

Proton Pump Inhibitors for the Prevention of Stress-Related Mucosal Disease in Critically-Ill Patients: A Meta-Analysis

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Background: Despite the scanty data, proton pump inhibitors (PPI) are widely used for stress-related mucosal disease (SRMD) prophylaxis. There were few studies using PPI for SRMD prophylaxis but the results were conflicting, most probably due to inadequate sample size. The present meta-analysis aimed to determine the efficacy of PPI, as compared to histamine-2 receptor antagonists (H₂RA) in the prevention of SRMD in critically-ill patients.

Material and Method: Meta-analysis of the randomized controlled trials comparing PPI versus H₂RA for SRMD prophylaxis was performed. Outcomes of interest were incidences of clinically important gastrointestinal bleeding and nosocomial pneumonia.

Results: Three studies involving 569 patients were included in the meta-analysis. The overall incidence of clinically important bleeding was significantly lower in the PPI group (3.5%) as compared to H₂RA (8%), odds ratio (OR) 0.42 (95% CI 0.20-0.91). The incidences of nosocomial pneumonia were not different (10.2% versus 10.1%, OR 1.02, 95% CI 0.59-1.75) between the two groups.

Conclusion: The use of PPI for SRMD prophylaxis was associated with a significantly lower rate of clinically important bleeding than H₂RA with similar rates of nosocomial pneumonia.

Keywords: Stress-related mucosal disease, Stress ulcer, Prophylaxis, Proton pump inhibitor, Omeprazole, Histamine-2 receptor antagonist

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Stress-related mucosal disease (SRMD) is a diffuse mucosal injury of the stomach that develops in critically-ill patients. The pathogenesis of SRMD is incompletely understood but major factors responsible for SRMD are the decrease in gastric mucosa blood flow, mucosal ischemia, and hypoperfusion-reperfusion injury⁽¹⁾. Clinical spectrum of SRMD can vary from asymptomatic mucosal lesions detected by endoscopy, occult gastrointestinal (GI) bleeding causing anemia to overt GI bleeding presenting with melena or hematochezia. However, the most severe manifestation of

SRMD is clinically important bleeding, defined by overt GI bleeding associated with hemodynamic instability or requiring blood transfusion since clinically important bleeding is associated with an increased morbidity and mortality of the patients⁽²⁾. Two well-established risk factors posing critically-ill patients at risk of SRMD with clinically important bleeding are mechanical ventilation for > 48 hours and coagulopathy (and/or thrombocytopenia)⁽³⁾. The overall incidence of clinically important bleeding is 1.5% in general, but rises to 3.7% if patients have either one of these factors, and in contrast, drops to only 0.1% in patients without these factors⁽³⁾.

Once established, the treatment of SRMD is usually ineffective. Thus, many strategies, particularly SRMD prophylaxis with pharmacological therapy

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have been studied including antacids, H₂-receptor antagonists (H₂RA) and sucralfate. A meta-analysis by Cook in 1996⁽⁴⁾ reported that prophylactic therapy with H₂RA (most of which was cimetidine) and sucralfate reduced the incidence of clinically important bleeding as compared to placebo. However, the subsequent largest randomized controlled trial (RCT) to date of SRMD prophylaxis showed that ranitidine is significantly more effective than sucralfate in reducing clinically important bleeding with a similar incidence of nosocomial pneumonia⁽⁵⁾. Since then, H₂RA has become a standard SRMD prophylaxis in most intensive care practices.

Proton pump inhibitors (PPI) are the most effective agents for suppressing gastric acid secretion. The superior efficacy of PPI over H₂RA has been demonstrated in various GI disorders, including peptic ulcer, gastroesophageal reflux disease, GI damage caused by non-steroidal anti-inflammatory drugs, and Zollinger-Ellison syndrome. Therefore, PPI are now considered the drugs of choice in the management of most acid-related GI disorders. The advantage of PPI over H₂RA is that there is no tachyphylactic phenomena reported in patients taking PPI, resulting in more predictable and sustained pH control than H₂RA. Adverse effects from PPI are also uncommon⁽⁶⁾.

