Trauma

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Should we routinely prescribe proton pump inhibitors peri-operatively in elderly patients with hip fractures? A review of the literature

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- Elderly hip fracture patients are at risk of stress-related gastric mucosal damage, and upper gastrointestinal bleeding is one of the underrecognized but devastating complications.
- Proton pump inhibitors (PPIs) offer effective prophylaxis against stress-related gastric mucosal damage.
- Systematic analysis of the literature revealed numerous articles on PPIs and hip fractures, but only three articles dedicated to the analysis of prophylactic use of PPIs in patients with a hip fracture.
- There is significant reduction in upper gastrointestinal bleeding following PPI prophylaxis and reduced 90-day mortality in elderly hip fracture patients on prophylaxis.
- PPIs are generally safe, cost-effective and based on available evidence. Their prophylactic use is justifiable in elderly patients with hip fractures.
- We suggest that PPIs be prescribed routinely peri-operatively in elderly hip fracture patients. Further level-one studies on the subject will allow for firmer recommendations.

Keywords: elderly; fracture; hip; intestinal bleed; prophylaxis; proton pump inhibitors

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Introduction

The burden of fragility fractures is on the rise due to the rapid increase in the ageing population.[1–4] Approximately 1.6 million hip fracture cases are reported worldwide each year and the number is projected to climb to between 4.5 and 6.3 million by 2050.[5] The mortality rate in hip fractures in the elderly is approximately 10% over the first month and 33% within the first year.[1,4,6,7] Peri-operative complications including gastrointestinal bleeding are the main determinants of outcomes and the leading cause of morbidity and mortality in elderly patients with hip fractures.[3,6–8]

Stress-related gastric mucosal damage (SRMD) describes a spectrum of pathology attributed to the acute, erosive, inflammatory insult to the upper gastrointestinal tract associated with critical illness.[1,9] This condition is commonly referred to as gastrointestinal stress ulceration and is induced by physiological stress secondary to critical illness.[9,10] It represents a continuum from asymptomatic superficial lesions, through to occult gastrointestinal bleeding causing anaemia and clinically significant overt gastrointestinal bleeding.[9,11] Endoscopic studies have identified that 74–100% of critically ill patients have stress-related mucosal erosions and subepithelial haemorrhage within 24 hours of admission.[9] Critical illness is defined as a life-threatening condition characterized by a severe cardiovascular, respiratory or neurological derangement, often in combination, reflected in abnormal physiological observations.[10,12] It is a sequelae of stress-related decompensation[10,12] and therefore, the majority of hip fractures in the elderly should be considered a critical illness.

The incidence of macroscopic upper gastrointestinal bleeding (UGIB) in critically ill patients who do not receive prophylaxis is 5–25%.[2] The incidence of peri-operative acute UGIB ranges between 0.39% and 15% in patients with hip fractures.[6,7] However, the incidence of clinically important UGIB is between 1% and 4% with a mortality rate as high as 50%.[9,13] Acute upper gastrointestinal bleeding is often overlooked as a potential major cause of morbidity and mortality in the elderly with femoral neck fractures.[1,7,11]

Material and methods

A review of the literature was performed to the identify studies on proton pump inhibitors (PPI) and hip fractures. A search of PubMed, MEDLINE, and Google Scholar was conducted using the following keywords: “hip fracture” OR “femoral neck fracture” AND “proton pump inhibitors” OR “stress ulcer prophylaxis”. The year of publication limit was set to January 2005 to May 2020 and only articles in English were included. In addition, reference lists of the included articles were manually checked by the authors for missed studies. The following data were extracted: year of publication, study type, study sample, impact of PPIs, type and dosing where applicable.

Results

A total of 134 articles were identified, of which 131 articles were excluded due to duplication and being unrelated to the subject matter. The vast majority of excluded articles (100) were related to PPIs and the risk of hip fractures (see Fig. 1). The three articles included comprised of 1430 patients and two were based on prospective studies (see Table 1).

