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Weighing risks and benefits of stress ulcer prophylaxis in critically ill patients

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Expanded abstract

Citation

Marik PE, Tajender Vasu T, Hirani A, Pachinburavan M: Stress ulcer prophylaxis in the new millennium: a systematic review and meta-analysis. *Critical Care Med* 2010, **38**:11.

Background

Recent observational studies suggest that bleeding from stress ulceration is extremely uncommon in intensive care unit patients. Furthermore, the risk of bleeding may not be altered by the use of acid suppressive therapy. Early enteral tube feeding (initiated within 48 h of intensive care unit admission) may account for this observation. Stress ulcer prophylaxis may, however, increase the risk of hospital-acquired pneumonia and *Clostridia difficile* infection.

Methods

Objective: A systematic review of the literature to determine the benefit and risks of stress ulcer prophylaxis and the moderating effect of enteral nutrition.

Design:

Data Sources: MEDLINE, Embase, Cochrane Register of Controlled Trials, and citation review of relevant primary and review articles.

Study Selection: Randomized, controlled studies that evaluated the association between stress ulcer prophylaxis and gastrointestinal bleeding. The authors included only those studies that compared a histamine-2 receptor blocker with a placebo.

Data Extraction: Data were abstracted on study design, study size, study setting, patient population, histamine-2 receptor blocker and dosage used, incidence of clinically significant gastrointestinal bleeding, hospital-acquired pneumonia, mortality, and the use of enteral nutrition.

Results

Seventeen studies (which enrolled 1836 patients) met the inclusion criteria. Patients received adequate enteral nutrition in three of the studies. Overall, stress ulcer prophylaxis with a histamine-2 receptor blocker reduced the risk of gastrointestinal bleeding (odds ratio 0.47; 95% confidence interval, 0.29–0.76; $P < 0.002$; Heterogeneity [I^2] = 44%); however, the treatment effect was noted only in the subgroup of patients who did not receive enteral nutrition. In those patients who were fed enterally, stress ulcer prophylaxis did not alter the risk of gastrointestinal bleeding (odds ratio 1.26; 95% confidence interval, 0.43–3.7). Overall histamine-2 receptor blockers did not increase the risk of hospital-acquired pneumonia (odds ratio 1.53; 95% confidence interval, 0.89 –2.61; $P = 0.12$; $I^2 = 41\%$); however, this complication was increased in the subgroup of patients who were fed enterally (odds ratio 2.81; 95% confidence interval, 1.20–6.56; $P = 0.02$; $I^2 = 0\%$). Overall, stress ulcer prophylaxis had no effect on hospital mortality (odds ratio 1.03; 95% confidence interval, 0.78–1.37; $P = 0.82$). The hospital mortality was, however, higher in those studies (n = 2) in which patients were fed enterally and received a histamine-2 receptor blocker (odds ratio 1.89; 95% confidence interval, 1.04–3.44; $P = 0.04$, $I^2 = 0\%$). Sensitivity analysis and meta-regression demonstrated no relationship between the treatment effect (risk of gastrointestinal bleeding) and the classification used to define gastrointestinal bleeding, the Jadad quality score or the year the study was reported.

Conclusions

The results of this meta-analysis suggest that, in those patients receiving enteral nutrition, stress ulcer prophylaxis may not be required and, indeed, such therapy may increase the risk of pneumonia and death. However, because no clinical study has prospectively tested the influence of enteral nutrition on the risk of stress ulcer prophylaxis, those findings should be considered exploratory and interpreted with some caution.

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Commentary

In 1969, Skillman *et al*. [1] reported a clinical syndrome of lethal "stress ulceration" in seven of 150 (5%) consecutive intensive care unit (ICU) patients. These patients had in common respiratory failure, hypotension, and sepsis. Subsequent studies confirmed this finding and two meta-analyses published by Cook *et al*. [2] demonstrated that both histamine-2 receptor blockers (H2RBs) and sucralfate decreased the risk of bleeding from stress ulceration when compared to a placebo. Stress ulcer prophylaxis (SUP) becomes regarded as the standard of care in patients admitted to the intensive Care Unit (ICU), and this intervention is currently endorsed by Surviving sepsis campaign and American Society of Health System Pharmacists (ASHP) guidelines. The universal use of SUP has been reinforced with the adoption of "ventilator bundles." Currently Joint Commission and the Institute for Healthcare Improvement recommend universal SUP as a core "quality" measure for mechanically ventilated patients.