In SRMD prophylaxis, PPI has widely been used despite the scanty data. There have been a few studies on the use of PPI for SRMD prophylaxis and the results are inconsistent and most studies had inadequate sample size⁽⁷⁻¹¹⁾. Meta-analysis of the RCT is therefore another way to solve this problem. Thus, the authors conducted a meta-analysis of the RCTs that compared the effectiveness of PPI with H₂RA in the prevention of clinically important bleeding in critically-ill patients and determine whether it increases the incidence of nosocomial pneumonia in these patients.

Material and Method

Identification of sources

The authors used Medline/ EMBASE search and covered the period from 1950 to January week 2, 2008. Using the term “prophylaxis”, “prevention”, “primary prevention” combined with “bleeding”, “hemorrhage”, and “omeprazole” or “proton pump inhibitors”. Terms were searched as subject headings and text words and search was limited to human, randomized controlled trial and studies in adults. In addition, evidence based medicine reviews including American College of Physicians journal club,

Cochrane controlled trials register, Cochrane database of systematic review and database of abstracts of reviews of effectiveness were search.

The inclusion criteria were RCTs comparing between PPI and H₂RA. The primary outcome of interest was clinically important bleeding and the secondary outcome was nosocomial pneumonia. Only studies that included critically-ill patients with any of the two risk factors (mechanical ventilation > 48 hours or coagulopathy) were selected.

Data extraction

Data were extracted by two reviewers (S.K. and C.N.) independently with a structured form. Differences in opinion between the two reviewers were resolved by consensus agreement.

Assessment of the quality of the trials

Five items were evaluated for each trial (patient selection, patient characteristics, randomization, blinding, definitions of bleeding and pneumonia). Methodological quality was graded for each of the five items on a scale of 0, 1, 2 (maximum score was 10). Three observers independently assessed the quality of the trials. Differences in opinion among reviewers were resolved by consensus agreement.

Results

The authors retrieved 24 potentially eligible citations, whose abstracts were reviewed. Twenty-one articles were excluded; 18 because of history of aspirin or NSAID use, active GI bleeding, or post-endoscopic treatment, and three because of the absence of interested outcome. Therefore, three studies involving 569 patients (282 patients in PPI group and 287 patients in H₂RA group) were finally included in the meta-analysis⁽⁹⁻¹¹⁾. The two reviewers had initial agreement on 3/3 (100%) entries regarding the study method and results. Details of the studies are shown in Table 1. The methodological quality rating of the three studies was 9-10 (Table 2).

Clinically important bleeding

The incidence of clinically important bleeding in the PPI group was 10/282 (3.5%) and the H₂RA group was 23/287 (8%). PPI was associated with significantly less clinically important bleeding than H₂RA with an OR 0.42 and 95% confidence interval (CI) of 0.20-0.91 (Table 3, Fig. 1). The absolute risk reduction of clinically important bleeding of PPI was 4.5% with a number needed to treat (NNT) of 22.

Table 1. Characteristics of the 3 included studies

Author, year	Study type	Evidence level	n	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding
Levy, 1999 ⁽⁹⁾	RCT	1	67	ICU patients, at least 1 of 9 risk factors: burn, coagulopathy, acute hepatic failure, major neurologic insult, acute renal failure, respiratory failure, sepsis, shock, and trauma	Omeprazole 40 mg oral or via nasogastric tube	Ranitidine 50 mg IV bolus then 150 mg IV drip daily or 50 mg IV q 8 hrs	Until discharge or death	Clinically important bleeding, nosocomial pneumonia	-	-
Kantorova, 2004 ⁽¹⁰⁾	RCT	1	143	Critically-ill patients in surgical ICU who required mechanical ventilation for ≥ 48 hrs, coagulopathy	Omeprazole 40 mg IV once daily	Famotidine 40 mg IV twice a day	Until discharge or death	Clinically significant bleeding, nosocomial pneumonia	-	Grants of IGA MZ CR ND
Conrad, 2005 ⁽¹¹⁾	RCT	1	359	ICU patients, who required mechanical ventilation for ≥ 48 hrs, had APACHE score of ≥ 11 at baseline, had an intact stomach with a nasogastric or orogastric tube in place, and had at least one additional risk factor for UGI bleeding: closed-head injury, multiple trauma, major surgical procedure, extensive burns, acute renal failure, acid-base disorder, coagulopathy, marked jaundice, coma, hypotension, shock, sepsis	Omeprazole 40 mg oral 2 doses in day 1, then 40 mg oral once daily	Cimetidine 300 mg IV bolus then IV drip 50 mg/hr	Until discharge or death	Clinically significant bleeding, any overt GI bleeding, inadequate pH control	-	Santarus, San Diego, CA

