

## Role of Rebamipide in Stress Ulcer Bleeding Prophylaxis for High-Risk Patients in Neurosurgical Intensive Care Unit : A Randomized, Prospective, Unblind Pilot Study

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### ABSTRACT

**Background and Aims:** Stress-related mucosal damage (SRMD) is an important cause of acute upper gastrointestinal bleeding (AUGIB) in high-risk critical patients. H<sub>2</sub> receptor blockers (H<sub>2</sub>RB), proton pump inhibitors (PPIs) and sucralfate are important prophylactic drugs. Nevertheless, these agents, especially H<sub>2</sub>RBs and PPIs, are associated with higher rates of hospital-acquired or ventilator-associated pneumonia (HAP or VAP) in such setting. The aim of this study was to evaluate the efficacy of rebamipide in comparison with an H<sub>2</sub>RB in SRMD bleeding prophylaxis for high-risk neurosurgical patients.

**Methods:** High-risk patients admitted to the neurosurgical ICU, Maharaj Nakorn Chiang Mai Hospital from July 2007 to December 2007 were recruited. Twenty-three patients who fulfilled inclusion and exclusion criteria were randomly divided to receive either oral rebamipide or intravenous ranitidine. Endpoints were UGIB, death, no further risk of SRMD bleeding, discharge from ICU or patient withdrawal. The measured study outcomes were UGIB rate, HAP/VAP rate, in-hospital mortality rate and percentages of changes in serum nitric oxide (NO) level.

**Results:** No statistical differences in any of the baseline clinical characteristics and laboratory data between the two groups (sex, age, previous history of PUD/UGIB, Glasgow coma score, mean arterial pressure, platelet count, INR, aPTT ratio, ALT, Cr, time of mechanical ventilation, NPO time, length of ICU stay or corticosteroid use) were noted. No adverse drug reactions were detected in the study. The results of endpoints were as follow: 6 UGIB (26.1%), 6 deaths (13%), 11 without further risk of SRMD bleeding (47.8%) and 3 withdrawals (13%). All outcomes (UGIB rate, HAP/VAP rate, in-hospital mortality rate, percentage of changes in serum NO) were not significantly different between the two groups.

**Conclusion:** No statistically significant differences between oral rebamipide and intravenous ranitidine in SRMD bleeding prophylaxis for high-risk neurosurgical patients were detected in this study. Rebamipide may have effective choice in SRMD bleeding prophylaxis strategy. Larger multicentre clinical trials are needed to confirm the observation.

**Key words :** Rebamipide, SRMD, UGIB

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## INTRODUCTION

Stress-related mucosal damage (SRMD) is an important cause of acute upper gastrointestinal bleeding (UGIB) in critically ill hospitalized patients, especially those with such significant risk factors as prolonged mechanical ventilation for more than 48 hours (odd ratio; OR 15.6) and coagulopathy (platelet count less than 50,000/mm<sup>3</sup>, INR >1.5 or aPTT ratio >2; OR 4.3),<sup>(1)</sup> and neurologic diseases causing impaired consciousness with Glasgow coma scale (GCS) less than 10.<sup>(1)</sup> The prevalence of SRMD bleeding varies from 1 to 100% depending on the diagnostic criteria used, such as occult, overt or clinically significant bleeding, although no relevant data had been reported in Thailand.<sup>(1-5)</sup> Some studies have shown that clinically significant bleeding from SRMD impacts on mortality, length of ICU or hospital stay and expenses, such that preventive strategies are important and useful.<sup>(1,6-8)</sup> Up to now, all proven preventive strategies for SRMD bleeding can be divided into non-pharmacologic and pharmacologic therapies. Non-pharmacologic therapy includes correction of risk factors, hemodynamic stabilization and early enteral nutrition.<sup>(9,10)</sup> Evidence-based effective pharmacologic agents for SRMD bleeding prophylaxis are H<sub>2</sub> receptor blockades (H<sub>2</sub>RB), proton pump inhibitors (PPI) and sucralfate.<sup>(9,11-16)</sup> However, an important disadvantage of H<sub>2</sub>RB or PPI is the development of hospital-acquired or ventilator-associated pneumonia (HAP or VAP) due to their strong acid suppressions.<sup>(16-20)</sup> Thus acid suppression therapy is not the best strategy for SRMD bleeding prevention. Currently, there are no definite recommendations on this issue.

