What is the optimum prophylaxis against gastrointestinal haemorrhage for patients undergoing adult cardiac surgery: histamine receptor antagonists, or proton-pump inhibitors?

Akshay J. Patel and Robin Som

Department of Cardiothoracic Surgery, St George’s Medical School, London, UK
Department of Vascular Surgery, John Radcliffe Hospital, Oxford, UK

* Corresponding author: Department of Vascular Surgery, John Radcliffe Hospital, Oxford, UK. Tel: +44-751-5517737; e-mail: rsom@doctors.org.uk (R. Som).

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Abstract

A best evidence topic was written according to a structured protocol. The question addressed was what is the optimum prophylaxis against gastrointestinal haemorrhage for patients undergoing adult cardiac surgery: histamine receptor antagonists (H2RA) or proton-pump inhibitors? A total of 201 papers were found; of which, 8 represented the best evidence. The authors, date, journal, study type, population, main outcome measures and results were tabulated. Only one randomized controlled trial (RCT) with relevant clinical outcomes was identified. The rest of the studies consisted of five prospective studies and two retrospective studies. In the RCT, there were no reported cases of gastrointestinal haemorrhage in the proton-pump inhibitor cohort, whereas 4 patients taking H2RA developed it. The rate of active gastrointestinal ulceration was higher in the H2RA cohort in comparison with the proton-pump inhibitor cohort (21.4 vs 4.3%). A prospective study followed 2285 consecutive patients undergoing cardiac surgery who received either no prophylaxis, or a proton-pump inhibitor. Chi-squared analysis showed the risk of bleeding to be lower in those receiving the proton-pump inhibitor (P < 0.05). Another study of 6316 patients undergoing coronary artery bypass grafting demonstrated a reduced risk of gastrointestinal bleed with prophylactic intravenous omeprazole (odds ratio = 0.2; confidence intervals = 0.1–0.9; P < 0.05). One study successfully showed that proton-pump inhibitors are effective in adequately suppressing gastric acid levels, regardless of Helicobacter pylori infection status; conversely, this study suggested that H2RAs were not. The evidence for H2RAs is marginal, with no study showing a clear benefit. One study showed that ulcer prophylaxis with H2RA did not correlate with the clinical outcome. Another study demonstrated gastric ulceration to be a common gastrointestinal complication in spite of regular H2RA use. There is also evidence to suggest that acid suppression increases the risk of nosocomial pneumonia, although open heart surgery may be a confounding factor in this association. Two RCTs showed that H2RAs may augment the immune system and reducing stress following cardiac surgery. Proton-pump inhibitors appear to be the superior agent for prophylaxis against gastrointestinal bleed in patients undergoing cardiac surgery, although rigorous comparative data are sparse. Furthermore, level-I evidence would confirm this.

Keywords: Haemorrhage • Gastrointestinal • Proton-pump inhibitor • Cardiac surgery • Histamine type 2 receptor antagonist • Prophylaxis

INTRODUCTION

A best evidence topic (BET) was constructed according to a structured protocol as outlined in the best BETS document which is fully described in the ICVTS [1].

THREE-PART QUESTION

In [adult patients undergoing cardiac surgery], is a [proton pump inhibitor] or a [histamine antagonist] the best agent for prophylaxis against [gastrointestinal haemorrhage]?

SCENARIO

You start at an adult cardiac surgery unit where intravenous (IV) ranitidine is used for prophylaxis against gastrointestinal (GI) haemorrhage (GIH). At your previous unit, omeprazole was used.

You wonder what the best agent is and resolve to search the literature yourself.