Although the Agency for Healthcare Research and Quality recommends using SUP only in patients on mechanical ventilation and high bleeding risk from coagulopathies, SUP is used in all critically ill patients and even outside the ICU setting. For example, estimates indicate that approximately 90% of critically ill patients admitted to the ICU receive some form of SUP [3], and up to 52% of non-ICU patients receive SUP [4,5]. SUP is not without risks. Acid suppressive therapy is associated with increased colonization of the upper gastrointestinal tract with potentially pathogenic organisms and may increase the risk of hospital-acquired pneumonia [5]. Furthermore, gastric acid is an important defense against the acquisition of *Clostridium difficile* spores, and the use of acid suppressive therapy has been linked to an increased risk of *Clostridium difficile* infection [6-8]. Thus, understanding risks and benefits of SUP is important. For example, patients receiving enteral alimentation have a lower incidence of stress ulceration than unfed patients [9]. Whether routine SUP in patients who receive enteral feeding is beneficial or harmful is not known.

Marik *et al*. [10] conducted a meta-analysis of 17 randomized clinical trials and postulated that SUP may have no added benefits in ICU patients who receive enteral nutrition. They examined the effect of different SUP regimes on the risk of gastrointestinal bleeding, hospital-acquired pneumonia, and mortality, stratifying the studies based on enteral nutrition.

The meta-analysis included a total of 1836 enrolled between the years 1980 and 2004. Overall, SUP with a H2RB reduced the risk of GI bleeding ($P < 0.002$) but had no effect on mortality. The beneficial effect of SUP was noted only in the subgroup of patients who did not receive enteral nutrition. SUP did not alter the risk of GI bleeding in patients who received enteral nutrition, and these individuals had higher risk of hospital-acquired pneumonia ($P = 0.02$, n = 9 studies) and mortality ($P = 0.04$, n = 2 studies).

The results of this meta-analysis suggest that SUP may not be beneficial in patients who are fed enterally. The strength of this review article includes the rigorous attempt to identify all relevant RCTs studies, consider and evaluate for possible confounding factors, such as year of publications, definition of gastrointestinal bleeding, quality of randomized controlled trials, and publication bias. Limitations of this article includes lack of homogeneity in patient population, difference in diagnostic criteria used for major end-points, and only three studies had patients with enteral nutrition.

Recommendation

SUP is beneficial in high risk patients, including those that are on mechanical ventilation and have coagulopathy. SUP may cause unfavorable outcomes, such as hospital-acquired pneumonia and *Clostridium difficile* infection, and clinicians must weigh risks and benefits in low-risk patients, such as those who are not requiring mechanical ventilation or are receiving enteral nutrition.

Competing interests
The authors declare that they have no competing interests.

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Stress ulcer prophylaxis in the new millennium: A systematic review and meta-analysis

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Background: **Recent observational studies suggest that bleeding from stress ulceration is extremely uncommon in intensive care unit patients. Furthermore, the risk of bleeding may not be altered by the use of acid suppressive therapy. Early enteral tube feeding (initiated within 48 hrs of intensive care unit admission) may account for this observation. Stress ulcer prophylaxis may, however, increase the risk of hospital-acquired pneumonia and *Clostridia difficile* infection.**

Objective: **A systematic review of the literature to determine the benefit and risks of stress ulcer prophylaxis and the moderating effect of enteral nutrition.**

Data Sources: **MEDLINE, Embase, Cochrane Register of Controlled Trials, and citation review of relevant primary and review articles.**

Study Selection: **Randomized, controlled studies that evaluated the association between stress ulcer prophylaxis and gastrointestinal bleeding. We included only those studies that compared a histamine-2 receptor blocker with a placebo.**

Data Extraction: **Data were abstracted on study design, study size, study setting, patient population, the histamine-2 receptor blocker and dosage used, the incidence of clinically significant gastrointestinal bleeding, hospital-acquired pneumonia, mortality, and the use of enteral nutrition.**

Data Synthesis: **Seventeen studies (which enrolled 1836 patients) met the inclusion criteria. Patients received adequate enteral nutrition in three of the studies. Overall, stress ulcer prophylaxis with a histamine-2 receptor blocker reduced the risk of gastrointestinal bleeding (odds ratio 0.47; 95% confidence interval, 0.29–0.76; $p < .002$; $I^2 = 44\%$); however, the treatment effect was noted only in the subgroup of patients who did not receive enteral nutrition. In those patients who were fed enterally, stress ulcer prophylaxis did not alter the risk of gastrointestinal bleeding (odds ratio 1.26; 95% confidence interval, 0.43–3.7). Overall histamine-2 receptor blockers did not increase the risk of hospital-acquired pneumonia (odds ratio 1.53; 95% confidence interval, 0.89–2.61; $p = .12$; $I^2 = 41\%$); however, this complication was increased in the subgroup of patients who were fed enterally (odds ratio 2.81; 95% confidence interval, 1.20–6.56; $p = .02$; $I^2 = 0\%$). Overall, stress ulcer prophylaxis had no effect on hospital mortality (odds ratio 1.03; 95% confidence interval, 0.78–1.37; $p = .82$). The hospital mortality was, however, higher in those studies (n = 2) in which patients were fed enterally and received a histamine-2 receptor blocker (odds ratio 1.89; 95% confidence interval, 1.04–3.44; $p = .04$, $I^2 = 0\%$). Sensitivity analysis and meta-regression demonstrated no relationship between the treatment effect (risk of gastrointestinal bleeding) and the classification used to define gastrointestinal bleeding, the Jadad quality score nor the year the study was reported.**