The pathogenesis of SRMD was an imbalance between gastric acid production and mucoprotective mechanism. In neurotraumatic patients, hypergastrinemia was observed particularly in the first 3-5 days after the onset from unopposed parasympathetic stimulation or absent sympathetic outflow.<sup>(16)</sup> Many factors such as bile reflux or uremic toxins also damage the glycoprotein mucus barrier of the gastric mucosa.<sup>(9)</sup> Furthermore, mucosal ischemia from either shock or sepsis, starvation, corticosteroid use and *H. pylori* infection may play a role.<sup>(9)</sup> Molecular biological studies have shown interactions among inflammatory cytokines, reactive oxygen species (ROS) and nitric oxide (NO) pathway.<sup>(15,21,22)</sup>

Rebamipide is an approved drug for treatment of peptic ulcer disease (PUD) and acute gastritis in

Thailand as from 2002. Its mechanisms of action include an increased mucosal blood flow via the prostaglandin pathway, activation of mucosal cell turnover and mucus production, and blocking of inflammatory cytokines and oxygen free radicals but not gastric acid.<sup>(23-25)</sup> Considering its action along with the pathogenesis of SRMD, this drug may thus be safely chosen for use in SRMD bleeding prophylaxis, with an expected lower rate of HAP/VAP in comparison with acid-suppressing agents. The reported adverse reactions of rebamipide are rather mild and infrequent such as rash, somnolence, dizziness, GI upsets, transaminitis, cytopenias and renal impairment.<sup>(23,24)</sup>

The aim of this study is to compare the outcomes, such as UGIB rate, HAP/VAP rate, mortality rate and altered serum NO level, after rebamipide use for SRMD bleeding prophylaxis in high-risk neurosurgical patients, comparing with conventional H<sub>2</sub>RB therapy.

## MATERIALS & METHODS

### Subjects

High-risk patients admitted to the neurosurgical ICU, Division of Neurosurgery, Maharaj Nakorn Chiang Mai Hospital between July 2007 and December 2007 were recruited. Twenty-three patients were enrolled with the following inclusion and exclusion criteria.

**Inclusion Criteria:** Neurosurgical patients aged over 18, male or female, with significant risk factors for SRMD bleeding, (such as prolonged mechanical ventilation for more than 48 hours or coagulopathy (platelet count less than 50,000/mm<sup>3</sup>, INR >1.5 or aPTT ratio >2). All patients or their delegates were informed about the objectives, methods and possible risks. Written informed consents were also obtained.

**Exclusion Criteria:** Patients with other additional risk factors for SRMD were excluded (such as burn more than 35% of body surface area, severe multiple trauma with injury severity score more than 16, liver failure, hepatic or renal transplantation, history of PUD or UGIB within 1 year and severe sepsis or profound shock).<sup>(1)</sup> Allergy or absolute contraindications to rebamipide or ranitidine treatment, detectable UGIB and HAP/VAP, high risk for blood swallowing (false positive UGIB), need for GI tract surgery or contraindications for enteral drug feeding, previous history of chronic liver disease or portal hypertension, recent treatment with SRMD prophylactic drugs, and patients

with grave prognosis were also excluded. Patients on significant corticosteroid therapy (equivalent dose of hydrocortisone more than 250 mg/day) or patients with chronic kidney disease were excluded.

### Study design

This pilot study was randomized, prospective and unblind. All selected patients were randomly divided to receive oral rebamipide or intravenous ranitidine. The standard dosage of rebamipide was 100 mg every 8 hours.<sup>(23,24)</sup> Ranitidine dosage was adjusted according to renal function: 50 mg every 8 hours for creatinine clearance (CCr) >50 ml/min, 50 mg every 12 hours for CCr 25-50 ml/min or on dialysis therapy and 50 mg once a day for CCr <25 ml/min.<sup>(17)</sup> At baseline, all patients had blood tests, chest radiographs. Medications were given continuously up to the endpoints.

