Pharmacy Education (2022) 22(2) 113 - 117
https://doi.org/10.46542/pe.2022.222.113117

IAI SPECIAL EDITION

REVIEW

Meta-analysis of the effectiveness of histamine-2 receptor antagonists as prophylaxis for gastrointestinal bleeding in intensive care unit patients

Fonny Cokro, Juliana Sumartono
Faculty of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, Jakarta, Indonesia

Keywords
Gastrointestinal bleeding
Histamine-2 receptor
Antagonist
Intensive care unit

Correspondence
Fonny Cokro
Pharmacy Study Programme
Faculty of Medicine and Health Sciences
Atma Jaya Catholic University of Indonesia
Jakarta
Indonesia
fonny.cokro@atmajaya.ac.id

Abstract

Background: The risk of upper gastrointestinal bleeding increases in critically ill patients admitted to an intensive care unit (ICU), with 50–77% mortality. Histamine-2 receptor antagonists (H2RAs) are frequently used to prevent gastrointestinal bleeding in ICU patients, but the tests on its effectiveness and safety are still conflicting. **Objective**: To determine the effectiveness and safety of H2RA in preventing gastrointestinal bleeding in ICU patients. **Methods**: Data on randomised controlled trials (RCTs) were collected from the MEDLINE database, ScienceDirect, ClinicalKey, and The Cochrane Library. Two investigators assessed the quality of the trials using the critical appraisal skills program (CASP) checklist for RCT studies, and fixed-effects meta-analysis was carried out using Review Manager software. **Results**: The 12 RCTs showed a reduced risk of gastrointestinal bleeding (RR = 0.40; 95% CI = 0.30 – 0.53; I-square = 38%; p <0.00001) and a decreased number of patients requiring blood transfusion in H2RA group (RR = 0.44; 95% CI = 0.23 – 0.82; I-square = 8%; p = 0.01), and these effects were significantly different from the placebo group. However, there was no significant difference in mortality between the two groups (RR = 0.99; 95% CI = 0.74 – 1.33; I-square = 0%; p = 0.96). Regarding its safety, the administration of H2RAs did not affect the incidence of nosocomial pneumonia (RR = 1.13; 95% CI = 0.82 – 1.55; I-square = 30%; p = 0.46). A sensitivity analysis with a random-effects model was also performed on eight articles with a low risk of bias. The statistical analyses of eight and 12 articles showed the same results—that H2RAs significantly reduced the risk of gastrointestinal bleeding. **Conclusion**: H2RA proves effective and safe in reducing the incidence of gastrointestinal bleeding, but not reducing the mortality in ICU patients.

Introduction

In critically ill patients, the inner lining or mucosa of the gastrointestinal (GI) tract does not function normally, making it highly susceptible to damage. Damages caused by stress potentially develop into ulcers, and bleeding occurs if an ulcer happens to form on top of a blood vessel (Krag *et al.*, 2015). The mortality rate of patients in an intensive care unit (ICU) with GI bleeding due to stress-related mucosal disease (SRMD) is about 50 - 77%, compared to 9 - 22% of patients who do not have GI bleeding (Spirt, 2004). In addition, ICU patients can also experience splanchnic hypoperfusion that may lead to inflammation and cell death, resulting in GI bleeding (Stollman & Metz, 2005). Until now, gastrointestinal bleeding prophylaxis still plays a crucial part in reducing bleeding occurrence (Daley *et al.*, 2004). Histamine-2 receptor antagonist (H2RA) is a group of drugs and one of the main therapies used to prevent gastrointestinal bleeding complications, although the tests of its effectiveness and safety remain inconclusive (Zhou *et al.*, 2019). H2RA works competitively with histamine to bind to histamine H2 receptors to inhibit gastric acid secretion (Nugent *et al.*, 2020). At present, meta-analysis studies about the effectiveness and safety of H2RA in terms of GI bleeding prophylaxis are still lacking, especially in critical adult patients hospitalised in ICU settings. The aim of this study is to investigate the effectiveness and safety of H2RA in adults 18 years old and above and in an ICU setting. The hypothesis for this study is H2RA can reduce the incidence of GI bleeding, mortality, and blood

transfusion requirements. Besides its efficacy, H2RA may increase the risk of nosocomial pneumonia.