Discussion

Pathophysiology of SRMD

Physiological stresses in critically ill patients often result in splanchnic vasoconstriction, with diversion of blood supply to vital organs ensuring adequate perfusion.[9,14] Mechanisms underlying SRMD include decreased gastric flow, leading to mucosal ischaemia and subsequent reperfusion injury.[1,9,14] During the ischaemic period, there is excess production of reactive oxygen free radicals with resultant mucosal damage.[14,15] The oxygen free radicals are normal by-products of normal cellular metabolism, but in excess, they are deleterious to the mucosal epithelium.[14,15]

Risk factors for SRMD

Risk factors for SRMD include critical illness, mechanical ventilation for more than 48 hours, coagulopathy, septic

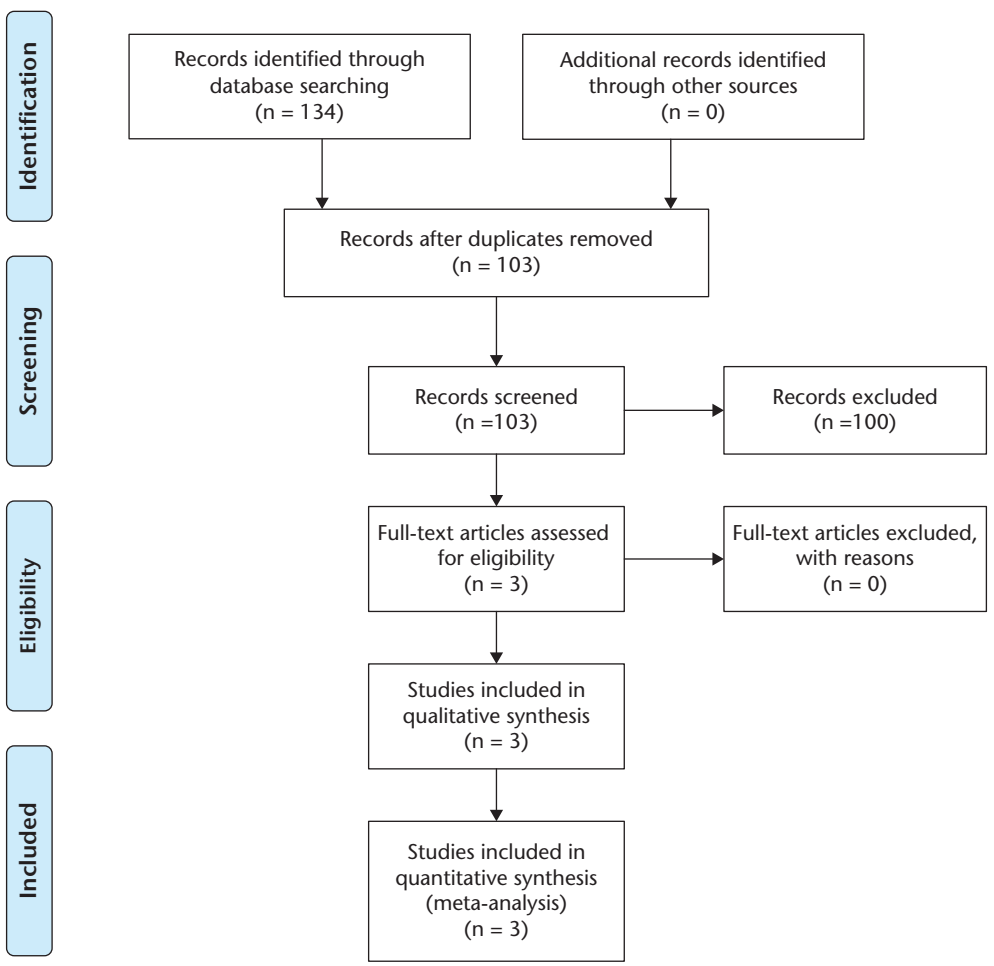

Fig. 1 PRISMA flow diagram.

Table 1. Summary of studies conducted on prophylactic use of proton pump inhibitors (PPIs) in patients with hip fractures

Author (year)	Study size	Age	Incidence	Comment on PPI	Dosing	Limitation
Fisher et al (2007)[7]	Older patients with HFs & RFs for UGIB (Observational group = 407, interventional group = 415) In interventional group only patients with at least one RF for AGIH were started on PPIs *n* = 139. Two-stage prospective	Observational group: 82.1±7.9 Interventional group: 81.7±8.3	AGIH observational group 16 (3.9%) of 407 patients. 1 (0.72%) in interventional group on PPIs *n* = 139 had AGIH. 3 (1.1%) in interventional group not on PPIs *n* = 276 had AGIH their risk factors were missed.	Prophylactic use of proton pump inhibitors in patients with risk factor for acute gastrointestinal haemorrhage significantly reduced the incidence of this complication (0.72% in treated patients vs. 13.4% in untreated; $P < 0.001$); the number needed to treat was 7.9.	111 (79.8%): pantoprazole, 16 (11.5%): omeprazole and 12(8.6%): esomeprazole.	Patients with pre-existing peptic ulcer disease were included.
Singh (2016)[11]	Prospective study. Control group: 262 Intervention group: 253	No mean, median provided. Author contacted. All patients > 60 years old.	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 there was no AGIH, melaena, coffee ground vomitus.	Following PPI prophylaxis, no patients developed gastric stress ulcer complications. The use of PPI prophylaxis could therefore represent a substantial cost benefit.	Omeprazole 40 mg once daily during admission	
Brozek et al (2017)[21]	Hip fractures (intervention = 1038 matched 1:1 with control group by age and gender) Retrospective sub-cohort	> 50 years old	N/A	Reduced 90-day mortality (Intervention = 0.19%) (Control = 3.47%)	N/A	