Table 2. Methodological quality rating scales of the included trials

Study	Patient selection	Patient characteristics	Randomization	Blinding	Definition	Total
Levy, 1997	2	1	2	2	2	9
Kantorova, 2004	2	2	2	2	2	10
Conrad, 2005	2	1	2	2	2	9

Patient selection (inclusion and exclusion criteria): 2 = clearly defined, 1 = inadequately defined, 0 = not defined

Patient characteristics: 2 = group comparable, 1 = inadequately described, 0 = obvious differences

Randomization: 2 = clearly described, 1 = unclear, 0 = no

Blinding: 2 = yes, 1 = some, 0 = no blinding or not mentioned

Definition of outcomes (clinically important bleeding, nosocomial pneumonia): 2 = clearly defined, 1 = inadequately defined, 0 = not defined

Table 3. Meta-analysis of the clinically important bleeding between PPI and H₂RA

Study	PPI	H ₂ RA	Odds ratio	95% CI
Levy, 1997	2/32	11/35	0.15	0.03-0.72
Kantorova, 2004	1/72	2/71	0.49	0.04-5.48
Conrad, 2005	7/178	10/181	0.70	0.26-1.88
Total	10/282	23/287	0.42	0.20-0.91

Test for heterogeneity: Q = 2.7176, DF = 2, P = 0

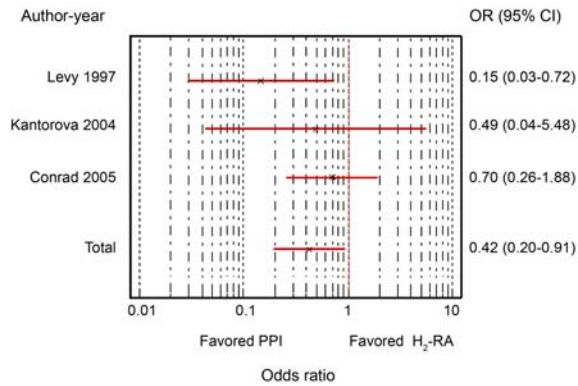


Fig. 1 Meta-analysis of the incidence of clinically important bleeding between PPI and H₂RA

Nosocomial pneumonia

The incidence of nosocomial pneumonia in patients using PPI was 29/282 (10.3%) and H₂RA was 29/287 (10.1%). The result was not statistically significant (Table 4, Fig. 2).

Discussion

In the present meta-analysis, the authors aimed to compare the efficacy of PPI to H₂RA in the prevention of SRMD in the critically-ill patients. The authors chose clinically important bleeding, which is the most important outcome affecting patients morbidity-mortality⁽²⁾ and nosocomial pneumonia, which is the most concerning issue for physicians regarding SRMD prophylaxis as main outcomes in the present meta-analysis. Although overt gastrointestinal bleeding is the more commonly observed outcome, its impact on patients' outcomes was found to be insignificant in contrast to clinically significant bleeding⁽²⁾.

