Prophylactic proton pump inhibitors in femoral neck fracture patients – A life- and cost-saving intervention

R Singh¹, R Trickett², CER Meyer³, S Lewthwaite³, D Ford³

¹Royal Shrewsbury Hospital, UK

²University Hospital of Wales, UK

³Robert Jones Oswestry Orthopaedic Hospital, UK

ABSTRACT

INTRODUCTION Acute gastrointestinal stress ulceration is a common and serious complication of trauma. Prophylactic proton pump inhibitors (PPIs) or histamine receptor antagonists have been used in poly-trauma, burns and head and spinal injuries, as well as on intensive care units, for the prevention of acute gastric stress ulcers.

METHODS We prospectively studied the use of prophylactic PPIs in with femoral neck fracture patients, gathering data on all acute gastric ulcer complications, including coffee-ground vomiting, malena and haematemesis. We then implemented a treatment protocol in which all patients were given prophylactic PPIs, again prospectively collecting all data.

RESULTS Five hundred and fifteen patients were included. Prior to prophylactic PPI, 15% of patients developed gastric stress ulcer complications, with 3% requiring acute intervention with oesophagogastroduodenoscopy (OGD), 5% requiring transfusions and 4% experiencing surgical delays. All patients had delayed discharges. Following PPI implementation, no patients developed gastric stress ulcer complications.

CONCLUSIONS Femoral neck fracture patients create a substantial workload for orthopaedic units. The increasingly elderly population often have comorbidities, and concomitantly use medications with gastrointestinal side effects. This, combined with the stress of a fracture and preoperative starvation periods increases the risk of gastric ulcers. Here, the use of prophylactic PPIs statistically reduced the incidence of gastric stress ulcers in patients with femoral neck fractures, resulting in fewer surgical delays, reduced length of hospital stay and reduced stress ulcer-related mortality.

KEYWORDS

Femoral neck fractures – Proton Pump Inhibitors – Ulcer – Orthopaedics

Accepted 29 December 2015

CORRESPONDENCE TO

Rohit Singh, E: rohitamolsingh@hotmail.com

The ageing population is leading to an ever-increasing burden of fragility fractures.^{1–4} The national hip fracture database (NHFD) reports an annual rate femoral neck fracture in England and Wales of over 65,000.⁵ Demographic projections indicate that these figures will continue to increase to over 80,000 by 2017.^{6–9} Hip fracture is the commonest reason for orthopaedic admission, at an estimated annual cost of over £2 billion pounds.^{5,6}

Patients with femoral neck fractures have a substantially increased risk of death and major morbidity.^{10,11} The mortality rate is approximately 10% over the first month, and one-third with the first year.^{8,12–14} However, the fracture is directly attributable as the cause of death in less than 50% of cases, with other common causes including bronchopneumonia, heart failure, poor nutrition, stroke and secondary infection.^{15,16}

As part of the routine morbidity and mortality meetings at our institution, root-cause analysis is undertaken to review unexpected deaths. One patient is undertaken to review a fractured femoral neck suffered an acute gastrointestinal bleed leading to death. This patient had been starved for almost 40 hours prior to surgery (including 12 hours starvation at home), and was receiving non-steroidal anti-inflammatory drugs (NSAIDs) with no mucosal protectants. It was felt that this death could have been prevented.

The NHFD includes data regarding admission to an orthopaedic ward, time to surgery, the development of pressure ulcers, completion of falls assessment, and bone protection medication, but does not record episodes of acute gastrointestinal bleeding. There is also sparse literature on acute gastrointestinal stress ulceration in femoral neck fracture patients.

In this study, we aim to assess the incidence of acute gastrointestinal stress ulceration in this patient group, as well as its impact on mortality and morbidity rates, length of stay and surgical delays. We also aim to define whether prophylactic mucosal protection can prevent complications arising from acute gastrointestinal stress ulceration.

Materials and Methods

All patients admitted to our trauma and orthopaedics department over a 2-year period (1 February 2011 to 1 February 2013) with a femoral neck fracture were reviewed. Patients were excluded if they had a previous history of gastroesophageal reflux disease, peptic ulcers or perforated peptic ulcer, or were already receiving a prophylactic proton pump inhibitor (PPI) or histamine receptor antagonist.