Notes. HFs (hip fractures), RFs (risk factors), UGIB (upper gastrointestinal bleeding), AGIH(acute gastrointestinal haemorrhage).

shock, renal failure, hepatic failure, head injury, major trauma, cigarette smoking, history of peptic ulcer and chronic use of aspirin and non-steroidal anti-inflammatory drugs (NSAIDs).[1,6,7,9,11,15,16] Aspirin and NSAIDs inhibit cyclooxygenase-1 with subsequent decrease in prostaglandin production.[16] Prostaglandins increase local blood flow and promote secretion of mucus and bicarbonate, thereby aiding gastroprotection.[16] Length of starvation period in the pre-operative phase in traumatized patients awaiting surgery is one of the less recognized modifiable risk factors.[11] During periods of starvation, the cytoprotection conferred by neutralization of the gastric acid with enteral feeds is negated thus making the mucosa vulnerable to damage.[17] Enteral feeds also increase gastric blood flow and induce the production of prostaglandins and mucus.[17] For most of the risk factors, irrespective of the causal mechanism, the common final pathway is splanchnic hypoperfusion.[1]

An additional compounding factor in elderly patients with hip fractures is the modality and the magnitude of surgery used to address the fracture itself.[18] These patients often undergo total hip replacement (THR) provided they fit the eligibility criteria.[11,18] The risk of UGIB following 'elective' THR is six-fold within the first two weeks compared to that of control subjects.[18] The risk is even higher in the context of THR for a fracture.[18]

Although subcutaneous low molecular weight heparin (LMWH) is generally not associated with an increased risk of UGIB, it deserves special mention as anti-thrombotic therapy significantly potentiates the risk of a major UGIB in patients over the age of 80 years.[18,19]

Clinical presentation

The patient may present with either overt or occult UGIB.[1,7,9] Patients with overt bleeding present with melaena stools or haematemesis of fresh or altered (coffee-ground) blood.[9,11,20] Patients with occult bleeding typically present with symptoms related to iron-deficiency anaemia (compounded by bleeding from the hip fracture). These symptoms amongst others include fatigue, dizziness and palpitations.[9,11,20]

Management

Principles constitute, firstly, identifying the patient at risk, secondly, modifying risk factors and, lastly, providing pharmacological prophylaxis.[1,7,9,11,18,21] Elderly patients with hip fractures are regarded as at high risk of SRMD due to their comorbidities, chronic medications, prolonged starvation periods prior to surgery and the physiological response to trauma itself.[7,9,18,21]

Pharmacological prophylaxis includes proton pump inhibitors (PPIs), histamine-2 receptor blockers (H2RBs),

and sucralfate.[1,5,7,9,11–13,15–18,22] PPIs inactivate the hydrogen-potassium pump ATPase at the secretory surface of the parietal cell, inhibiting the secretion of hydrogen ions and thereby increasing the pH of the gastric contents.[1,7,9,11,16,18,22] H2RBs block the action of histamine on parietal cells.[2,22] Sucralfate is a barrier agent and provides a protective layer by coating the gastric mucosa.[22] Although sucralfate has been shown to be beneficial, it is the least effective when compared to PPIs and H2RBs.[22]

Misoprostol, a prostaglandin E1 analogue that decreases gastric acid secretion, has not been proven to be beneficial in prevention of SRMD and is thus not recommended.[22] Alhazzani et al proved that PPIs are more effective than H2RBs, hence, they are considered as first-line prophylactic therapy.[2] Pantoprazole is the most potent of the PPIs and is the ideal drug for SRMD prophylaxis as it is also available in intravenous form.[22]