Conclusions: **The results of this meta-analysis suggest that, in those patients receiving enteral nutrition, stress ulcer prophylaxis may not be required and, indeed, such therapy may increase the risk of pneumonia and death. However, because no clinical study has prospectively tested the influence of enteral nutrition on the risk of stress ulcer prophylaxis, our findings should be considered exploratory and interpreted with some caution. (Crit Care Med 2010; 38:2222–2228)**

Key Words: stress ulcer prophylaxis; histamine receptor blocker; proton pump inhibitor; enteral nutrition; systematic review; meta-analysis

In 1969, Skillman et al (1) reported a clinical syndrome of lethal "stress ulceration" in seven of 150 (5%) consecutive intensive care unit (ICU) patients. These patients had in common respiratory failure, hypotension, and sepsis. Pathologic examination demonstrated multiple superficial ulcers that were confined to the gastric fundus. Following this report, these authors performed a randomized controlled study in which 100 critically ill ICU patients at risk of stress ulceration were randomized to either antacid prophylaxis (titrated to keep the gastric pH above 3.5) or no prophylaxis (2). Two of 51 (4%) treated patients had significant gastrointestinal (GI) bleeding as compared to 12 of 49 (25%) control patients ($p < .005$). Subsequent studies confirmed this finding and two meta-analyses published by Cook et al (3, 4) demonstrated that both histamine-2 receptor blockers (H2RBs) and sucralfate decreased the risk of bleeding from stress ulceration when compared to a placebo. Stress ulcer prophylaxis (SUP) become regarded as the standard of care in patients admitted to the ICU, and this intervention is currently endorsed by many professional bodies (5, 6). The universal use of SUP has been reinforced with the adoption of "ventilator bundles." Currently *The Joint Commission* and the *Institute for Healthcare Improvement* recommend universal SUP as a core "quality" measure for mechanically ventilated patients (7). Estimates indicate that approximately 90% of critically ill patients admitted to the ICU receive some

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form of SUP (8). This practice has now extended outside the ICU with up to 52% of non-ICU patients receiving SUP (9, 10). Furthermore, although proton-pump inhibitors (PPIs) have never been demonstrated to reduce the rate of bleeding from stress ulceration (as compared to a placebo), these agents are commonly prescribed for the prevention of this condition (11, 12). However, a recent meta-analysis did not find strong evidence that "PPIs were different from H2RBs in terms of stress-related GI bleeding prophylaxis, pneumonia, and mortality among patients admitted to ICUs" (13).

SUP is not without risks. Acid suppressive therapy is associated with increased colonization of the upper gastrointestinal tract with potentially pathogenic organism. This has been demonstrated to increase the risk of hospital-acquired pneumonia (HAP) (10). Furthermore, gastric acid is an important defense against the acquisition of *Clostridium difficile* spores, and the use of acid suppressive therapy has been linked to an increased risk of *Clostridium difficile* infection (14–16). Furthermore, these agents have important interactions with other drugs as well as having agent-specific side effects.

Most of the clinical trials on which the current recommendations are based were performed in the 1980s and early 1990s when it was common to keep ICU patients nil-per-os and when the early initiation of enteral nutrition was uncommon. It has been suggested that patients receiving enteral alimentation have a lower incidence of stress ulceration than unfed patients (17). In animal models, enteral alimentation has been demonstrated to protect the gastric mucosa from stress-related gastric mucosal damage (18, 19). We postulated that SUP may have no added benefits in ICU patients receiving enteral nutrition, and indeed, such therapy may have an unfavorable risk-benefit profile. We, therefore, performed a meta-analysis to assess the effect of SUP on the risk of GI bleeding, grouping the studies by those that used or did not use enteral nutrition. The latter group included patients receiving parenteral nutrition and those who were initially nil-per-os and then transitioned to an oral diet as well as studies that used inadequate enteral nutrition. Our secondary aims were to determine the effect of SUP on the incidence of HAP and mortality. As almost of all the placebo-controlled clinical trials reported to date have investigated the role of H2RBs in preventing stress ulceration, with only one study investigating a PPI, (12) we confined our meta-analysis to randomized controlled trials (RCTs) that compared a H2RB to a placebo (or control).