During the first year of the study, patients had their hip fractures managed in line with the best practice tariff guidelines (control group). These patients were reviewed prospectively using root-cause analysis, with the results discussed at clinical governance, which included the mortality described above. A practice change was subsequently implemented, with all femoral neck fracture patients routinely prescribed a course of PPIs. A clinical audit was conducted within an ethical framework, ensuring patient confidentiality and appropriate data collection and storage. Liaison and advice was received by our local research ethics committee. As this study was a clinical audit and due to the lack of random patient selection, formal ethical approval was not required.^{17,18}

During the second study year, all patients were given PPIs as part of the hip fracture treatment pathway (intervention group), and were reviewed prospectively.

All data was obtained from patient records. Data concerning the time of admission, time of fall, mechanism of fall, medical and drug history, place of residence, starvation period, time to theatre and complications were obtained for all patients. Periods of starvation were divided into two groups: starvation at home; and starvation prior to surgery, which is the time between the last meal and surgery.

Although several medications, include aspirin, NSAIDs, bisphosphonates and potassium supplements, are considered a risk factor for peptic ulceration, the literature indicates that aspirin and NSAIDs are associated with the greatest risk.^{19,20} We therefore collected data on the use of these two medications, describing patients taking them as on 'high-risk' medications.

The symptoms of acute gastric stress ulceration vary from non-specific abdominal pain to life-threatening haemorrhage.^{21–25} For the current study, we classified positive acute stress peptic ulceration symptoms as: coffee-ground vomiting; melaena; and haematemesis. We did not include reductions in haemoglobin levels alone as a potential indicator of stress ulcers, as this may be due to either the fracture or the surgery.

The results were tabulated using Excel (Microsoft, Redmond, WA, USA). Observed differences between the control and intervention groups were analysed using both

parametric and non-parametric statistical tests, the latter consisting of the two-sided Chi-squared test and Fisher's Exact test (where the expected cell count was less than 5). SPSS Statistics version 20 (IBM, Armonk, NY, USA) was used to perform the analyses. A p value <0.05 was considered statistically significant.

Results

A total of 624 patients were admitted to our trauma and orthopaedic unit during the study period, of whom 109 were excluded (Figure 1). Two hundred and sixty two patients were analysed as the control group, while 153 formed the intervention group. There were no differences in baseline demographics between the two groups on non-parametric analysis (Table 1).

During the 2-year study period, the majority of patients had a starvation period at home of over 12 hours (n=340, 66%), and a total starvation period (starvation at home and at hospital) prior to surgery of 24 hours (n=268, 52%). There were no observed differences in the length of starvation between the control and intervention groups. In the control group, 173 (66%) patients were starved for longer than 12 hours before reaching hospital, of whom 136 (52%) were starved for a total of more than 24 hours. In the intervention group, the corresponding figures were 166 (66%) and 131 (52%), respectively.

Table 1 Demographic data of included patients

	Control Group	Intervention Group	Total
Male	80	71	151
Female	182	182	364
Age Group 60 to 69	12	19	31
70 to 79	60	51	111
80 to 89	131	127	258
Over 90	59	56	115

A total of 216 (42%) patients were on high-risk medications prior to admission, 198 (38%) of whom were without any prophylactic cover. There was no statistical difference in the number of patients on high-risk medications with or without prophylactic cover between the control and intervention groups.

Forty one control group patients (15.6%) developed complications as a result of stress ulceration (Figure 2). Of those, 7 (2.7%) required admission to the intensive care unit (ITU), 13 (5%) required a blood transfusion and 8 (3%) required an oesophagogastroduodenoscopy (OGD). Moreover, 36 (13%) patients experienced a surgical delay, which consisted of being carried over to the next available trauma list. No intervention group patients developed stress ulceration complications.

Non-parametric analysis of observed differences between control and intervention groups for episodes of coffee-ground vomiting, malaena or haematemesis, the need for ITU admission, transfusion or OGD and in-patient mortality are shown in Table 2A–H. Acute stress ulceration was confirmed in all eight patients undergoing endoscopic examination of the gastric mucosa.