PPIs in hip fractures

PPIs confer survival advantage if prescribed during hospital stay and briefly after discharge particularly in elderly patients.[7,11,18,21] There seems to be a considerable decrease in the incidence of UGIB, length of hospital stay and mortality in patients older than 70 years of age.[7,11,21]

Side effects of PPI use

Headache, dizziness, skin reactions and arthralgia are by far the commonest side effects of PPI use.[11,13,23,24] Although complications related to acute use of PPIs are relevant in this context, it is also important to recognize that there is a suggestion that long-term use is associated with osteoporosis and increased hip fracture risk.[9,21,25,26] Increased gastrin production and hypochlorhydria are identified as the two main mechanisms that affect bone remodelling, mineral absorption, and muscle strength, contributing to increased risk of osteoporosis and hip fractures.[9,11,21,25,27,28] However, the long-term effects of PPIs on hip fracture incidence are still unclear, and the available evidence is conflicting.[25–28]

PPIs, Clostridium difficile *infection and pneumonia*

Gastric acid plays a vital role in host defence, with an intragastric pH of less than 4 being optimal for bacterial inactivation.[2,8,9,11] PPIs suppress gastric acid production and create a higher pH gastric environment, potentially increasing colonization by pathogenic organisms.[1,9,11,21] *Clostridium difficile* infection (CDI) and nosocomial pneumonia have been singled out as possible infective consequences of PPI use.[1,9,11,21,27,29] The use of PPIs is associated with a two-fold increase in CDI incidence.[30,31] This risk is further increased to a greater extent by concurrent use of broad-spectrum antibiotics, especially cephalosporins, fluoroquinolones, clindamycin and some penicillins.[31,32,33] There is an associated increased risk of both community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP) in patients exposed to PPIs.[9,13,34] The identification of preventable risk factors and careful patient selection is essential in prevention of these complications.[31,33] In high-risk patient populations, PPI use will be guided by benefits versus risks.[23] However, much controversy surrounds the subject of PPIs potentiating CDI and pneumonia. The evidence is not clear cut and the literature is often contradictory.[2,8,9,11,27] Furthermore, most of the data used to arrive at these assertions is observational and often fails to prove a cause–effect relationship. Hence, high-quality prospective studies are still required to assess PPI use and the risk of CDI and pneumonia.[9,13,31]

PPIs and cardiovascular effects

The use of PPIs is associated with an increased risk of adverse cardiac events, especially acute myocardial infarction and heart failure.[35,36] The exact causative mechanism is, however, unclear. Juurlink et al initially indicated that the association is spurious and not cause and effect, but recent literature suggests impairment of endothelial function and accelerated endothelial ageing.[36] This is, however, pertinent to long-term PPI use.[35,36]

Duration of prophylaxis

Short-term treatment of not more than four weeks is approved and deemed safe by the United States Food and Drug Administration (US FDA).[35,36] In situations where PPIs are clinically indicated, the course should be limited to the shortest possible duration and the lowest effective dose.[23]

Cost-effectiveness of PPIs

There is considerable variability in the actual cost of PPIs in different hospital settings.[7,11,21] Given that patients with a hip fracture with acute gastrointestinal bleeding have an average length of hospital stay 18 days longer than the national average,[7,11,21] the price of a course of PPIs compared to an acute hospital bed proves to be more cost-effective. It is also important to note that routine use of stress ulceration prophylaxis in patients without risk factors for a clinically significant bleed is unlikely to be cost-effective and should probably be avoided.[7,9,18,21] Routine use would increase the cost per event averted.[2] PPIs would need to be routinely administered to 900 hospitalized patients to prevent one episode of a clinically significant bleed.[2,9] As a result, models of cost-effectiveness advocate that the use of prophylactic therapy be limited to those with established risk factors for a clinically significant bleed.[2,9] Elderly patients with hip fractures fall into this category.

Conclusion

Elderly patients with hip fractures are at elevated risk of SRMD and subsequent UGIB. Due to the devastating and at times fatal complications of SRMD, preventative measures are mandatory. PPIs are readily available, and they are highly effective prophylaxis against SRMD. They are well tolerated, have a good safety profile and they are cost-effective in elderly patients with hip fractures. However, routine prescription of PPI to reduce the risk of SRMD and UGIB in this population group is currently not part of national guidelines.[4] Based on the available evidence we recommend the rational use of PPIs peri-operatively in all elderly patients with a hip fracture. There is a need for more level-one studies to add to the body of evidence.

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