METHODS

Identification of Trials

Our aim was to identify all relevant randomized controlled trials that evaluated the role of H2RBs in the prevention of stress ulceration. We restricted this analysis to human adults; there was no restriction, however, as to the type of patient or the setting where the study was performed or the language of the publication. We used a multi-method approach to identify relevant studies for this review. All authors independently searched the National Library of Medicine's MEDLINE database for relevant studies in any language published from 1966 to September 2009 by using the following Medical Subject Headings (MeSH) and keywords: stress ulcer prophylaxis, cimetidine, ranitidine or famotidine and critical care or intensive care, and randomized controlled trial (publication type). In addition, we searched Embase and the Cochrane Database of Systematic Reviews. Bibliographies of all selected articles and review articles that included information on SUP were reviewed for other relevant articles. In addition, we searched the "gray literature" to avoid any reporting bias; this included studies published in abstract only. This search strategy was done iteratively, until no new potential citations were found on review of the reference lists of retrieved articles. We performed this meta-analysis according to the guidelines proposed by the QUOROM group (20).

Study Selection and Data Extraction

Only randomized, placebo-controlled studies that evaluated the role of a H2RB in preventing bleeding from stress ulceration were included in the meta-analysis. In those studies with a third or fourth treatment arm (sucralfate, PPI, or pirenzepine), only patients who received the H2RB and a placebo were included in the analysis. The primary end-point was the incidence of clinically significant GI bleeding (as defined in each study). If the study did not report the incidence of clinically significant bleeding, the incidence of bleeding as determined by endoscopy was used. Secondary end-points included the incidence of HAP (as defined in each study) and hospital mortality. All authors independently abstracted data from all studies by using a standardized form. Data were abstracted on study design, study size, study setting, patient population, the H2RB used and its dosage, incidence of clinically significant GI bleeding, HAP, hospital mortality, and whether the patients received enteral nutrition. For the purposes of our meta-analysis, we included studies in the enteral nutrition subgroup if the authors specifically reported that $\geq$50% of enrolled patients received enteral nutrition. Patients were considered to be nil-per-os if they had a nasogastric tube that was placed to gravity drainage and/or the total gastric outputs were being measured. Attempts were made to contact the primary authors for missing data elements.

All reviewers independently assessed allocation concealment and the likelihood of bias to determine the methodologic quality of the included trials. The allocation concealment was ranked as adequate, uncertain, or inadequate, and the likelihood of bias was scored on the Jadad 5-point scale, which contains two questions each on randomization and masking and one question on the reporting of dropouts and withdrawals (21). Any disagreement between reviewers was resolved by consensus.

Data Analysis

Statistical analysis was performed by using Review Manager 5.023 (Cochrane Collaboration, Oxford, U.K.) and Comprehensive Meta-analysis 2.0 (Biostat, Englewood, NJ). We assessed heterogeneity among studies by using the Cochran Q statistic, with $p \leq .10$ indicating significant heterogeneity, (22) and I^2 with suggested thresholds for low (25–49%), moderate (50–74%), and high (>75%) values (23, 24). We used a random effects model if the Q statistic was significant; otherwise we used a fixed effects model. Summary effects estimates are presented as odds ratio (OR) with 95% confidence interval (CI); we considered $p \leq .05$ (two-sided) as significant. Subgroup analysis was performed by grouping the studies by enteral nutrition or no enteral nutrition. Summary estimates are presented as OR with 95% CI. The relationship among the treatment effect (reduced risk of GI bleeding) and the date of study publication and the Jadad score was assessed by meta-regression. The presence of publication bias was assessed visually with a funnel plot. We performed a sensitivity analysis to determine the effect of the definition of GI bleeding and the Jadad score on the treatment effect (risk of GI bleeding). In addition, we performed meta-regression to determine the relationship between the treatment effect and the year the study was reported.

RESULTS

The initial search strategy generated 56 citations; of these 21 were excluded because they did not include a placebo

Table 1. Randomized controlled trials comparing stress ulcer prophylaxis with placebo: Characteristics of studies included in meta-analysis

Author (reference)	Year	n	Agent	Dose	Type ICU	Enteral Feeds[a]
Halloran (25)	1980	50	Cimetidine	300 mg/every 4 hrs	Head injury	N
Zinner (26)	1981	200	Cimetidine	300 mg/every 6 hrs	SICU	N
Peura (27)	1985	39	Cimetidine	300 mg/every 6 hrs	MICU	N
Cheadle (28)[b]	1985	195	Cimetidine	200 mg/every 6 hrs	Postabdominal surgery	N
van den Berg (29)	1985	28	Cimetidine	20 mg/kg/24 hr	GICU	Y
Groll (30)	1986	221	Cimetidine	300 mg/every 6 hrs	GICU	N
Reusser (31)	1990	40	Ranitidine‡	50 mg/every 6 hrs	Neurosurgery	N
Karlstadt (32)[c]	1990	87	Cimetidine	Infusion at 50 mg/hr	GICU[d]	N
Ruiz-Santana (33)	1991	49	Ranitidine	50 mg/every 6 hrs	GICU + TPN	N
Apte (34)	1992	34	Ranitidine	50 mg/every 6 hrs	Tetanus and tracheostomy	Y
Metz (35)	1993	167	Ranitidine	Infusion at 6.25 mg/hr	Head injury	N
Martin (36)	1993	131	Cimetidine	Infusion at 50–100 mg/hr	GICU[d]	N
Ben-menachem (37)[e]	1994	200	Cimetidine	Infusion at 900 mg/day	MICU	Y
Burgess (38)	1995	34	Ranitidine	Infusion at 6.25 mg/hr	Head injury	N
Chan (39)	1995	101	Ranitidine	50 mg/every 6 hrs	Neurosurgical	N
Hanisch (40)[g]	1998	114	Ranitidine	50 mg/every 8 hrs	SICU[d]	N
Kantorova (12)[f]	2004	146	Famotidine	40 mg/every 12 hrs	SICU[d]	N

