ORIGINAL ARTICLES

A multicentre feasibility study evaluating stress ulcer prophylaxis using hospital-based registry data

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Stress ulcer prophylaxis (SUP), with either histamine-2 receptor blockers (H$_2$RBs) or proton pump inhibitors (PPIs), is a common therapy for mechanically ventilated patients in the intensive care unit.[1,2] Existing evidence suggests that, compared with H$_2$RBs, PPIs are associated with a reduced risk of developing upper gastrointestinal (GI) bleeding, but an increased risk of developing infections, in particular pneumonia and *Clostridium difficile* colitis.[3-10] However, this information is not of sufficient quality to allow assessment of the risks and benefits for decisions about medication. This results in substantial practice variation[1,2,11] with associated clinical uncertainty and health care cost implications.

Given the frequent use of SUP therapy, determining the optimal treatment approach is a research priority but, based on previous experience from high-quality trials involving ICU patients, the mortality difference attributable to the choice of SUP medicine is likely to be small.[12] Consequently, the sample size required to detect a realistic treatment effect for a conventional individual patient randomised controlled trial (RCT) would be prohibitively large in terms of logistics and cost. A potential alternative to an individual patient RCT is a registry-based, cluster-crossover, randomised trial.[13] In a study with this design, the unit of randomisation would be the ICU rather than the individual patient. Each participating ICU would be randomly assigned to one treatment for a time before being crossed over to the other treatment after a washout period. Crossing over greatly mitigates the power loss associated with cluster randomisation,[14] and the logistical efficiencies gained by implementing a study intervention ICU-wide would make it possible to enrol large numbers of patients in a short time. Baseline, process-of-care and outcome data could be collected through existing registries rather than with a study-specific case report form. This has several benefits including minimising the need for time-intensive, study-specific, data collection; increasing the opportunities to extend study participation to sites without traditional research infrastructure and expertise; maximising the scope of data collection; and significantly reducing the study cost.[15,16] The feasibility of a registry-based, cluster-crossover, randomised trial design depends on researchers being able to collect the required study data from existing databases and/or registries.

We hypothesised that the data necessary to conduct a registry-based RCT of SUP in Australia and New Zealand

ABSTRACT

Background: It is unclear whether histamine-2 receptor blockers (H$_2$RBs) or proton pump inhibitors (PPIs) are preferred for stress ulcer prophylaxis (SUP) in intensive care unit patients. Suitably powered comparative effectiveness trials are warranted.

Objective: To establish the feasibility of collecting process-of-care and outcome data relevant to a proposed interventional trial of SUP using existing databases.

Design, setting and participants: A retrospective cohort study conducted in seven Australia and New Zealand tertiary ICUs, including all patients $\geq$ 18 years admitted between 1 January 2011 and 31 December 2012.

Main outcome measures: Doses of dispensed PPIs and H$_2$RBs, upper gastrointestinal bleeding events, upper respiratory tract colonisation with pathogenic bacteria, *Clostridium difficile* infections and inhospital mortality.

Results: All sites were able to contribute to the study and investigators reported that data were generally easy to obtain. A median dose/ICU of 477 g of PPIs (interquartile range [IQR], 430.5–865 g), and 408.5 g (IQR, 109–1630.2 g) of H$_2$RBs, were dispensed over the 2 years of the study. The median proportion of patients/ICU with upper GI bleeding complicating admission was 1.4% (IQR, 0.3%–1.8%). Colonisation of the respiratory tract with gram-negative bacteria occurred in a median of 7.1% of patients/ICU (IQR, 6.3%–14.1%). Pseudomembranous colitis occurred in hospital in a median of 1.4% of patients (IQR, 0.9%–2%) and inhospital mortality was 10.6% (95% CI, 9.5%–11.7%).