SEARCH STRATEGY


SEARCH OUTCOME

The search yielded 201 papers; all relevant papers were screened and their reference lists were cross-checked. This process extracted eight papers that were deemed to offer the best evidence. The papers are detailed in Table 1.
### Table 1: Details of included studies

<table>
<thead>
<tr>
<th>Author, date, journal and country</th>
<th>Study type and level of evidence</th>
<th>Patient group characteristics</th>
<th>Outcomes measured</th>
<th>Key results</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Fan et al. (2010), Surg Today, China [3]</td>
<td>Retrospective cohort study (level 2b)</td>
<td>6316 coronary patients undergoing CABG; study period 1998–2005 Female 1062, male 5254 Average age 60.0 ± 8.2 years</td>
<td>Incidence of upper GI bleeds</td>
<td>Of the 6316 patient cohort, 21 suffered an upper GI bleed (0.33%)</td>
<td>Study identified key differences between 2 patient groups and used uni- and multivariate analysis to identify risk factors for upper GI bleeds post-surgery</td>
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<td>Two groups; with upper GI bleed, n = 21. Without upper GI bleed, n = 6295 1327 patients in the cohort were given prophylactic IV omeprazole</td>
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<td>Predictive risk factors for upper GI bleeding were age (P &lt; 0.01), extracorporeal circulation time (P &lt; 0.01), prophylactic omeprazole protected against upper GI bleeding (P &lt; 0.05)</td>
<td>Dose not stated</td>
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<td>Retrospective analysis of data from patients who incurred a major GI bleed</td>
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<td>Retrospective, single-centre study thus potential selection bias, results' reliability may be affected</td>
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<td>Six-month post-surgery follow-up for all patients and yearly thereafter</td>
<td>Mean follow-up time across cohort, 5.4 ± 2.0 years</td>
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<td>Gon et al. (2006), Jpn J Thorac Cardiovasc Surg, Japan [4]</td>
<td>Prospective cohort study (level 2b)</td>
<td>33 patients undergoing elective open heart surgery; study period July 2000–February 2001. Allocated to either famotidine (H2RA) or rabeprazole (PPI)</td>
<td>Perioperative gastric and oesophageal pH readings</td>
<td>No postoperative bleeding in either group</td>
<td>Prospective cohort study</td>
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<td>Association of H. pylori infection was also looked at</td>
<td>Postoperative mean gastric pH readings were &gt;6 in both groups</td>
<td>Dose and route of administration not specified. Famotidine appeared to have an insufficient effect on gastric pH levels for H. pylori-negative patients. Rabeprazole suppressed pH adequately irrespective of H. pylori status</td>
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<td>Hata et al. (2005), Circulation, Japan [5]</td>
<td>Randomized controlled study (level 1b)</td>
<td>210 patients undergoing cardiac surgery (CABG: 140, valve replacement: 42, aortic surgery: 28) divided into three groups Group I: 70 patients with mucosal protection (trepeneone 150 mg/day, per oral) Group II: 70 patients with H2RA (ranitidine 300 mg/day, per oral) Group III: 70 patients with a proton-pump inhibitor (rabeprazole 10 mg/day, per oral)</td>
<td>Comparison between groups made using endoscopic findings and perioperative details</td>
<td>Four patients (5.7%) had gastric bleeding complications in each of Groups I and II; 2 died of coagulopathy Group III: no gastric bleeding complications</td>
<td>Prospective randomized trial comparing 3 patient groups</td>
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<td>Incidence of gastric pain</td>
<td>Incidence of haemorrhagic gastritis in Groups I, II and III was 22.9, 15.7 and 2.9%, respectively</td>
<td>Gastric fibroscopy used in all patients at postoperative days 5–7</td>
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<td>Upper GI bleeding</td>
<td>Active ulceration in Groups I, II and III was 28.6, 21.4 and 4.3%, respectively</td>
<td>CABG or aortic surgery patients given aspirin (81 mg/day) and valve surgery patients given warfarin (2–3 mg/day)</td>
</tr>
<tr>
<td>Johnston et al. (1992), Am J Surg, USA [6]</td>
<td>Prospective series (level 2b)</td>
<td>5438 patients underwent cardiac surgery; study period January 1983–July 1991 Three groups based on postoperative GI complications Group I: without GI complications (5369) Group II: acid peptic complications (41) Group III: other GI complications (28)</td>
<td>Acid peptic, gastric or duodenal ulceration, erosion, perforation, bleeding</td>
<td>73 complications in 69 patients. 36 patients had upper GI bleeding with six mortalities. GI complications were significantly associated with older patients and valve surgery. Acid peptic complications positively correlated with longer perfusion times, increased use of vasopressors and balloon pump</td>
<td>Prospective series study to correlate risk factors with the incidence of GI complications post-cardiac surgery</td>
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<td>Patients with persistently low gastric pH values or guaiac positive nasogastric aspirates were started on H2RA</td>
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<td>Most frequent complication was gastric ulceration despite routine use of H2RA. Neither H2RA nor dose was specified</td>
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<td>All GI bleeding patients underwent endoscopy</td>
<td>Number of patients on prophylaxis not specified. Less than 15% of patients on prophylaxis in Group II received the medication for &gt;24 h</td>
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Table 1: (Continued)