**Endpoints:** The end point was marked if the patient developed UGIB, expired from any cause, significant risk factors for SRMD were no longer evident, was discharged from ICU, or refused to complete the study (Figure 1).

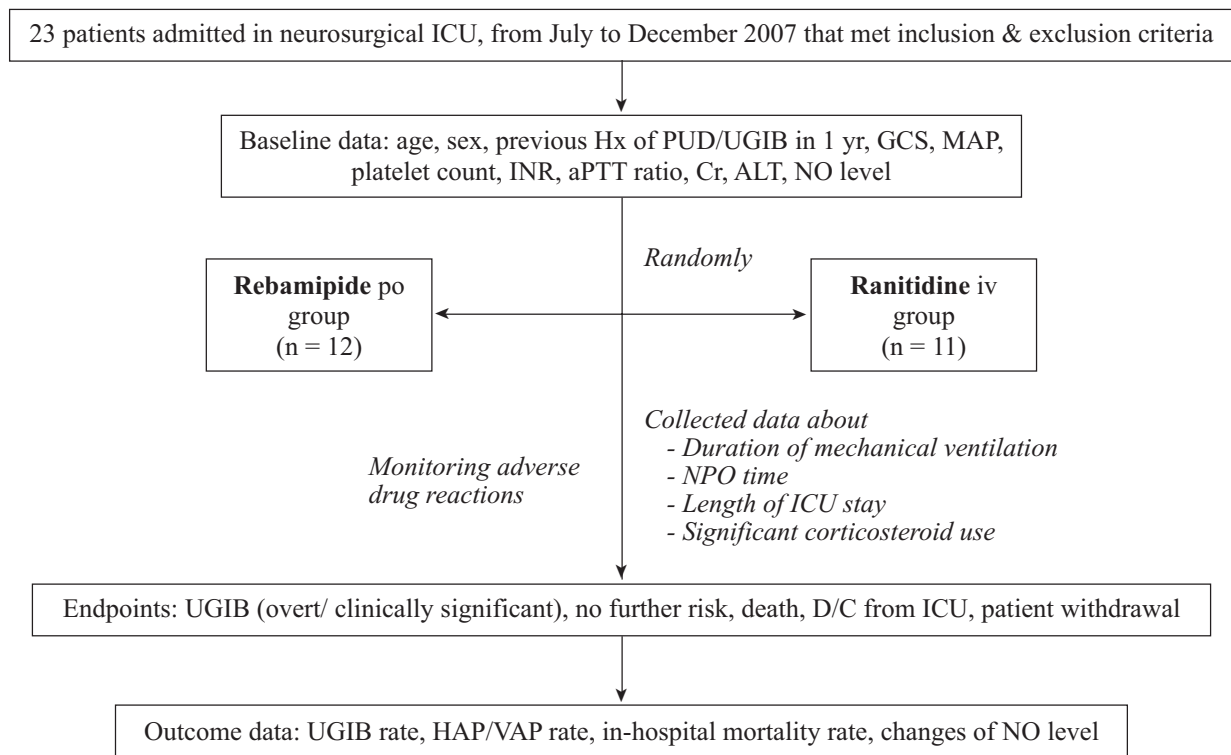
Patients who developed overt or clinically significant UGIB would receive standard medical care, namely initial resuscitation, intravenous PPI, blood component transfusion, esophagogastroduodenoscopy

(EGD) or surgery as indicated. Subsequent HAP/VAP were treated with suitable intravenous antibiotics. Causes of death were reviewed.

### Data collection

At baseline, the following data were collected: sex, age, past history especially UGIB or PUD within a year, the first GCS, and mean arterial pressure (MAP) on the day of admission. Blood tests were taken for platelet count, INR, aPTT ratio, creatinine (Cr), alanine aminotransferase (ALT) and NO level prior to drug therapy. During the study, duration of mechanical ventilation, NPO time, corticosteroid use, length of ICU stay and adverse drug reactions were also recorded. Finally, the outcomes such as UGIB, HAP/VAP, mortality and altered serum NO level were decided, based on appropriate definitions (Figure 1).