ICU, intensive care unit; SICU, surgical ICU; MICU, medical ICU; GICU, mixed ICU; TPN, total parenteral nutrition.
[a]50% of patients received enteral nutrition; [b]also randomized to nasogastric tube or no nasogastric tube; [c]antacid; [d]high risk patients; [e]also included a sucralfate arm; [f]also included a PPI and sucralfate arm; [g]also included a pirenzepine arm.

Table 2. Quality assessment of studies included in meta-analysis

Author	Clinician Blinding	Intention to Treat	Allocation Concealment	Jadad Score (0–5)
Halloran (25)	Yes	Yes	Adequate	5
Zinner (26)	No	Yes	Adequate	3
Peura (27)	Yes	Yes	Uncertain	4
Cheadle (28)	Yes	Yes	Adequate	5
van den Berg (29)	Yes	Yes	Uncertain	4
Groll (30)	Yes	Yes	Uncertain	4
Reusser (31)	No	Yes	Uncertain	3
Karlstadt (32)	Yes	Yes	Uncertain	3
Ruiz-Santana (33)	No	Yes	Adequate	3
Apte (34)	No	Yes	Uncertain	2
Metz (35)	Yes	Yes	Adequate	5
Martin (36)	Yes	Yes	Adequate	5
Ben-Menachem (37)	No	Yes	Adequate	3
Burgess (38)	Yes	Yes	Adequate	5
Chan (39)	Yes	Yes	Uncertain	4
Hanisch (40)	Yes	Yes	Adequate	5
Kantorova (12)	Yes	Yes	Adequate	5

arm (compared two or more SUP agents), seven were excluded because they evaluated the pharmacokinetics/pharmacodynamics of H2RBs/PPIs or they did not report the end-point of interest (20 studies). An additional nine studies were identified from the bibliographies of the selected articles and review articles. No studies were identified that were published in abstract only. The 17 studies included in the meta-analysis enrolled a total of 1836 patients between the years 1980 and 2004 (12, 25–40). These studies are summarized in Table 1, and the methodologic quality of the studies is provided in Table 2. In three studies, patients received adequate enteral nutrition (29, 34, 37).

The incidence of clinically significant bleeding was reported in 16 studies; in one of these studies the source of bleeding was confirmed by endoscopy (37). The study by Peura et al (27) evaluated the incidence of endoscopic signs of bleeding. Overall, SUP with a H2RB reduced the risk of GI bleeding (OR 0.47; 95% CI, 0.29–0.76; $p < .002$; $I^2 = 44\%$); however, the treatment benefit was noted only in the subgroup of patients who did not receive enteral nutrition (Fig. 1). In those studies in which patients were fed enterally, SUP did not alter the risk of GI bleeding (OR 1.26; 95% CI, 0.43–3.7). The incidence of HAP was reported in nine studies. Overall H2RBs did not increase the risk of HAP (OR 1.53; 95% CI, 0.89–2.61; $p = .12$; $I^2 = 41\%$), however, this complication was increased in the subgroup of patients who were fed enterally (OR 2.81; 95% CI, 1.20–6.56; $p = .02$; $I^2 = 0\%$; Fig. 2). Mortality was reported in 14 studies. Overall, SUP had no effect on hospital mortality (OR 1.03; 95% CI, 0.78–1.37; $p = .82$; Fig. 3). The hospital mortality was, however, higher in those studies (n = 2) in which patients were fed enterally and received a H2RB (OR 1.89; 95% CI, 1.04–3.44; $p = .04$, $I^2 = 0\%$). Visual inspection of the funnel plots failed to reveal a publication bias (Fig. 4). Meta-regression demonstrated no relationship between the treatment effect (risk of GI bleeding) and the year the study was reported (Fig. 5). Similarly, there was no relationship between the treatment effect and the classification used to define GI bleeding nor the Jadad score (data not shown).