The average length of hospital stay in patients with acute gastrointestinal stress ulcers was 38 days. There was

Figure 2 Bar chart showing the number of control patients with acute stress ulceration complications

Table 2 2 × 2 contingency tables for: A, coffee ground vomit episodes; B, malaena episodes; C, haematemesis episodes; D, ITU admission; E, blood transfusion; F, OGD; G delay to surgery beyond best practice tariff; H, mortality

A	Coffee Ground Vomit		Total
	No	Yes	
Control	250	12	262
Intervention	253	0	253
Total	503	12	515
$\chi^2(1) = 11.9, p < 0.001$			
B	Malaena		Total
	No	Yes	
Control	246	16	262
Intervention	253	0	253
Total	499	16	515
$\chi^2(1) = 16.0, p < 0.001$			
C	Haematemesis		Total
	No	Yes	
Control	249	13	262
Intervention	253	0	253
Total	502	13	515
$\chi^2(1) = 12.9, p < 0.001$			
D	ITU Admission		Total
	No	Yes	
Control	255	7	262
Intervention	253	1	253
Total	508	7	515
Fisher's Exact Test $p = 0.015$			
E	Transfusion Requirement		Total
	No	Yes	
Control	249	13	262
Intervention	253	5	253
Total	502	13	515
$\chi^2(1) = 12.9, p < 0.001$			
F	OGD Requirement		Total
	No	Yes	
Control	254	8	262
Intervention	253	0	253
Total	507	8	515
$\chi^2(1) = 7.8, p = 0.005$			

G	Delay to Surgery		Total
	No	Yes	
Control	226	36	262
Intervention	253	20	253
Total	479	36	515
$\chi^2(1) = 37.4, p < 0.001$			
H	Mortality		Total
	No	Yes	
Control	255	7	262
Intervention	248	5	253
Total	503	12	515
$\chi^2(1)$ no significant difference Abbreviations: ITU, intensive care unit; OGD, oesophagogastroduodenoscopy.			

a statistically significant difference in length of stay between the two groups, with the intervention group going home 2.9 days earlier than the control group ($p < 0.001$, two-tailed Student's *t*-test; $p = 0.001$ Mann-Whitney U test).

Discussion

Stress-related mucosal damage resulting from acute gastrointestinal stress ulceration describes the spectrum of pathology due to the acute, erosive, inflammatory insult to the upper gastrointestinal tract.²⁴ This was first characterised in 1969 following the postmortem examination of critically ill patients.²⁵ Endoscopic studies have since shown that up to 85% of critically ill patients have stress-related mucosal erosions and sub-epithelial haemorrhage within 24 hours of hospital admission.²⁶ The underlying pathological processes are reduced gastric blood flow, leading to mucosal ischemia and subsequent reperfusion injury.²⁷ In our study, the majority of patients with a clinical picture suggestive of acute gastrointestinal stress ulceration also suffered symptoms within 24 hours of admission ($n = 36$), which led to surgical delays.

The data also highlights the length of time that the patients were starved at home and in hospital. This, combined with high-risk medications, stress responses to the fall, the fracture and the pain, all point to an increased risk of developing acute gastrointestinal stress ulceration. Starvation periods should therefore be highlighted as an important modifiable risk factor. Furthermore, five of the seven deaths in the control group had acute gastrointestinal bleeding documented on the corresponding death certificates. In the intervention group, acute gastrointestinal bleeding was not documented on any of the death certificates. The role of stress ulcer prophylaxis has been established in patients with burns, head injuries, spinal injuries and poly trauma, and in critical care, for over 15 years.²⁸ Our study has shown that patients with femoral neck fractures are also at high risk, and may warrant the same stress ulcer prophylaxis.