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<tr>
<td>Katoh et al. (1998), J Thorac Cardiovasc Surg, Japan [7]</td>
<td>20 patients divided into two groups; study period 7 days</td>
<td>Natural killer cell (CD56, CD16) markers and T-lymphocyte markers (CD8, CD11)</td>
<td>Natural killer cell activity was considerably higher in Group I postoperatively. T-lymphocyte suppressor activity significantly lowered in Group I postoperatively.</td>
<td>Prospective randomized study to ascertain effect of cimetidine (H2RA) on cellular immunity post-cardiac surgery. Small sample sizes: lacks power. Conclusions: cimetidine promotes postoperative cellular immunity and thus may reduce susceptibility to infection.</td>
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<tr>
<td>Randomized controlled trial (level 1b)</td>
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<tr>
<td>Retrospective cohort study (level 2b)</td>
<td>Perioperative ulcer prophylaxis administered (cimetidine 300 mg orally or IV every 6 h plus antacid) with equal frequency in both groups (Group I: 15, Group II: 15)</td>
<td>Ulcer prophylaxis did not appear to correlate with outcome</td>
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<tr>
<td>Retrospective cohort study (level 2b)</td>
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<td>Tayama et al. (2001), Ann Thorac Surg, Japan [10]</td>
<td>40 patients undergoing scheduled CABG procedures; study period 5 days Group I: 20 patients; cimetidine group Group II: 20 patients, no treatment group Excluded severely diabetic or COPD patients Two doses of 200 mg cimetidine orally preoperatively; 400 mg IV infusion intraoperatively; 200 mg IV every 6 h postoperatively until Day 2</td>
<td>Neutrophil elastase Plasma IL-6 Plasma IL-8 White cell count C-reactive protein (CRP) Creatine kinase MB Oxygenation index Lymphocyte recovery ratio</td>
<td>Lower IL-8 and neutrophil elastase levels in Group I at 2 h after CPB termination Group I demonstrated a higher lymphocyte recovery ratio and a lower CRP level on postoperative day 5 Conclusion: cimetidine may reduce surgical stress and augment the immune system after cardiac surgery with CPB</td>
<td>Randomized controlled trial No comparison made between H2RAs and PPIs, similarly no direct relation made to likelihood of upper GI bleeding. Small sample size in each group: study lacks power. Lymphocyte recovery ratio was calculated by dividing the actual circulating lymphocyte count by the preoperative lymphocyte count. Postoperative blood loss and requirements for blood products was comparable in both groups—no actual values stated.</td>
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</table>
DISCUSSION

A recent BET discussed whether routine stress ulcer prophylaxis is warranted [2]. Our BET seeks to answer which agent is superior.

Fan et al. [3] followed up 6316 patients undergoing coronary artery bypass grafting (CABG) over 7 years and the frequency of GI complications. Univariate and multivariate analyses were conducted. Incidence of GIH was 0.33%. A total of 1327 patients within the cohort were given prophylactic IV omeprazole, which decreased the postoperative risk of GIH (P < 0.05) in comparison with patients who did not receive prophylaxis.

Gon et al. [4] compared how famotidine and rabeprazole affected perioperative gastric acid suppression, and the role of *Helicobacter pylori* infection in this. Thirty-three patients undergoing cardiac surgery were allocated to either agent. No GIH occurred in either group. Rabeprazole achieved sufficient acid suppression (average postoperative gastric pH >6) regardless of *H. pylori* status, unlike famotidine.