DISCUSSION

The results of this meta-analysis suggest that in patients who are fed enterally, SUP does not reduce the risk of bleeding from stress ulceration. Furthermore, in patients receiving SUP, our data suggest that enteral feeding may increase the risk of pneumonia and death. The results of our meta-analysis are supported by recent observational studies that have demonstrated that the risk of clinically significant bleeding from stress ulceration is very low (approximately 1%) in ICU patients and that SUP does not alter this risk. Faisy et al (41) compared

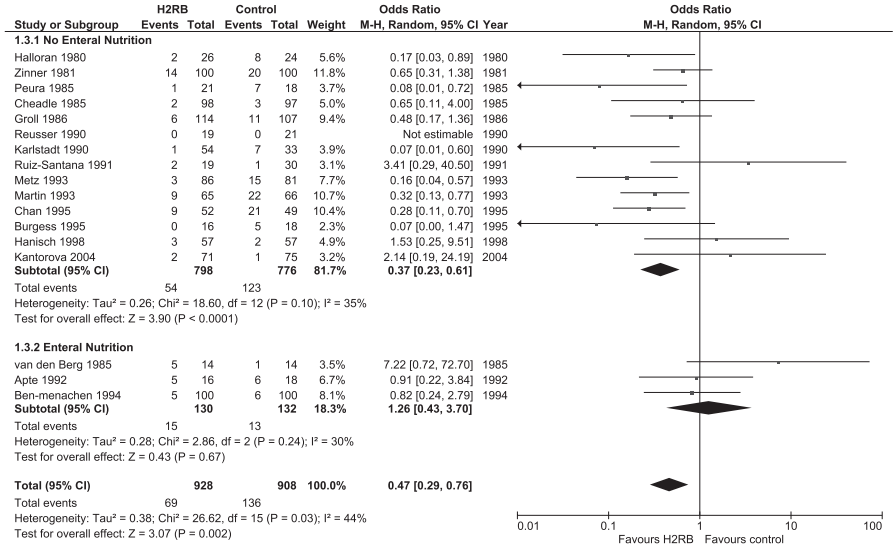

Figure 1. Effect of stress ulcer prophylaxis (*SUP*) on the risk of gastrointestinal (*GI*) bleeding. Studies are grouped by the use or nonuse of enteral nutrition. Weight is the relative contribution of each study to the overall treatment effect (odds ratio [*OR*] and 95% confidence interval [*CI*]) on a log scale assuming a random effects model. *H2RB*, histamine-2 receptor blocker.

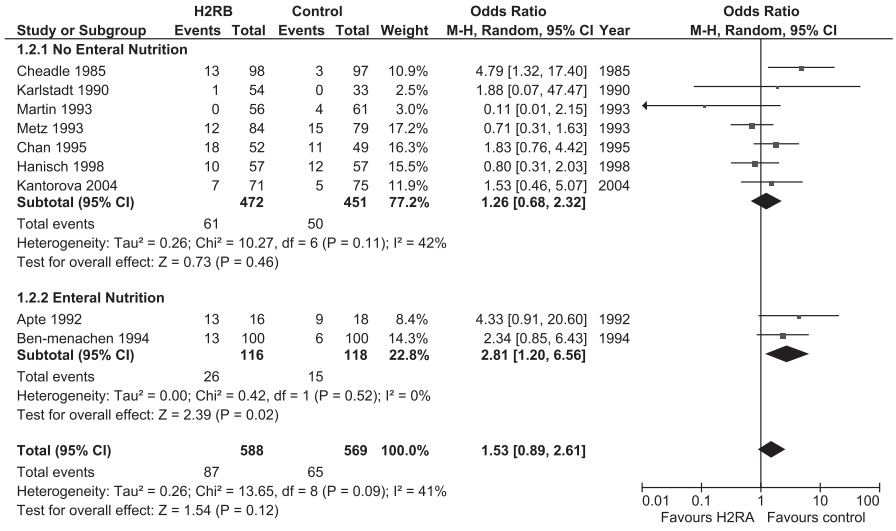

Figure 2. Effect of stress ulcer prophylaxis (*SUP*) on the risk of hospital-acquired pneumonia (*HAP*). Studies are grouped by the use/nonuse of enteral nutrition. Weight is the relative contribution of each study to the overall treatment effect ([*OR*] and 95% confidence interval [*CI*]) on a log scale assuming a random effects model. *H2RB*, histamine-2 receptor blocker.

the rate of clinically significant GI bleeding during two sequential time periods. During the first phase all patients (n = 736) received SUP, whereas SUP was withheld during the second period (n = 737). Although the patients during the second phase of the study were sicker (higher SAPS II score), the rate of overt (1.9% vs. 1.6%) and clinically significant bleeding (1.4% vs. 1.1%) as well as the use of blood products was similar between the two time periods. During both time periods, patients received early enteral feeding (within 48 hrs of ICU admission). Zandstra and Soutenbeek (42) reported that one of 183 patients (0.6%) receiving prolonged mechanical ventilation without any SUP developed stress ulcer-related bleeding. Erstad et al (43) conducted a prospective study on 543 patients and reported clinically significant gastrointestinal bleeding rates were similar for those patients with and without appropriate SUP. Kantorova et al (12) performed a randomized, placebo-controlled study in critically ill patients at high risk for stress-related GI bleeding (mechanical ventilation >48 hrs and coagulopathy) in which they compared three SUP regimens (omeprazole, famotidine, and sucralfate) with placebo. The overall bleeding rate was 1% with no significant difference between treatment groups (bleeding rate was 1% in the placebo group). More aggressive resuscitation and the early initiation of enteral nutrition were postulated to account for the low incidence of bleeding from stress ulceration in these studies (41).