**UGIB:** UGIB was classified into overt, clinically significant and late bleeding. Overt UGIB manifested as hematemesis, melena, hematochezia, and bloody or coffee ground NG content.<sup>(17)</sup> Clinically significant UGIB was more severe and was evident with at least one of the followings: systemic hypotension (SBP or DBP decrease >20 mmHg) within a day and without other identifiable causes, postural hypotension (SBP decrease >10 mmHg or heart rate increase >20/min in



**Figure 1.** Flow chart of study protocol.

an upright position), hemoglobin (Hb) decrease >2 g/dL requiring packed red cell (PRC) transfusion >2 units/24 hours.<sup>(17)</sup> Late UGIB meant overt or clinically significant bleeding that occurred outside of the period of drug therapy.

**HAP/VAP:** The diagnostic criteria of HAP from the US FDA guidance, CDER 1998 were employed, namely, onset of symptoms >72 hours after admission or not more than a week after the last hospital discharge, new or evolving infiltrates without other explainable causes, new onset of purulent sputum or increased amount of sputum, and including one of the followings: fever (oral temperature >38°C), hypothermia (oral temperature <35.5°C), total white blood cell (WBC) count >10,000/mm<sup>3</sup> or <4,500/mm<sup>3</sup>, and band form polymorphonuclear cells (PMN) >15%.<sup>(26)</sup> VAP was HAP occurring while the patient is on mechanical ventilator more than 48 hours, (classified into early onset and late onset categories). Sputum Gram's stain, sputum culture and other invasive investigations such as bronchoalveolar lavage or protected brushed-catheter sampling might be needed for microbiologic purposes.

**Measurement of Serum NO Level:** The Griess reagent system (Promega Corporation, WI, USA) was employed to measure amounts of stable nonvolatile breakdown products, serum nitrite (NO<sub>2</sub><sup>-</sup>), by means of absorbance spectrum of the purple-colored azo compound from Griess reaction between sulfanilamide and N-1-naphthylethylenediamine dihydrochloride (NED) solutions.<sup>(27)</sup> Serum NO levels were reported in µM.

### Statistical Analysis

All categorical variables were summarized in frequencies and percentages. Continuous variables were reported as means, standard deviations (SD), medians

and ranges. Differences between the continuous variables of the two study groups were assessed by student's *t* test and Mann-Whitney U test for parametric and nonparametric data respectively. Differences between the categorical data were assessed by Chi-square ( $\chi^2$ ) or Fisher's exact test. A *p* value of less than 0.05 was considered statistically significant. All statistical analyses were performed by using the SPSS version 15.

### RESULTS

The 23 patients in this study were mostly male (16, 69.6%) and had a mean age of 43.87 ± 19.70 years (range 18-78). Female patients were older, with a mean age of 48.86 ± 20.48 (mean age for male 41.69 ± 19.62). On the first day of admission to ICU, the entire group had a median GCS of 6 (range 2-10), mean MAP of 112.35 ± 25.67 mmHg, mean platelet count 278.87 ± 97.34 × 10<sup>3</sup> cells/mm<sup>3</sup>, mean INR 1.24 ± 0.17, mean aPTT ratio 1.04 ± 0.15, mean Cr level 1.12 ± 0.73 mg/dL and mean ALT level 41.52 ± 36.27 U/L. Nearly all had no previous history of UGIB or PUD within a year (unknown in 2 cases). All baseline characteristics and laboratory data for the rebamipide and the ranitidine groups were not significantly different (Table 1).