Methods

Searching strategy

This research used randomised controlled trial (RCT) studies to report on the effectiveness and safety of using H2RA compared with placebo treatment or no prophylaxis. This stage included searching for relevant published articles through the MEDLINE database, ScienceDirect, The Cochrane Library, and ClinicalKey. In the MEDLINE database, the keywords used were according to following MeSH terms: "*Intensive Care Units"[Mesh]* AND "*Histamine H2 Antagonists"[Mesh]* OR "*Histamine H2 Antagonists"[Pharmacological Action]* AND "*prevention and control*" *[Subheading]*; and "*Intensive Care Units"[Mesh]* AND "*Histamine H2 Antagonists"[Mesh]* OR "*Ranitidine"[Mesh]* OR "*Cimetidine"[Mesh]* OR "*Famotidine"[Mesh*] AND "*prevention and control" [Subheading]* AND "*Gastrointestinal Hemorrhage"[Mesh]*.

Selection of relevant studies

Published articles relevant to the research topic were selected using the population, intervention, comparison, and outcome (PICO) framework. (1) The population was adult patients who received treatments in an ICU (>18 years old), and (2) intervention was the administration of H2RAs to prevent GI bleeding. (3) For comparison, patients receiving placebo or no prophylaxis were also observed. Lastly, (4) the outcome included the incidence of gastrointestinal bleeding, mortality, blood transfusion, and pneumonia. Studies that did not meet the PICO criteria were excluded.

Risk of bias assessment

Two investigators assessed the risk of bias, including allocation concealment, participant blinding, outcome assessor blinding, similarity characteristics of groups at the start of the trial, equal treatment, intention-to-treat, minimum risk of selective reporting, and precision stated. Low risk of bias occurs when the article meets most or all of the assessment criteria, and reversely, a high risk of bias is considered when the overall standards are not met.

Outcome

The primary outcome observed in this research is the incidence of GI bleeding. Meanwhile, the secondary outcomes are the mortality rate, blood transfusion requirement, and the incidence of nosocomial pneumonia in the ICU.

Data synthesis and statistical analysis

The data were synthesised using Review Manager version 5.4 (RevMan | Cochrane Training, n.d.). All outcomes were estimated using the Risk Ratio (RR) and 95% Confidence Interval (CI). The Mantel-Haenszel statistical method was used for dichotomous data. The analytical model used for each outcome was a fixed-effect model and I^2 statistics for heterogeneity. At this stage, a sensitivity analysis was performed to determine the effects of bias on the overall results. A subgroup analysis was also conducted using two groups of H2RAs, namely cimetidine and ranitidine.

Results

Identified and selected studies

There were 170 articles obtained from the literature search (identification stage). After the screening, it was found that 30 articles were duplicates, and 128 did not meet the inclusion criteria and were thereby excluded from the research. Finally, 12 articles were obtained and later used for qualitative and quantitative analysis.

Data extraction and quality assessment

Two investigators identified the quality of each article using the CASP checklist. Of the 12 papers, eight had a low risk of bias, whereas four were categorised into fairly high risk of bias. The distribution of the risk of bias is presented in Figure 1.