The present meta-analysis could demonstrate that PPI was more effective than H₂RA in the prevention

Table 4. Meta-analysis of the incidence of nosocomial pneumonia between PPI and H₂RA

Study	PPI	H ₂ RA	Odds ratio	95% CI
Levy, 1997	1/32	5/35	0.19	0.02-1.76
Kantorova, 2004	8/72	7/71	1.14	0.39-3.34
Conrad, 2005	20/178	17/181	1.22	0.62-2.42
Total	29/282	29/287	1.02	0.59-1.75

Test for heterogeneity: Q = 2.495, DF = 2, P = 0.287

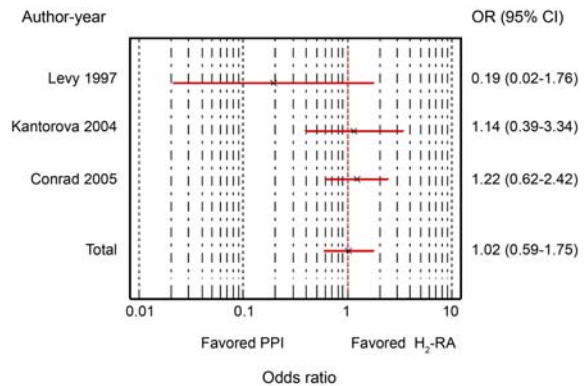


Fig. 2 Meta-analysis of the incidence of nosocomial pneumonia between PPI and H₂RA

of clinically important bleeding from SRMD, while the incidences of nosocomial pneumonia were similar between both groups. The absolute risk reduction of clinically important bleeding of PPI was 4.5% over H₂RA with a NNT of 22 without increasing the incidence of pneumonia might support PPI to be the first-line option of SRMD prophylaxis.

Nevertheless, in the interpretation of the present meta-analysis, the following aspects deserve attention. Firstly, the three studies included some different high-risk patients for SRMD and used some different definitions of the clinically important bleeding and nosocomial pneumonia. Although each study used reasonable and acceptable definitions, they were still different and might somehow affect the reported incidence of the outcomes of interest in the present meta-analysis.

Secondly, although all three studies used a similar type and dosage of PPI (omeprazole 40 mg per day), they compared PPI to the different types of H₂RA (ranitidine⁽⁹⁾, famotidine⁽¹⁰⁾ and cimetidine⁽¹¹⁾). Recent meta-analysis of SRMD prophylaxis by Messori⁽¹²⁾

suggested that individual H₂RA had different efficacy on SRMD prophylaxis. Cimetidine was found to be the only H₂RA that was more effective than placebo, while ranitidine was not.

Finally, all three studies, although were graded as good qualities, they all included relatively low numbers of patients. As a result, 569 patients in the present meta-analysis were relatively low in case of SRMD prophylaxis. It was estimated that in order to detect a significant difference in the incidence of clinically important bleeding with SRMD prophylaxis, which was found in only 3-4% (3.7% in the present meta-analysis), at least 1,000 patients are required. Although the present meta-analysis showed a significant difference in the incidence of clinically important bleeding between PPI and H₂RA, this difference was very marginal (RR 0.42, 95% CI 0.20-0.91). If only another study was excluded, this statistical difference would no longer be present (data not shown). The decision to include the study by Levy⁽⁹⁾ into the present meta-analysis is very important, since it was the study that mainly contributed to the superiority of efficacy of PPI over H₂RA. However, this present study had some pitfalls in patients' randomization since patients were more severe in the H₂RA group than those in the PPI group. As a result, patients in the H₂RA group had a very high incidence of clinically important bleeding (31%) which was too high for patients receiving prophylactic H₂RA in the previous largest study⁽⁵⁾. Nevertheless, the quality of this present study was graded to be as good as the other two studies, thus it was eventually included into the present meta-analysis. For this reason, the authors believe that large well-conducted RCT are still required to add in the meta-analysis before the authors can firmly conclude that PPI is superior to H₂RA for SRMD prophylaxis.