PPIs work by inactivating the hydrogen potassium ATPase enzyme at the secretory surface of the parietal cell, inhibiting the secretion of hydrogen ions and thereby increasing the pH of the gastric contents.²⁹ PPIs are more effective than histamine receptor antagonists at reducing clinically important and overt upper gastrointestinal bleeding, without appearing to increase the risk of nosocomial pneumonia or inducing tolerance.²²

There is controversy surrounding the relationship between the use of stress ulcer prophylaxis and the development of subsequent *Clostridium difficile* infection. Stress ulcer prophylaxis that increases the intra-gastric pH above 4 inhibits the bactericidal action of the host community, thus potentially increasing colonization of the stomach by pathogenic organisms.³⁰ Yearsley *et al* reported an increase in *C. difficile*-associated diseases in patients receiving PPIs in a case-control study,³¹ as did a secondary analysis of previously collected data by Howell *et al*.³² However, there is no epidemiological evidence to support this. In our cohort, there were 13 (5%) microbiologically confirmed *C. difficile* cases in the control group, compared to 12 (5%) in the intervention group.

The cost of a 40 mg capsule of Omeprazole is approximately £0.15.³³ The cost of an acute hospital bed in the UK is approximately £250.³⁴ In our cohort, those patients suffering from acute stress ulceration had an average length of hospital stay of 38 days, 18 days longer than the national average of 20 days.⁵ The use of PPI prophylaxis could therefore represent a substantial cost benefit.

One of the limitations of our study is that common adverse effects of PPIs, such as headache, dizziness, skin reactions and arthralgia,³⁵ were not recorded in our cohort. Ethical approval was not formally required for this clinical audit; however, a prospective randomised controlled trial to confirm our findings would be valuable.

Conclusion

Femoral neck fracture patients are at high risk of acute stress ulceration secondary to their comorbidities, medication, starvation periods and physiological response to the fracture. Patients with acute gastrointestinal stress ulceration had an average length of stay 18 days longer than the national average. Prophylactic PPIs may help to minimise the risk of acute stress ulceration, thus reducing the length of stay and rates of ulcer-related mortality.

References

1. Kannus P, Parkkari J, Sievanen H *et al*. Epidemiology of hip fractures. *Bone* 1996; **18**: 575–635.
2. Huddleston JM, Whitford KJ. Medical care of elderly patients with hip fractures. *Mayo Clin Proc* 2001; **76**: 295–298.
3. Dy CJ, McCollister KE, Lubarsky DA *et al*. An economic evaluation of a systems-based strategy to expedite surgical treatment of hip fractures. *J Bone Joint Surg Am* 2011; **93**: 1,326–1,334.
4. Brauer CA, Coca-Perraillon M, Cutler DM *et al*. Incidence and mortality of hip fractures in the United States. *JAMA* 2009; **302**: 1,573–1,579.
5. National Hip Fracture Database Annual Report 2012–13. NHS England <https://data.england.nhs.uk/dataset/national-hip-fracture-database-annual-report-2012-13>. (cited 2015 December).