Outcome and statistical analysis

GI Bleeding as the primary outcome

The statistical analysis results showed that H2RA significantly reduced the incidence of GI bleeding in ICU patients compared with placebo (RR = 0.40; 95% confidence interval [CI] = 0.30 – 0.53; I^2 = 38%; p < 0.00001). In the sensitivity analysis, four papers with a fairly high risk of bias were excluded, and the statistical analysis of the remaining eight papers showed a similar result to that of all 12 papers (RR = 0.40; 95% CI = 0.27 – 0.58; I^2 = 36%; p < 0.00001). Because several studies had a small sample size, the analysis employed a random-effects model, and the results were the same for the incidence of GI bleeding (RR = 0.43, 95% CI = 0.26–0.74, I^2 = 36%, p = 0.002). Subgroup analysis was performed on two different groups of H2RAs: cime-tidine and ranitidine. Substantially reduced cases of GI bleeding were found in the cimetidine group (RR = 0.40; 95% CI = 0.29–0.55; I^2 = 31%; p < 0.00001) and in the ranitidine group (RR = 0.4; 95% CI = 0.22–0.78; I^2 = 59%; p = 0.007).

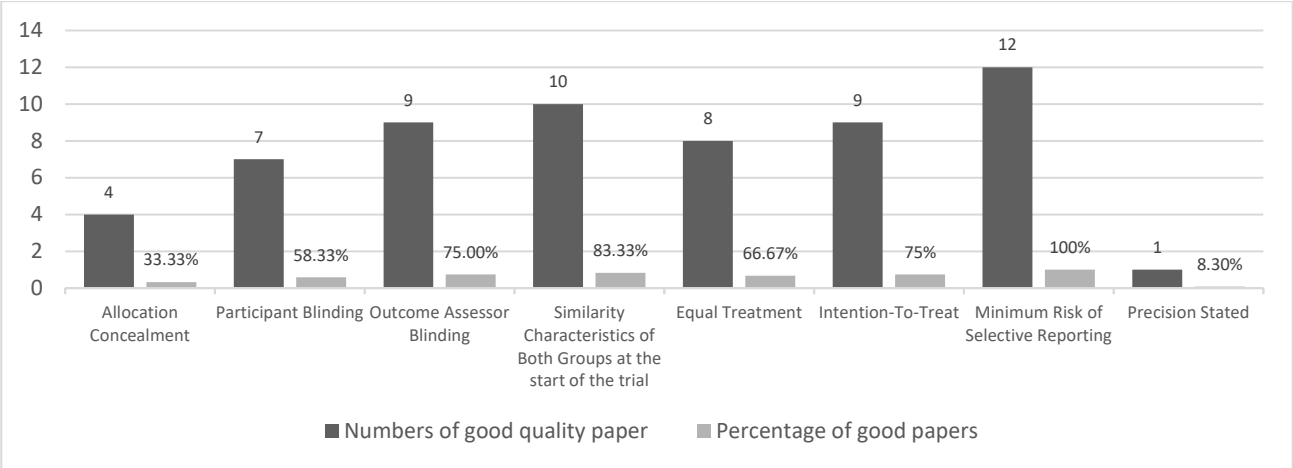

Figure 1: Quality parameter assessments of the 12 screened RCTs

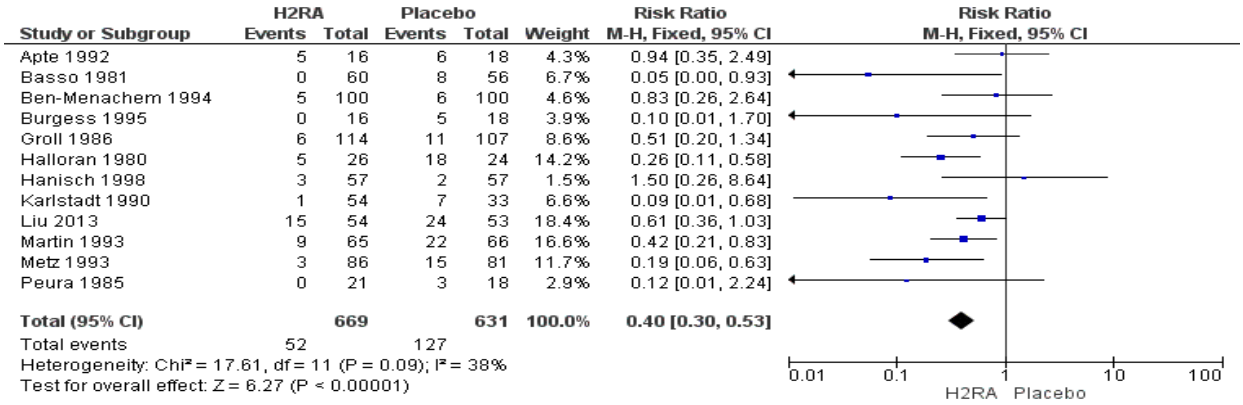

Figure 2: Forest plot of the efficacy of H2RA compared with placebo based on incidence of gastrointestinal bleeding, generated by Review Manager version 5.4. M-H, Mantel-Haenszel; CI, Confidence Interval

Secondary outcomes

Of the 12 RCT papers, the incidence of nosocomial pneumonia, the incidence of mortality, and number of patients requiring blood transfusion were reported. There was no significant difference between the H2RA and placebo groups in nosocomial pneumonia (RR = 1.13, 95% CI = 0.82 – 1.55, I^2 = 30%, p = 0.46) and mortality (RR = 0.99, 95% CI = 0.74 – 1.33, I^2 = 0%, p = 0.96). However, H2RAs significantly decreased the need for blood transfusion (RR = 0.44; 95% CI = 0.23 – 0.82, I^2 = 8%, p = 0.01).

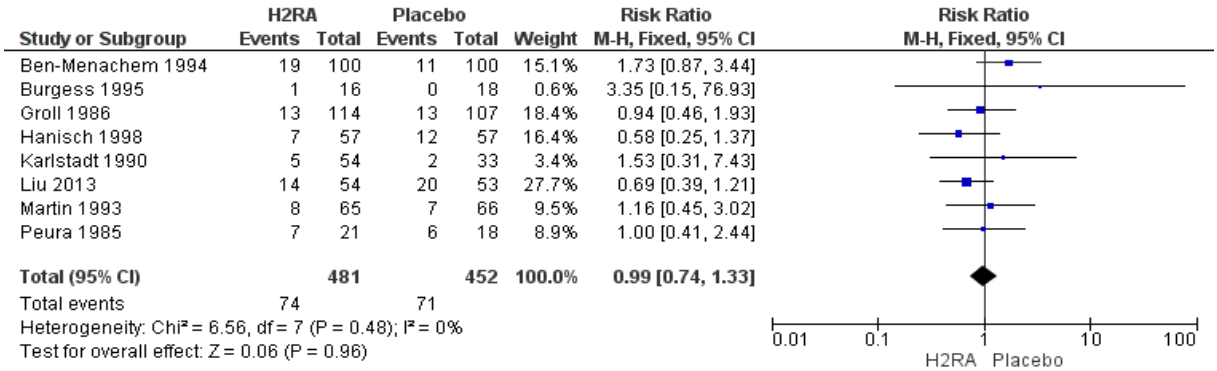

Figure 3: Forest plot of the efficacy of H2RA compared with placebo based on mortality, generated by Review Manager version 5.4. M-H, Mantel-Haenszel; CI, Confidence Interval