Over the study period, the overall mean time of mechanical ventilation was 9.13 ± 9.71 days (range 1-39), the overall mean NPO time was 2.61 ± 1.73 days (range 1-7), the overall mean time of ICU stay was 10.04 ± 9.52 days (range 1-39), and only 4 patients (35.6%) received significant corticosteroid therapy. No statistically significant differences were detected between these data in the two groups (Table 2). There were no confirmed adverse drug reactions in both

**Table 1.** Demographic characteristics and baseline laboratory data of the patients.

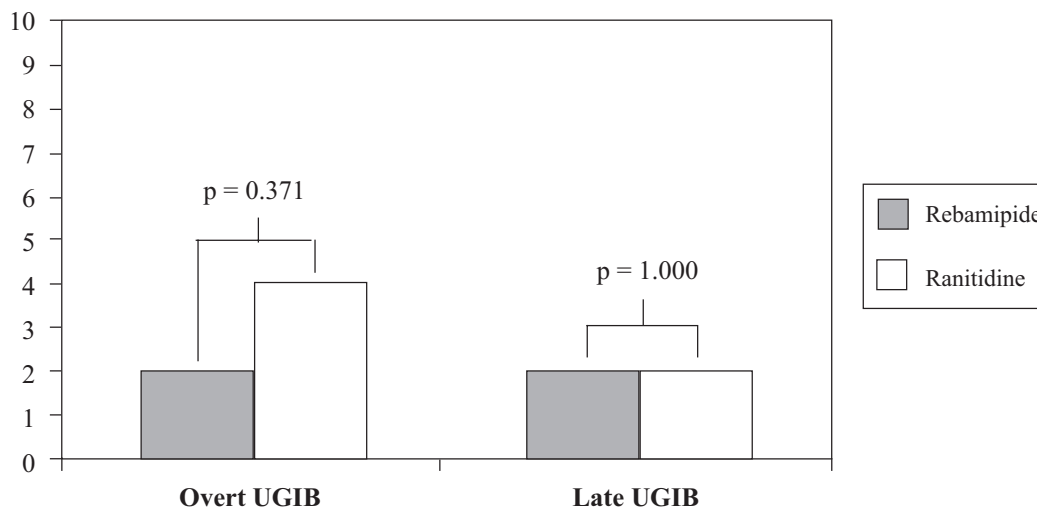
Parameters	Rebamipide group (n = 12)	Ranitidine group (n = 11)	<i>p</i> value
Gender (male/female)	7/5	9/2	0.371
Mean age ± SD (years)	37.83 ± 18.12	50.45 ± 20.03	0.127
Median GCS (range)	6 (2-9)	6 (3-10)	0.947
Mean MAP ± SD (mmHg)	104.08 ± 17.75	121.36 ± 30.52	0.108
Mean platelet count ± SD (× 10 <sup>3</sup> cells/mm <sup>3</sup> )	290.50 ± 119.85	266.18 ± 68.60	0.951
Mean INR ± SD	1.27 ± 0.16	1.20 ± 0.18	0.358
Mean aPTT ratio ± SD	1.04 ± 0.11	1.05 ± 0.18	0.689
Mean ALT ± SD (U/L)	54.67 ± 45.81	27.18 ± 12.29	0.294
Mean Cr ± SD (mg/dL)	0.91 ± 0.15	1.36 ± 1.02	0.367

**Table 2.** Other observed factors that could impact outcomes of the patients during the study.

Observed factors	Rebamipide group (n = 12)	Ranitidine group (n = 11)	p value
Mean time of mechanical ventilation $\pm$ SD (days)	8.83 $\pm$ 10.87	9.45 $\pm$ 8.79	0.711
Mean NPO time $\pm$ SD (days)	2.58 $\pm$ 1.73	2.64 $\pm$ 1.80	0.898
Mean time of ICU stay $\pm$ SD (days)	10.25 $\pm$ 10.45	9.82 $\pm$ 8.90	0.975
Significant corticosteroid use (%)	1 (8.3)	3 (27.3)	0.317

**Table 3.** The Endpoints of the study.

Endpoints	Rebamipide group (n = 12)	Ranitidine group (n = 11)	p value
UGIB:			
overt (%)	2 (16.7)	4 (36.4)	0.371
clinically significant (%)	-	-	-
Death (%)	1 (8.3)	2 (18.2)	0.590
No further risk of SRMD bleeding (%)	7 (58.3)	4 (36.4)	0.414
Discharge from ICU (%)	-	-	-
Patient withdrawal (%)	2 (16.7)	1 (9.0)	1.000

**Figure 2.** Incidence of UGIB in this study.

groups.

