been reported to be a risk factor for bleeding in other critically ill patients.\textsuperscript{19,20} This study has identified two other parameters that can predict symptomatic bleeding and can easily be monitored at the patient's bedside. These parameters may alert neurosurgeons to institute more vigorous measures at an early stage to prevent occurrence of these bleeding episodes.

\textbf{Conclusions}

Ranitidine is useful in preventing overt stress-related bleeding after surgery for patients with nontraumatic neurosurgical disease. We recommend its use in all high-risk patients undergoing neurosurgery.

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