Enteral nutrients buffer acid and may act as a direct source of mucosal energy, induce the secretion of cytoprotective prostaglandins and mucu,s and improve mucosal blood flow (18, 19). Mucosal immunity may be enhanced via stimulation of the gut-associated lymphoid tissue. In addition, it has been postulated that stress triggers vagal stimulation of the stomach through central nervous system pathways; these pathways may be blunted by enteral nutrition (44, 45). Bonten et al (46) demonstrated that continuous enteral nutrition was more likely to raise gastric pH to >3.5 than patients receiving H2RBs or PPIs. Rodent restraint models have demonstrated that enteral nutrition provides better protection against stress ulceration than the intragastric administration of an antacid or sucralfate or intravenous administration of cimetidine (18, 47–49). In a retrospective analysis of prospectively collected data, Raff et al (50) demonstrated that early (within 12 hrs posttrauma) enteral nutrition was more effective in preventing overt upper GI bleeding than cimetidine and antacids (3.3% vs. 8.3%, $p < .05$) in a cohort of 526 severely burned patients. Patients in the cimetidine group received antacids if the intragastric pH dropped below 3.5 with all the patients receiving parenteral nutrition. Similarly, in a cohort of 146 severely burned patients, Choctaw et al (51) reported major upper GI bleeding in 30% of patients who received "the usual diet" compared with 3% ($p < .05$) in patients who received a continuous infusion of an elemental diet. Pingleton et al (17) reported similar findings in 43 ventilated patients; 14 of 20 patients receiving antacids and seven of nine patients receiving cimetidine had evidence of upper GI bleeding; however, none of the patients (n = 14) receiving enteral alimentation had evidence of bleeding.

An intriguing finding of this study was the observation that the incidence of HAP was increased in the subgroup of patients who received both a H2RB and enteral nutrition. Patients who received a H2RB and were not fed enterally did not have an

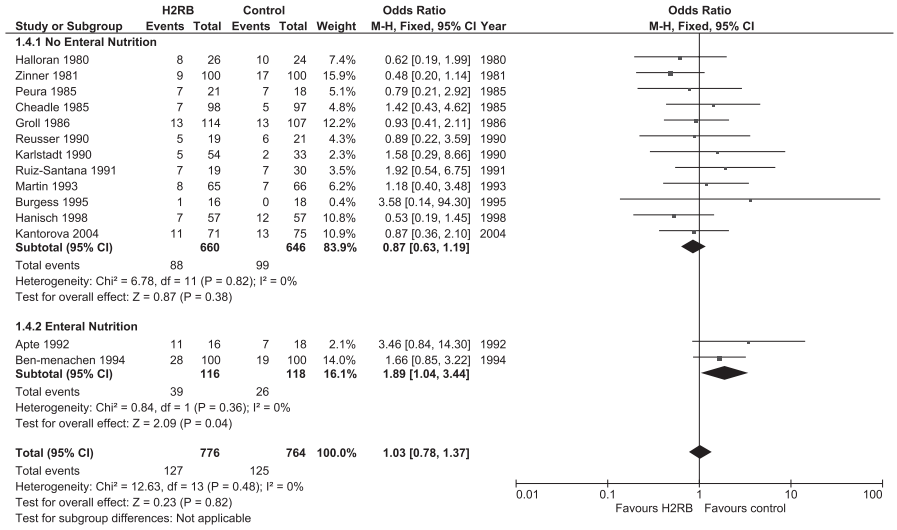

Figure 3. Effect of stress ulcer prophylaxis (*SUP*) on the mortality. Studies are grouped by the use/nonuse of enteral nutrition. Weight is the relative contribution of each study to the overall treatment effect ([*OR*] and 95% confidence interval [*CI*]) on a log scale assuming a fixed effects model. *H2RB*, histamine-2 receptor blocker.

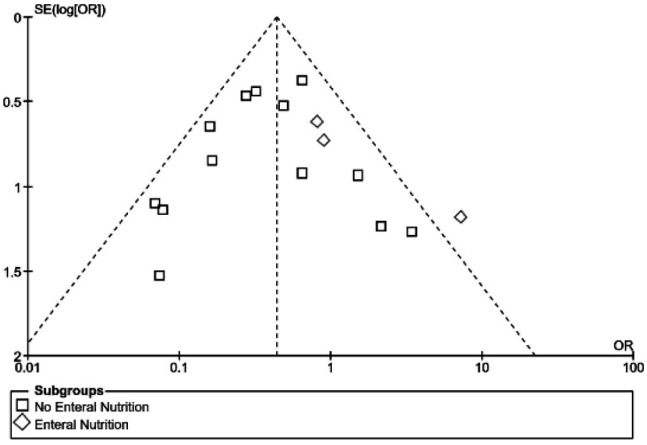

Figure 4. Funnel plot for potential publication bias. *SE*, standard error; *OR*, odds ratio.