Conclusions: It is feasible to use existing data sources to measure process-of-care and outcome data necessary for a registry-based interventional trial of SUP.

were readily available in existing databases. Therefore, our aim was to describe SUP therapy and upper GI bleeding events, and the morbidity potentially attributable to complications of SUP in seven Australian and New Zealand ICUs, using only aggregate, registry-based data.

Methods

This study was a retrospective cohort study using data collected from existing sources relevant to a future cluster-crossover trial of SUP. The study population was all adult patients admitted to seven study ICUs between 1 January 2011 and 31 December 2012. The seven study ICUs were all major metropolitan tertiary referral centres. Two of the ICUs were in New Zealand and five were in Australia. The study was approved by the New Zealand Central Health and Disability Ethics Committee (14/CEN/30) and a waiver of individual consent was granted, given the low-risk observational nature of the study.

Data were collected in aggregate form for each study ICU by calendar year, using a prespecified case report form. Data were extracted from the following databases: hospital discharge coding, pharmacy, ICU, microbiology and endoscopy. These databases were used to obtain information regarding the use of PPIs and H_2RBs in the study ICUs, episodes of upper GI bleeding, colonisation of the upper respiratory tract with pathogenic bacteria, episodes of *C. difficile* infection and inhospital mortality.

For acute upper GI bleeding episodes we determined the number of bleeding events excluding ICU admissions for upper GI bleeding. Specifically, we determined the number of new upper GI bleeding episodes complicating ICU admission and confirmed by gastroscopy; episodes of haematemesis or melaena (International Classification of Diseases 10th revision Australian modification [ICD-10-AM] hospital discharge codes K92.0 and/or K92.1), and diagnoses of acute gastric ulcer, duodenal ulcer, peptic ulcer and gastrojejunal ulcer (codes K25.0, K25.1, K25.2, K26.0, K26.1, K27.0, K27.1, K27.2, K28.0, K28.1, K28.2).

We determined the number of patients with gram-negative bacilli cultured from the lower respiratory tract while in the ICU and the growth of a number of specific organisms from respiratory specimens obtained in the ICU. These organisms were: *Staphylococcus aureus*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* spp, *Serratia* spp, *Citrobacter* spp, *Morganella morganii*, *Stenotrophomonas maltophilia* and *Acinetobacter baumannii*.

We determined the number of patients with *C. difficile* toxin-positive stool samples obtained during an ICU admission and the number of patients diagnosed with pseudomembranous colitis during their hospital stay (ICD-10-AM code A04.7).

Site investigators were asked for qualitative reports about the processes and methods of data collection.

Descriptive statistics are presented as total number and range, median and interquartile range (IQR), or as a percentage with 95% confidence interval as appropriate.

Table 1. Data availability, by site

Data	Site 1	Site 2	Site 3	Site 4	Site 5	Site 6	Site 7
Intensive care and inhospital mortality data	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Endoscopy data	Yes	Yes	Yes	Yes	No	Yes	Yes
Upper gastrointestinal bleeding discharge codes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Clostridium difficile colitis discharge codes	Yes*	Yes	Yes	Yes*	Yes	Yes	Yes
Microbiological data	No	Yes	Yes	No	Yes*	Yes	Yes
Pharmacy data	Yes	Yes	Yes	Yes	Yes	Yes	Yes

* Data available at the site but not provided for this study.

Results

Database availability and ease of data collection

All seven study sites were able to contribute registry data to the study and investigators reported that data were generally easy to obtain. For the calendar years 2011 and 2012, ICU mortality, SUP medicine dispensing, and hospital coding data for upper GI bleeding complications and episodes of pseudomembranous colitis were available at all sites. However, data from a microbiology database were not easily available at all sites and there were variations in source, method of acquisition and completeness of data obtained (Table 1).