6. Hip fracture: final scope. National Institute for Clinical Excellence. <http://www.nice.org.uk/guidance/cg124/resources/hip-fracture-final-scope> (cited 2015 December).
7. Wu TY, Jen MH, Bottle A *et al.* Admission rates and in-hospital mortality for hip fractures in England 1998 to 2009: time trends study. *J Public Health (Oxf)* 2011; **33**: 284–291.
8. Quah C, Boulton C, Moran C. The influence of socioeconomic status on the incidence, outcome and mortality of fractures of the hip. *J Bone Joint Surg Br* 2011; **93**: 801–805.
9. Guillely E, Herrmann F, Rapin CH *et al.* Socioeconomic and living conditions are determinants of hip fracture incidence and age occurrence among community-dwelling elderly. *Osteoporos Int* 2011; **22**: 647–653.
10. Wolinsky FD, Fitzgerald JF, Stump TE. The effect of hip fracture on mortality, hospitalization, and functional status: a prospective study. *Am J Public Health* 1997; **87**: 398–403.
11. Bentler SE, Liu L, Obrizan M *et al.* The aftermath of hip fracture: discharge placement, functional status change, and mortality. *Am J Epidemiol* 2009; **170**: 1,290–1,299.
12. Frost SA, Nguyen ND, Black DA *et al.* Risk factors for in-hospital post-hip fracture mortality. *Bone* 2011; **49**: 553–558.
13. Orces CH. In-hospital hip fracture mortality trends in older adults: the National Hospital Discharge Survey, 1988–2007. *J Am Geriatr Soc* 2013; **61**: 2,248–2,249.
14. Parsons N, Griffin XL, Achten J *et al.* Outcome assessment after hip fracture: is EQ-5D the answer? *Bone Joint Res* 2014; **3**: 69–75.
15. Baumgaertner MR, Higgins TF. Femoral neck fractures. In: Bucholz RW, Heckman JD, Rockwood CA *et al.*, eds. *Rockwood and Green's Fractures in Adults*. Philadelphia: Lippincott Williams & Wilkins, 2002. pp1,579.
16. Melton LJ, 3rd. Who has osteoporosis? A conflict between clinical and public health perspectives. *J Bone Miner Res* 2000; **15**: 2,309–2,314.
17. Wade DT. Ethics, audit, and research: all shades of grey. *BMJ* 2005; **330**: 468–471.
18. Ougin D, Banarsee R. Clinical Audit. *BMJ Careers* 2006; **333**: 68–69.
19. Sennerby U, Melhus H, Gedeberg R *et al.* Cardiovascular diseases and risk of hip fracture. *JAMA* 2009; **302**: 1,666–1,673.
20. Kate V, Ananthakrishnan N, Tovey FI. Is *Helicobacter pylori* Infection the Primary Cause of Duodenal Ulceration or a Secondary Factor? A Review of the Evidence. *Gastroenterol Res Pract* 2013; **2013**: 425840.
21. Plummer MP, Blaser AR, Deane AM. Stress ulceration: prevalence, pathology and association with adverse outcomes. *Crit Care* 2014; **18**: 213.
22. Alhazzani W, Alenezi F, Jaeschke RZ *et al.* Proton pump inhibitors versus histamine 2 receptor antagonists for stress ulcer prophylaxis in critically ill patients: a systematic review and meta-analysis. *Crit Care Med* 2013; **41**: 693–705.
23. Faisy C, Guerot E, Diehl JL *et al.* Clinically significant gastrointestinal bleeding in critically ill patients with and without stress-ulcer prophylaxis. *Intensive Care Med* 2003; **29**: 1,306–1,313.
24. Peura DA. Stress-related mucosal damage. *Clin Ther* 1986; **8 Suppl A**: 14–23.
25. Skillman JJ, Bushnell LS, Goldman H *et al.* Respiratory failure, hypotension, sepsis, and jaundice. A clinical syndrome associated with lethal hemorrhage from acute stress ulceration of the stomach. *Am J Surg* 1969; **117**: 523–530.
26. Mutlu GM, Mutlu EA, Factor P. GI complications in patients receiving mechanical ventilation. *Chest* 2001; **119**: 1,222–1,241.
27. Marik PE, Vasu T, Hirani A *et al.* Stress ulcer prophylaxis in the new millennium: a systematic review and meta-analysis. *Crit Care Med* 2010; **38**: 2,222–2,228.
28. Stollman N, Metz DC. Pathophysiology and prophylaxis of stress ulcer in intensive care unit patients. *J Crit Care* 2005; **20**: 35–45.
29. Netzer P, Gaia C, Sandoz M *et al.* Effect of repeated injection and continuous infusion of omeprazole and ranitidine on intragastric pH over 72 hours. *Am J Gastroenterol* 1999; **94**: 351–357.
30. Heyland D, Bradley C, Mandell LA. Effect of acidified enteral feedings on gastric colonization in the critically ill patient. *Crit Care Med* 1992; **20**: 1,388–1,394.
31. Yearsley KA, Gilby LJ, Ramadas AV *et al.* Proton pump inhibitor therapy is a risk factor for *Clostridium difficile*-associated diarrhoea. *Aliment Pharmacol Ther* 2006; **24**: 613–619.
32. Howell MD, Novack V, Grgurich P *et al.* Iatrogenic gastric acid suppression and the risk of nosocomial *Clostridium difficile* infection. *Arch Intern Med* 2010; **170**: 784–790.
33. Omeprazole. British National Formulary. <https://www.evidence.nhs.uk/formulary/bnf/current/1-gastro-intestinal-system/13-antisecretory-drugs-and-mucosal-protectants/135-proton-pump-inhibitors/omeprazole> (cited 2016 February).
34. Friedman AB. Economic incentives and use of the intensive care unit. *JAMA* 2014; **311**: 2,336–2,337.