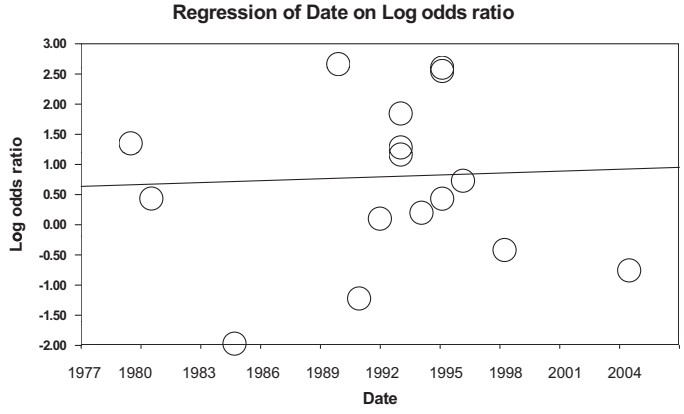

Figure 5. Meta-regression of treatment effect (reduced risk of gastrointestinal bleeding) and date of study publication.

increased risk of HAP. Gastric microbial growth is pH dependent (52). Normally, the fasting stomach maintains sterility by maintaining an acid pH, and an increase in pH may allow the stomach to become colonized. Both H2RBs and enteral feeding increase gastric pH and gastric colonization (53). Bonten et al (46) demonstrated that the combination of acid suppressive therapy and enteral feeding resulted in a significantly higher pH than either intervention alone, and this was associated with an increased rate of gastric colonization. This observation likely explains the increased risk of HAP in the patients receiving a H2RB and enteral feeds. The increased risk of HAP may explain the increased mortality in this group of patients. In a large prospective pharmacoepidemiologic cohort study involving hospitalized non-ICU patients, Herzig et al (10) demonstrated that acid-suppressive medication was associated with a 30% increased odds ratio of developing HAP. The results of our meta-analysis suggest that enteral nutrition provides adequate protection against stress ulceration and that the addition of acid suppressive therapy serves only to increase the risk of HAP and the risk of dying.

It should be noted that in many of the studies in which patients did not receive enteral tube feeds, "oral feedings" were restarted as soon as the "patient's condition permitted" or on day 2–3 after surgery. Delayed oral feeding, therefore, would appear not to protect against stress ulceration. This is supported by the study of Choctaw et al (51) wherein the risk of serious bleeding from stress ulceration was significantly lower in the patients who received a continuous intragastric infusion of an elemental diet as compared with the patients who received the usual diet.

The strength of our review includes the rigorous attempt to identify all relevant studies and the inclusion of only randomized controlled studies. However, our meta-analysis has many of the limitations that apply to meta-analyses in general, including lack of homogeneity of patient populations and the use of somewhat different criteria for the major endpoints (for the diagnosis of clinically significant bleeding and HAP) (54–56). Although we could not use standardized end-points for both bleeding and HAP (as the required data were not collected and reported), the same diagnostic criteria

were used in both the treatment and control groups in each study, making it likely that any differences were real. Furthermore a sensitivity analysis did not demonstrate a relationship between the classification used to define GI bleeding and the treatment effect. A major limitation of our meta-analysis is that adequate enteral nutrition was provided in only three of the studies. Furthermore, in the absence of an individual patient data analysis or a prespecified standardized protocol for administering enteral nutrition that would not introduce a systematic bias, it is likely that the patients who received enteral nutrition varied in their acuity of illness compared with the nonenteral nutrition group. This may explain the finding of increased mortality, and even perhaps HAP, in that subgroup. The studies included in our meta-analysis spanned a long period of time (25 yrs), during which both the standard of care as well the conduct of clinical trials has changed enormously. However, metaregression failed to demonstrate a relationship between the year of publication of the study and the treatment effect. Despite these limitations, the results of our meta-analysis are supported by experimental animal models and more recent observational studies.

In conclusion, the results of this meta-analysis suggest that in those patients who received enteral tube feeds, SUP may not be required. Indeed, in these patients, SUP is likely to increase the risk of complications. Furthermore, the results of our study suggest that the use of SUP in the ICU should no longer be used as a "quality" indicator. However, because no clinical study has prospectively tested the influence of enteral nutrition on the risk of SUP, our findings should be considered exploratory and interpreted with some caution. Additional studies are required to confirm the findings of our meta-analysis.

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