Baseline, process and outcome data

Between 1 January 2011 and 31 December 2012 there was a total of 25 795 admissions (range across individual ICUs, 1841–6568) to the seven participating ICUs. Inhospital mortality was 10.6% overall (95% CI, 9.5%–11.7%), and 13.1% for patients receiving mechanical ventilation (95% CI, 10.8%–15.4%). Doses of dispensed SUP medicines were high, with a median per-ICU dose for PPIs of 477 g (IQR, 430.5–865 g) and a median per-ICU dose for H_2RBs of 408.5 g (IQR, 109–1630.2 g) over the 2 years of the study (see Table 2). The choice of SUP therapy varied substantially between sites, with two out of seven sites dispensing greater total quantities of H_2RBs and five out of seven sites dispensing greater total quantities of PPIs (see Figure 1).

Excluding those with an ICU admission diagnosis of upper GI bleeding, a median of 1.8% of patients/ICU (IQR, 1.2%–2.4%) underwent upper GI endoscopy. A median of 1.4% of patients/ICU (IQR, 0.3%–1.8%) developed new upper GI bleeding complicating their ICU admission. Respiratory samples were sent from a median of 24% of patients/ICU (IQR, 14.5%–50.4%), with a median of 7.1%

Table 2. Baseline, process-of-care and outcome variables, by year

Baseline, process and outcome variables	2011	2012	Total	ICUs[†]
Admissions,* N (range)	12 679 (948–3272)	13 116 (893–3296)	25 795 (1841–6568)	7
Admissions receiving MV, n (range)	8138 (822–1605)	8136 (796–1590)	16 274 (1618–3195)	7
Mean admissions receiving MV/ICU, % (95% CI)	68.5% (56%–81%)	67% (53%–81%)	63.1% (54.6%–80.9%)	7
Inhospital deaths, n (range)	1274 (107–333)	1127 (85–288)	2401 (192–621)	6
Mean inhospital deaths/ICU, % (95% CI)	11.4% (10.5%–12.3%)	9.8% (8.3%–11.2%)	10.6% (9.5%–11.7%)	6
Inhospital deaths in patients receiving MV, n (range)	1015 (96–268)	871 (80–218)	1886 (176–486)	6
Mean inhospital deaths in patients receiving MV/ICU, % (95% CI)	13.9% (11.7%–16.2%)	12.2% (9.8%–14.7%)	13.1% (10.8%–15.4%)	6
Median total PPI dispensed per ICU, g (IQR)	253 (237.2–420.3)	238.6 (177.4–444.7)	477 (430.5–865)	7
Median total H_2RB dispensed per ICU, g (IQR)	199.6 (9.1–815.1)	209 (79.2–815.1)	408.5 (109–1630.2)	7
Median admissions* complicated by requirement for upper GI endoscopy, % (IQR) (n = 506)	1.8% (0.9%–2.5%)	1.9% (1.3%–2.5%)	1.8% (1.2%–2.4%)	6
Median admissions* complicated by upper GI bleed, % (IQR) (n = 295)	1.5% (0.3%–2%)	1.5% (0.3%–1.6%)	1.4% (0.3%–1.8%)	7
Median admissions* with respiratory specimen samples, % (IQR) (n = 3413)	24.2% (13.2%–49.6%)	23.9% (15.7%–51.2%)	24.0% (14.5%–50.4%)	4
Median respiratory specimens with no growth, % (IQR) (n = 6102)	13.9% (10.5%–47.4%)	13.5% (8.8%–47.6%)	13.6% (9.5%–47.6%)	4
Median admissions* with respiratory specimen samples with gram-negative bacilli, % (IQR) (n = 1057)	7.2% (5.8%–13.3%)	7.1% (6.6%–14.5%)	7.1% (6.3%–14.1%)	4
Median admissions* with stool sample positive for *Clostridium difficile* toxin, from microbiology database, % (IQR) (n = 93)	0.7% (0.3%–1.4%)	0.6% (0.4%–1.4%)	0.6% (0.4%–1.4%)	4
Median admissions* with *C. difficile* colitis, from coding, % (95% CI) (n = 163)	1.5% (1.1%–1.8%)	1.6% (0.9%–2.6%)	1.4% (0.9%–2%)	4