Hata et al. randomized patients to teprenone, ranitidine or rabeprazole, with GIH as a primary outcome [5]. There were no reported cases of GIH in the proton pump inhibitor cohort, whereas 4 patients developed bleeding complications in each of the other groups (P < 0.006). The incidence of haemorrhagic gastritis was also higher in these groups (teprenone = 22.9%; ranitidine = 15.7%) compared with the rabeprazole cohort (2.9%; P = 0.0003). Furthermore, active ulceration was significantly higher in these two cohorts compared with those taking PPI (P < 0.0001). Patients with ulceration were completely healed with 2 weeks of PPI therapy.

A prospective series conducted by Johnston et al. correlated risk factors with the incidence of GI complications post-cardiac surgery [6]. A total of 5438 patients were stratified according to their postoperative complications—no complications (Group I; n = 5369); acid peptic complications (Group II; n = 41) and other GI complications (Group III; n = 28). Patients with persistently low gastric pHs were started on H2RAs. Seventy-three complications were noted in 69 patients. Gastric ulceration was the most frequent complication despite routine use of H2RAs. However, >15% of patients on prophylaxis in Group II received the medication for over 24 h.

A randomized controlled trial (RCT) assessed the effect of cimetidine on cellular immunity after cardiac surgery [7]. Twenty patients either received IV cimetidine pre- and postoperatively or were allocated to a control group. Natural killer cell activity was augmented and T-lymphocyte suppressor activity was decreased post-surgery in the test group. This suggests that cimetidine augments cellular immunity post-surgery, and may help prevent infection, e.g. from *H. pylori*.

Rosen’s group [8] retrospectively matched 32 patients who developed postoperative life-threatening peptic ulcer complications (Group I) with 32 randomly selected patients (Group II) to compare risk factors and outcome. Perioperative IV cimetidine was administered to 15 patients in each group. Ten patients in each group had a history of previous peptic ulcer disease. In Group I, 11 mortalities occurred; of which, 7 were patients receiving prophylaxis. Group II incurred no mortality. The study deemed that ulcer prophylaxis did not correlate with the outcome. However, the average age of Group I was far greater than that of Group II. The authors also postulate that the degree of prophylaxis may have been inadequate.

Stchepinsky et al. [9] prospectively followed up 2285 consecutive patients; of whom 1151 received no GIH prophylaxis and 1134 received a PPI. Eight bleeding ulcers were noted in the former group, with 1 bleeding ulcer in the latter. There was no difference in the average age between the two populations. Chi-squared analysis showed a lower risk of bleeding in Group II (P < 0.05).

Tayama et al. [10] randomized 40 patients to cimetidine or a control cohort. Inflammatory markers were measured in all patients pre- and postoperatively. The treatment group yielded a postoperative decrease in IL-8, neutrophil elastase and C-reactive protein; and a concurrent increase in the lymphocyte recovery ratio. This suggests that cimetidine may help to reduce surgical stress and augment the immune system after cardiac surgery.

CLINICAL BOTTOM LINE

Prophylaxis against GIH in patients undergoing cardiac surgery has been part of routine perioperative practice for several decades [11], but there are no guidelines regarding this. The data from the aforementioned RCT [5] indicate that PPIs are superior to H2RAs for GIH prevention following cardiac surgery; although H2RAs may have a role in enhancing immunity and diminishing postoperative stress [7, 10]. However, it is difficult to answer our central question—comparative, level-I evidence regarding the superior agent for this is sparse, with only two of the eight studies reviewed contrasting the two agents.

Acid suppression is not without its risks—it may be associated with an increased rate of nosocomial pneumonia in mechanically ventilated patients [12–14], (although open heart surgery may be a confounding factor in this association). Several studies have indicated that PPIs may reduce the effectiveness of clopidogrel, a commonly prescribed agent for these patients [15–17].

Conclusions drawn from the recent BET are similar to ours—the evidence is in favour of PPIs over other agents for GIH prophylaxis [2]. The quality and quantity of evidence are poor—only further comparative RCTs can confirm the superiority of PPIs.

REFERENCES