The endpoints for all cases were classified as follows: occurrence of UGIB in spite of prophylactic therapy in 6 patients (26.1%), death in 3 patients (13%), no further significant risk of SRMD bleeding in 11 cases (47.8%) and 3 cases withdrawals (13%). The reasons for withdrawal were refusal of further treatment due to very poor prognosis (1), suspected concomitant esophageal injury (1), and precipitated

cardiac event requiring aspirin therapy (1). No significant differences of endpoints were detected between the two groups (Table 3).

The overall outcomes in our study were UGIB occurring in 10 patients (43.5%), which were classified into overt bleeding during prophylactic therapy in 6 patients (26.1%) and late UGIB after the study endpoints in four (17.4%) (Figure 2). No clinically significant UGIB occurred in any cases and also no sig-



**Table 4.** The outcomes of the study.

Outcomes	Rebamipide group (n = 12)	Ranitidine group (n = 11)	p value
Primary			
UGIB:			
none (%)	8 (66.7)	5 (45.5)	0.632
overt (%)	2 (16.7)	4 (36.4)	
clinically significant (%)	-	-	
late (%)	2 (16.7)	2 (18.2)	
Secondary			
HAP/VAP			
none (%)	8 (66.7)	9 (81.8)	0.590
early (%)	1 (8.3)	-	
late (%)	1 (8.3)	2 (18.2)	
others- CAP (%)	2 (16.7)	-	
In-hospital mortality (%)	1 (8.3)	3 (27.3)	0.317
Mean change in serum NO level ± SD (%)	-5.44 ± 43.89	-14.48 ± 30.86	1.000

nificant differences in bleeding rate of any kinds between the two groups (Table 4).

HAP/VAP, occurred in 4 cases (17.4%). Only 1 patient (4.3%) developed early HAP/VAP (onset less than one week), while 3 patients (13%) developed late HAP/VAP (onset after one week). Two of 23 patients (8.7%) developed pneumonia less than 72 hours after admission, apparently community-acquired (CAP). Sputum culture in early HAP/VAP was revealed *Pseudomonas aeruginosa*, while the pathogens in late HAP/VAP were *Acinetobacter baumannii* (1), *Pseudomonas aeruginosa* (1), *Klebsiella rhinoscleromatis* (1) and *Hemophilus influenzae* (1). In CAP, *Klebsiella pneumoniae* (non-ESBL) was detected (no data in 1 case). No significant differences were noted between the two groups regarding the occurrence of HAP/VAP or CAP (Table 4). Four patients in this study (17.4%) expired, from *Klebsiella* spp. sepsis and 3 cases from severe brain injury.

The overall mean change in serum NO level was  $-9.75 \pm 37.59\%$  (range  $-70.59$  to  $91.89$ ), 5 cases (21.74%) with an increased level and 16 cases (69.57%) with a decreased level. Data for changes in serum NO levels were missing in 2 cases (8.67%). No significant differences between the two groups were detected (Table 4).

## DISCUSSION

Our study is the first to demonstrate the efficacy

of rebamipide in SRMD bleeding prophylaxis for high-risk patients. We chose to study patients in the neurosurgical ICU because of rather uniform baseline characteristics and a relatively high incidence of SRMD (12.5% from autopsy review).<sup>(28)</sup> We chose rebamipide because of its opposing mechanism of action in the pathogenesis of SRMD, its safety profile, convenient route of administration, and its relatively low cost. Although the major pathogenesis of SRMD in neurologic patients is believed to be related to disorders in hormonal brain-gut axis (vagal hyperactivity), many studies have reported the prophylactic efficacy of sucralfate alone without other acid suppression methods.<sup>(16)</sup> We also wanted to observe the rate of HAP/VAP after drug therapy, that was postulated in many studies of H<sub>2</sub>RB and PPI to be a risk factor.