ICU = intensive care unit. MV = mechanical ventilation. PPI = proton pump inhibitor. H_2RB = histamine-2 receptor blocker. GI = gastrointestinal. IQR = interquartile range. * Admissions to the ICU. † Number of ICUs contributing data.

of patients/ICU (IQR, 6.3%–14.1%) testing positive for one or more gram-negative bacilli. The number of patients from whom various respiratory pathogens were grown for each year of the study is shown in Table 3. *C. difficile* toxin-positive stool samples were obtained during the ICU stay in a median of 0.6% of patients/hospital (IQR, 0.4%–1.4%), and *C. difficile* colitis occurred inhospital in a median of 1.4% of patients/hospital (IQR, 0.9%–2%) (see Table 2). The overall frequency of upper GI bleeds, *C. difficile* toxin-positive stool samples, and growth of respiratory pathogens were similar for the calendar years 2011 and 2012.

Discussion
Summary of major findings
In this large, retrospective cohort study, we showed that it is feasible to collect information from existing databases and

registries on dispensing of PPIs and H_2RBs, episodes of upper GI bleeding, complications that may be related to the use of SUP medicines (such as *C. difficile* infection and bacterial colonisation of the respiratory tract), and ICU and hospital mortality rates. The event rates we observed were similar for each of the 2 years of the study. We have shown that collection of data on outcomes relevant to an interventional trial of SUP therapy in the ICU, using only existing data sources, is feasible in a cohort of Australian and New Zealand ICUs. Our data confirm that in the study ICUs, large amounts of PPIs and H_2RBs are dispensed to patients. Moreover, there is variation in the most commonly dispensed SUP medicines between sites. Given the lack of evidence to guide practice, this geographical variation is idiosyncratic and supports the ethical reasons for conducting an interventional trial using a cluster-crossover design.

scribed H$_2$RBs, and in 5.9% of patients prescribed PPIs.[19,20] We observed that upper GI bleeding occurred more frequently than *C. difficile* infection.

In all previous studies, pneumonia has been reported to occur more frequently than GI bleeding or *C. difficile* infection. We saw a relatively high frequency of colonisation of the respiratory tract with gram-negative organisms, which is consistent with these previous observations.[3,8,21] A recent cost-effectiveness study highlighted that any variable effect of PPIs and H$_2$RBs on the risk of pneumonia was likely to the greatest determinant of which form of SUP therapy is the most cost-effective.[20]

Clinical implications

There is currently insufficient evidence to state whether PPIs or H$_2$RBs are preferred for patients who need SUP in the ICU, and several recent publications have highlighted the need for a large-scale intervention trial of PPIs versus H$_2$RBs.[3,19,21] Our study supports the feasibility of performing such a trial using a cluster-crossover design and taking advantage of existing registry data to simplify data collection.

Strengths and weaknesses

Our study has several strengths: it is the first large retrospective cohort study evaluating the prevalence of upper GI bleeding and SUP-related complications in Australian and New Zealand ICUs, and includes data collected from 23 954 patients from seven ICUs in two countries.

However, although we were able to show that it is feasible to use registry data for process-of-care and outcome measures in a large interventional study, our study findings need to be considered with some caveats. First,

Figure 1. Comparison of proton pump inhibitors (PPIs) and histamine-2 receptor blockers (H$_2$RBs) dispensed, by site
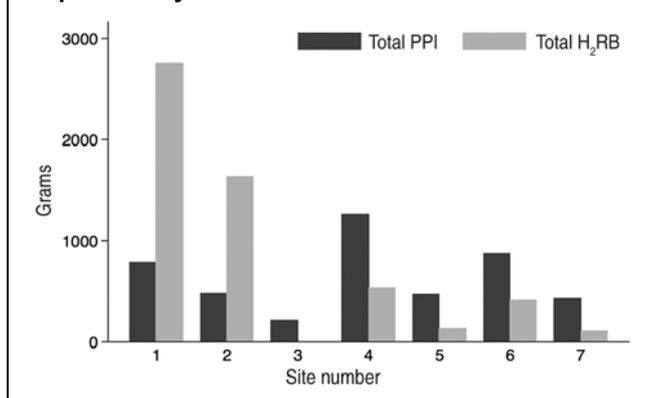
Comparison with previous studies