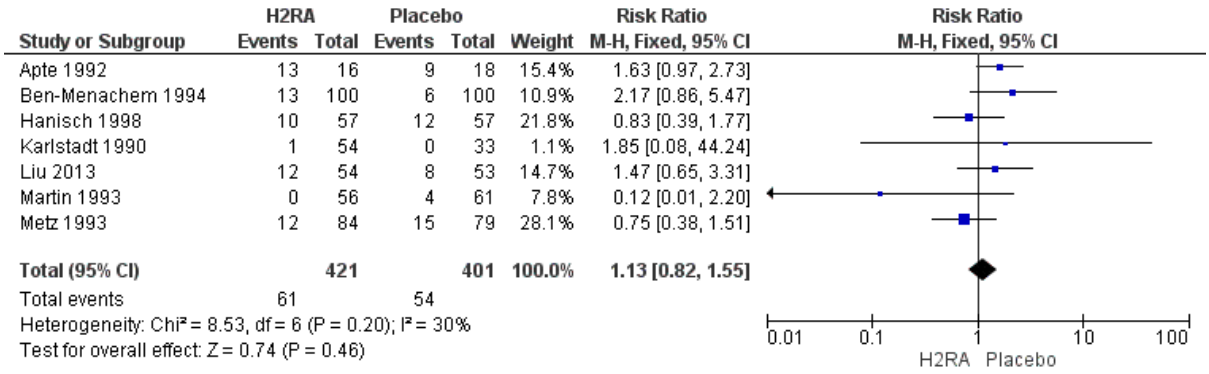

Figure 4: Forest plot of the safety of H2RA compared with placebo based on incidence of nosocomial pneumonia, gen*erated by Review Manager version 5.4. M-H, Mantel-Haenszel; CI, Confidence Interval*

Discussion

This review includes 12 RCTs that assessed the effectiveness and safety of H2RAs as a prophylactic agent for GI bleeding, with a total of 1,554 adult patients. The efficacy and safety are determined from the incidence of GI bleeding and secondary outcomes like nosocomial pneumonia, mortality, and the need for blood transfusions. The research found results similarities with previous systematic reviews and meta-analyses. For example, 24 previous studies involving ICU patients of any age, including pediatric, have confirmed the beneficial effects of H2RA drugs compared with placebo or no prophylaxis on the occurrence of GI bleeding (p = 0.000059) (Toews *et al.*, 2018). Regarding secondary outcomes, there is no evidence that H2RA can induce the incidence of nosocomial pneumonia compared with no prophylaxis in ICU patients of any age, with RR = 1.12 and 95%; CI = 0.85 - 1.48; and p = 0.40 (Toews *et al.*, 2018). Another study found different results, suggesting that stress ulcer prophylaxis (SUP) increases the risk of ventilator-associated pneumonia, with RR = 1.53; 95% CI = 1.04 - 2.27; and p = 0.03, but the SUP comprises not only H2RAs but also proton pump inhibitors (Huang *et al.*, 2018).

The analysed articles reported that there is no significant difference between administrating H2RA, placebo, and no prophylaxis on the rate of mortality associated with GI bleeding in ICU patients (RR = 1.03 and 95%; CI = 0.94 - 1.14; p = 0.52) (Barbateskovic *et al.*, 2019). Factors other than GI bleeding are known causes of mortality, such as patient's comorbidities, such as organ failure, septicemic factors, and systemic inflammatory response syndrome (Peura & Johnson, 1985; Liu *et al.*, 2013;).

Apart from GI bleeding, the effectiveness of H2RA can be seen from the number of participants requiring blood transfusions. This review has found supporting moderate evidence that is consistent with previous systematic reviews and meta-analyses. It shows H2RA decreased the number of blood transfusion requirements compared to placebo (RR = 0.58; 95% CI = 0.36 - 0.95; p = 0.03) (Toews *et al.*, 2018).

Nevertheless, this meta-analysis study has many limitations, including the scope of the search strategy associated with access and heterogeneity. The authors did not have any access to gain RCT studies from the EMBASE database. Another limitation to this study is related to heterogeneity. Most of the I^2 results in this study are fairly low (I^2 < 50%). Sub-group analysis for the cimetidine group and ranitidine group showed the consistency that each of both groups significantly reduced GI bleeding (p < 0.05). However, there was quite high heterogeneity in the ranitidine group (I^2 > 50%). For further research, subgroups between the adult and geriatric patients can be carried out.

Conclusions

This meta-analysis study has found that H2RAs are a class of drugs effectively used as prophylaxis for GI bleeding. Their effectiveness is evident from the reduced incidence of GI bleeding (primary outcome of H2RAs) and the low number of patients requiring blood transfusions (secondary outcome) after treatment. However, H2RA did not affect mortality and incidence of nosocomial pneumonia.