Recently, the important issue in SRMD prophylaxis has become whether SRMD prophylaxis with H₂RA or PPI are really better than placebo. Since the meta-analysis by Cook in 1996⁽⁴⁾ suggested that H₂RA was more effective than placebo in SRMD prophylaxis, H₂RA has become standard SRMD prophylaxis in high-risk patients for SRMD and all the studies on SRMD prophylaxis used H₂RA as controls. Although the recent meta-analysis by Messori⁽¹²⁾ has pointed out that most H₂RA that demonstrated efficacy on SRMD in the meta-analysis by Cook was cimetidine⁽⁴⁾, which is rarely used now⁽¹³⁾ and meta-analysis of ranitidine showed no benefit of ranitidine over placebo for SRMD prophylaxis⁽¹²⁾. However, to

conduct a RCT on SRMD prophylaxis using placebo as a control may face with the ethical issue. This issue also holds true for PPI that it is unclear whether SRMD prophylaxis with PPI is actually better than placebo.

Conclusion

PPI is superior to H₂RA in the prevention of clinically important bleeding from SRMD with a similar rate of nosocomial pneumonia.

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การใช้ยาขับยั้งโปรตอนปั๊มเพื่อป้องกันภาวะแผลในกระเพาะอาหารในผู้ป่วยวิกฤต: เมตาอานาลิซิส

สุพจน์ พงศ์ประสพชัย, สำรวย กริตกระโทก, เชิดชัย นพมณีจำรัสเลิศ

ภูมิหลัง: ยาขับยั้งโปรตอนปั๊มเป็นยาที่มีการใช้อย่างแพร่หลายในการป้องกันภาวะแผลในกระเพาะอาหารในผู้ป่วยวิกฤต แม้ว่าจะมีข้อมูลการศึกษาน้อยและได้ผลขัดแย้งกัน เนื่องจากส่วนใหญ่จำนวนผู้ป่วยในการศึกษาไม่มากพอ เมตาอานาลิซิสนี้มีจุดประสงค์เพื่อเปรียบเทียบประสิทธิภาพระหว่างยาขับยั้งโปรตอนปั๊มกับยาขับยั้งฮิสตามีน-2 ในการป้องกันภาวะแผลในกระเพาะอาหารในผู้ป่วยวิกฤต

วัตถุประสงค์และวิธีการ: ได้นำการศึกษาที่เปรียบเทียบประสิทธิภาพระหว่างยาขับยั้งโปรตอนปั๊มกับยาขับยั้งฮิสตามีน-2 ในการป้องกันภาวะแผลในกระเพาะอาหารในผู้ป่วยวิกฤตมาทำเมตาอานาลิซิส ผลลัพธ์ที่สนใจคืออุบัติการณ์ของภาวะเลือดออกที่มีนัยสำคัญทางคลินิก และการเกิดปอดอักเสบในโรงพยาบาล

ผลการศึกษา: มีการศึกษาทั้งหมด 3 ชิ้น รวมผู้ป่วยทั้งหมด 569 คน อุบัติการณ์ของภาวะเลือดออกที่มีนัยสำคัญทางคลินิกในผู้ป่วยที่ได้รับยาขับยั้งโปรตอนปั๊มเท่ากับร้อยละ 3.5 เทียบกับร้อยละ 8 ในผู้ป่วยที่ได้รับยาขับยั้งฮิสตามีน-2 คิดเป็น 0.42 เท่า (ค่าความเชื่อมั่นร้อยละ 95 เท่ากับ 0.20-0.91) อุบัติการณ์ของการเกิดปอดอักเสบในโรงพยาบาลเท่ากับ ร้อยละ 10.2 และร้อยละ 10.1 ตามลำดับ คิดเป็น 1.02 เท่า (ค่าความเชื่อมั่นร้อยละ 95 เท่ากับ 0.59-1.75) ซึ่งไม่แตกต่างกันอย่างมีนัยสำคัญ

สรุป: ยาขับยั้งโปรตอนปั๊มสามารถป้องกันการเกิดภาวะเลือดออกที่มีนัยสำคัญทางคลินิกจากแผลในกระเพาะอาหารในผู้ป่วยวิกฤตได้ดีกว่ายาขับยั้งฮิสตามีน-2 โดยมีอุบัติการณ์ของการเกิดปอดอักเสบในโรงพยาบาลไม่แตกต่างกัน