No previous studies have specifically sought to establish whether it is possible to collect relevant outcome variables for an interventional trial of SUP therapy using only registry data. The prevalence of upper GI bleeding and SUP-related complications observed in our study is broadly consistent with previous studies from other parts of the world. The most widely cited publication evaluating upper GI bleeding risk in ICU patients is a prospective study conducted by the Canadian Critical Care Trials Group and published in 1994.[17] In this study, the prevalence of clinically important GI bleeding (defined as overt GI bleeding with haemodynamic compromise or a need for blood transfusion) was 1.5% (95% CI, 1.0%–2.1%).[17] Recently published retrospective studies have reported a wide range of rates of upper GI bleeding, ranging from 0.16% in a cohort of cardiac surgical patients[3] to 5.9% in a United States cohort of mechanically ventilated patients treated with PPIs for more than 48 hours.[8] In our study, new upper GI bleeding occurred in a median of 1.4% of patients/ICU (IQR, 0.3%–1.8%).

In recent studies, the relative frequency of GI bleeding compared with *C. difficile* has varied between studies.[8,18] One recent single-centre European study of patients staying in the ICU for ⩾48 hours showed that *C. difficile* infection occurred in 3.3% of patients, compared with GI bleeding which occurred in 0.9% of patients.[18] A larger multicentre observational study of patients administered SUP medicines for ⩾48 hours while mechanically ventilated showed that *C. difficile* infection occurred in 2.2% of patients prescribed H$_2$RBs, and in 3.8% of patients prescribed PPIs. GI haemorrhage occurred in 2.1% of patients pre-

Table 3. Respiratory pathogens and numbers of intensive care patients with positive specimens, by site and year

Pathogen	Site 2		Site 3		Site 6		Site 7	
	2011	2012	2011	2012	2011	2012	2011	2012
Staphylococcus aureus	46	45	13	21	40	48	51	67
Haemophilus influenzae	17	18	29	33	37	36	39	43
Pseudomonas sp	37	37	7	17	50	47	31	20
Escherichia coli	7	6	10	13	48	38	16	26
Klebsiella sp	9	10	7	21	46	52	15	10
Enterobacter sp	12	13	12	14	55	52	15	11
Serratia sp	8	8	6	14	9	6	3	4
Citrobacter sp	5	5	2	2	5	11	3	4
Morganella sp	5	5	0	1	2	0	1	6
Stenotrophomonas sp	8	8	1	2	7	12	2	6
Acinetobacter sp	4	3	2	2	18	18	6	5

although we sought to examine feasibility in several study sites, all were large, metropolitan, tertiary-referral centres. Whether our findings are generalisable to other centres is unknown. Second, because we used retrospective registry data, the cumulative incidence of complications may be inaccurate because of incomplete or inaccurate coding. It is reassuring that, even if this is the case, the data within individual centres appear to be stable over time, which reduces the chances of differential bias between treatment groups in an interventional trial resulting from inaccuracies in coding. Finally, the variable availability and quality of data between sites suggests that it would be prudent to ensure in advance that any sites interested in participating in a large-scale, cluster-crossover RCT of SUP were able to collect the required data. Prospectively defined and piloted data collection methods may help to ensure consistency of data collection methods between sites.

Conclusion

It is possible to collect information about SUP medicines use, upper GI bleeding events, *C. difficile* infections and respiratory tract colonisation using existing data sources, which suggests the feasibility of conducting a registry-based, interventional trial.

Competing interests

None declared.

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