There were no significant differences in baseline characteristics, laboratory data and other observed factors in the two study groups. The overall rate of UGIB of about 43.5% in this study was rather high, although there were no cases of clinically significant bleeding. The bleeding rate in the ranitidine group (36.4%) appeared higher than in many previous studies (1.7-31%), possibly due to our small sample size and the different definitions of UGIB used.<sup>(17,29)</sup> Looking at the relation between the overall death rate and the overall rate of UGIB, we found no significant correlation ( $p = 0.604$ ). The only observed factor correlated to the occurrence of UGIB was corticosteroid usage. ( $p = 0.024$ ) There was no significant difference in the effectiveness

between using rebamipide or ranitidine as a prophylactic drug. Furthermore, mean NPO time in this study was rather short ( $2.61 \pm 1.73$  days, range 1-7 drugs), reflecting the use of early enteral nutrition as another SRMD bleeding prophylactic strategy as evident in some reports.<sup>(9,10)</sup>

HAP/VAP occurred in about 17.4% and there were no detectable differences between the two groups. Other modifying factors, such as duration of mechanical ventilation, duration of SRMD prophylaxis, or prior infection, which were important risks for HAP/VAP according to a previous report from Thailand<sup>(30)</sup>, did not appear significant in our study. Lastly, the occurrence of HAP/VAP appeared to bear no significant correlation with the length of ICU stay and the mortality rate ( $p = 0.080$  and  $p = 1.000$  respectively).

The overall in-hospital mortality rate was 17.4%, with no differences between the two study groups. There were also no significant correlations between other relevant factors and the in-hospital mortality (including the occurrence of UGIB and HAP/VAP).

The percentages of changes in serum NO levels were not associated with the occurrence of UGIB ( $p = 0.620$ ), while no other factors affected changes in NO levels either. No significant differences in altered serum NO levels between the two groups were detected, although more patients in the rebamipide group showed decreasing levels (83.3% vs 72.7%). The reasons were due to our small sample size. Secondly, a wide variation of NO level in each case was detected (mean baseline level  $27.50 \pm 10.54$ , range 16.85-64.76), thus causing variations in statistical calculations. Thirdly, normal values of serum NO level have not been established. Fourthly, many factors also impacted the results, such as the timing of test, blood samples and reagent system needed for light protection. And ideally, if we could have tested for subtypes of nitric oxide synthase (NOS, enzymes that produce NO, such as iNOS, eNOS or nNOS), the results would have been better.

## CONCLUSION

In this study, there were no significant differences between using oral rebamipide or intravenous ranitidine in SRMD bleeding prophylaxis among high-risk neurosurgical patients, with regard to UGIB rate, HAP/VAP rate, in-hospital mortality or percentages of changes in serum NO level. A larger clinical study

with adequate sample size is needed to verify these observations. Rebamipide in future may well be another alternative in SRMD bleeding prophylactic strategy.

## REFERENCES

1. Cook D, Fuller HD, Guyatt GH, *et al.* Risk factors for gastrointestinal bleeding in critically ill patients. Canadian critical care trial groups. *N Eng J Med* 1994; 330:377-81.
2. Ben-Menachem T, Fogel R, Patel RV, *et al.* Prophylaxis for stress-related gastric hemorrhage in the medical intensive care unit: A randomized controlled single blind study. *Ann Intern Med* 1994;121:568-75.
3. Shuman RB, Schuster DP, Zuckerman GR. Prophylactic therapy for stress ulcer bleeding: A reappraisal. *Ann Intern Med* 1987;106:562-7.
4. Smythe MA, Zarowitz BJ. Changing perspectives of stress gastritis prophylaxis. *Ann Pharmacother* 1994;28:1073-85.
5. Pruitt BA Jr, Goodwin CW Jr. Stress ulcer disease in the burned patient. *World J Surg* 1981;5:209-22.
6. Navab F, Steingrub J. Stress ulcer: is routine prophylaxis necessary? *Am J Gastroenterol* 1995;90:708.
7. Ritchie W. Role of bile acid reflux in acute hemorrhagic gastritis. *World J Surg* 1981;5:189.
8. Schindlbeck NE, Lippert M, Heinrich C, *et al.* Intra-gastric bile acid concentrations in critically ill, artificially ventilated patients. *Am J Gastroenterol* 1989;84:624.
9. Friedman S, Manaker S, Weinhouse GL. Stress ulcer prophylaxis in the intensive care unit. *UTD* 2006;14:2.
10. Raff T, Germann G, Hartmann B. The value of early enteral nutrition in the prophylaxis of stress ulceration in the severely burned patient. *Burns* 1997;23:313.
11. Cheatham ML. Surgical critical care and medical critical care services at Orlando regional medical center. Revised guidelines for stress ulcer prophylaxis 2005.
12. Baghaie AA, Mojtahedzadeh M, Levine RL, *et al.* Comparison of the effect of intermittent administration and continuous infusion of famotidine on gastric pH in critically ill patients: Results of a prospective randomized cross-over study. *Crit Care Med* 1995;23:687.
13. Ballesteros MA, Hogan DL, Koss MA, *et al.* Bolus or intravenous infusion of ranitidine: effects on gastric pH and acid secretion. *Ann Intern Med* 1990;112:334.
14. Pemberton LB, Schaefer N, Goehring L, *et al.* Oral ranitidine as prophylaxis for gastric stress ulcers in intensive care unit patients: Serum concentrations and cost comparisons. *Crit Care Med* 1992;21:339.
15. Metz DC. Preventing the gastrointestinal consequences of stress-related mucosal disease. *Curr Med Res Opin* 2005;21:11-7.
16. Lu WY, Rhoney DH, Boling WB, *et al.* A review of stress ulcer prophylaxis in the neurosurgical intensive care unit. *Neurosurgery* 1997;41:416-26.