Acknowledgement

This article was presented at the 2021 Annual Scientific Conference of the Indonesian Pharmacist Association.

References

Barbateskovic, M., Marker, S., Granholm, A., Anthon, C.T., Krag, M., Jakobsen, J. C., Perner, A., Wetterslev, J., & Møller, M. H. (2019). Stress ulcer prophylaxis with proton pump inhibitors or histamin-2 receptor antagonists in adult intensive care patients: A systematic review with meta-analysis and trial sequential analysis. *Intensive Care Medicine*, **45**(2), 143–158. https://doi.org/10.1007/s00134-019-05526-z

Daley, R.J., Rebuck, J.A., Welage, L.S., & Rogers, F.B. (2004). Prevention of stress ulceration: Current trends in critical care. *Critical Care Medicine*, **32**(10), 2008–2013. https://doi.org/10.1097/01.CCM.0000142398.73762.20

Huang, H. Bin, Jiang, W., Wang, C. Y., Qin, H. Y., & Du, B. (2018). Stress ulcer prophylaxis in intensive care unit patients receiving enteral nutrition: A systematic review and meta-analysis. *Critical Care*. https://doi.org/10.1186/s13054-017-1937-1

Krag, M., Perner, A., Wetterslev, J., Wise, M. P., Borthwick, M., Bendel, S., McArthur, C., Cook, D., Nielsen, N., Pelosi, P., Keus, F., Guttormsen, A. B., Moller, A.D., & Møller, M.H. (2015). Prevalence and outcome of gastrointestinal bleeding and use of acid suppressants in acutely ill adult intensive care patients. *Intensive Care Medicine*. https://doi.org/10.1007/s00134-015-3725-1

Liu, B. L., Li, B., Zhang, X., Fei, Z., Hu, S. J., Lin, W., Gao, D. K., & Zhang, L. (2013). A randomised controlled study comparing omeprazole and cimetidine for the prophylaxis of stress-related upper gastrointestinal bleeding in patients with intracerebral haemorrhage: Clinical article. *Journal of Neurosurgery*. https://doi.org/10.3171/2012.9.JNS12170

Nugent, C., Flakson, S., & Terrell, J.M. (2020). H2 Blockers. In *Stat Pearls*. Treasure Island (FL): StatPearls Publishing

Peura, D.A., & Johnson, L.F. (1985). Cimetidine for prevention and treatment of gastroduodenal mucosal lesions in patients in an intensive care unit. *Annals of Internal Medicine*. https://doi.org/10.7326/0003-4819-103-2-173

Spirt, M.J. (2004). Stress-related mucosal disease: Risk factors and prophylactic therapy. *Clinical Therapeutics*. https://doi.org/10.1016/S0149-2918(04)90019-7

Stollman, N., & Metz, D.C. (2005). Pathophysiology and prophylaxis of stress ulcer in intensive care unit patients. In *Journal of Critical Care*. https://doi.org/10.1016/j.jcrc.2004.10.003

Toews, I., George, A.T., Peter, J.V., Kirubakaran, R., Fontes, L.E.S., Ezekiel, J.P.B., & Meerpohl, J.J. (2018). Interventions for preventing upper gastrointestinal bleeding in people admitted to intensive care units. *Cochrane Database of Systematic Reviews*, **2018**(6). https://doi.org/10.1002/14651858.CD008687.pub2

Zhou, X., Fang, H., Xu, J., Chen, P., Hu, X., Chen, B., Wang, H., Hu, C., & Xu, Z. (2019). Stress ulcer prophylaxis with proton pump inhibitors or histamine 2 receptor antagonists in critically ill adults—A meta-analysis of randomised controlled trials with trial sequential analysis. *BMC Gastroenterology*, **19**(1), 193. https://doi.org/10.1186/s12876-019-1105-y