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17. Cook D, Guyatt G, Marshall J, *et al.* A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. *N Engl J Med* 1998;338:791-6.
18. Cook DJ, Reeve BK, Guyatt GH, *et al.* Stress ulcer prophylaxis in critically ill patients: Resolving discordant meta-analysis. *JAMA* 1996;275:308.
19. Levy MJ, Seelig CB, Robinson NJ, *et al.* Comparison of omeprazole and ranitidine for stress ulcer prophylaxis. *Dig Dis Sci* 1997;42:1255-9.
20. Conrad SA, Gabrielli A, Margolis B, *et al.* Randomized double-blind comparison of immediate-release omeprazole oral suspension vs intravenous cimetidine for the prevention of upper gastrointestinal bleeding in critically ill patients. *Crit Care Med* 2005; 33:760.
21. Bandyopadhyay D, Chattopadhyay A. Reactive oxygen species-induced gastric ulceration: protection by melatonin. *Current Medicinal Chemistry* 2006;13:1187-202.
22. Elliott SN, Wallace JL. Nitric Oxide: A regulator of mucosal defense and injury. *J Gastroenterol* 1998;33:792-803.
23. Thomson Micromedex 2000. Drugdex drug evaluation: rebamipide. [online]. Available: <http://micromedex.hsis.uci.edu/120/mdxcgi/display.exe?CTL=E:\micromedex\120\mdxcgi\MEGAT.SYS&SET=1C48AB228AE12C80&SYS=1&T=1745&D=1> [Accessed data 2004 Aug 10]
24. Otsuka Pharmaceutical CO.,Ltd. 2000. Mucosta®. [online]. Available: <http://www.jpma.or.jp/jpr/PDF/OTSUPII.PDF>. [Accessed data 2004 Aug 10]
25. Arakawa T, *et al.* *Dig Dis Sci* (9) 55-135.
26. Guidance for industry: Nosocomial Pneumonia. Developing antimicrobial drugs for treatment (draft). US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Available at: <http://www.fda.gov/cder/guidance/2571 dft.pdf>. Accessed Jan 30, 2005.
27. Promega corporation. Technical bulletin: Griess reagent system- instructions for use of product G2930.
28. Karch S. Upper gastrointestinal bleeding as a complication of intracranial disease. *J Neurosurg* 1972;37:27-9.
29. Levy MJ, Seelig CB, Robinson NJ, *et al.* Comparison of omeprazole and ranitidine for stress ulcer prophylaxis. *Dig Dis Sci* 1997;42:1255-9.
30. Jamulitrat S, Seeluengsawat S, Boonkasem T, *et al.* Letter to the editor: Stress ulcer prophylaxis and risk of developing ventilator-associated pneumonia. *AJIC* 2003:52.