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RISK FACTORS FOR THE DEVELOPMENT OF GASTROINTESTINAL BLEEDS AND ULCERS AFTER FORMULARY CHANGE IN THE NEUROSCIENCE INTENSIVE CARE UNIT

By: Sarah Jung

A project submitted in partial fulfillment of the requirements for the degree of MASTER

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RISK FACTORS FOR THE DEVELOPMENT OF GASTROINTESTINAL BLEEDS AND ULCERS AFTER FORMULARY CHANGE IN THE NEUROSCIENCE INTENSIVE CARE UNIT

To the faculty of the University of Houston College of Pharmacy:

The members of the committee appointed to examine the project of Sarah Jung find it satisfactory and recommend that it be accepted on May 18, 2015.

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Committee Chair, Sujit S. Sansgiry, PhD

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Committee Member, Teresa Allison, PharmD, BCPS

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Finally, thank you to all my family, friends, and colleagues whom have been my strength and support throughout this time.

Dedication

I would like to dedicate this project to my parents, Charles and Sooaei Jung, who have never stopped loving me and have been my greatest support. Without you, I would not be where I am today.

Risk Factors for the Development of Gastrointestinal Bleeds and Ulcers After Formulary Change in the Neuroscience Intensive Care Unit

Abstract

Objective: The objective of this study was to evaluate the efficacy of prophylactic administration of histamine-2-receptor antagonists in preventing gastrointestinal (GI) bleeds and ulcers after formulary interchange. Mortality was a secondary endpoint.

Method: This study was conducted as a retrospective chart review of patients admitted into the neuroscience intensive care unit (NSICU) and received an esophagogastroduodenoscopy (EGD) in years 2013 and 2014. All patient records were obtained from Memorial Hermann-Texas Medical Center in Houston, Texas. Data regarding prophylactic stress ulcer medications and incidence of GI bleeds or ulcers was collected on paper data collection sheets then formatted electronically. Data was collected and analyzed using descriptive analysis, bivariate analysis, and logistic regression.

Results: A total of 72 patients were included for analysis. No factors were statistically significant. There was a total rate of 73.61% of GI ulcers and 75% of GI bleeds. 50% of all patients received ranitidine, 25% received famotidine, and 25% received PPI's as SUP. Incidence of GI bleeds and ulcers by treatment group was almost identical: the ranitidine group (n=36) had 26 (72.22%) GI ulcers and 27 (75%) GI bleeds, the famotidine group (n=18) had 12 (66.67%) GI ulcers and 12 (66.67%) bleeds, and the PPI group (n=18) had 15 (83.33%) GI ulcers and 15 (83.33%) GI bleeds. Mortality included only 1 patient (1.39%). Factors predictive for developing GI ulcer may include use of famotidine (p=0.07). On the other hand, factors predictive for developing GI bleed may include use of ranitidine (p=0.09) and having SUP

medication regimen switched (p=0.08). For mortality, no factors were considered significant in correlation to having mortality or predicting mortality, including APACHE II scores.

Conclusion: Although the results were not statistically significant, the trend in data points shows that use of ranitidine and switching SUP medications may have predisposed patients to developing GI bleeds. Furthermore, compared to those who received PPI's, those on either famotidine or ranitidine had higher rates of GI injury. No factors were correlated closely with mortality. While the use of ranitidine was initiated from a cost-savings perspective, increases in GI injury may render the formulary interchange ineffective. Future studies with a higher sample size would be able to strengthen these findings of the incidence of GI bleeds and ulcers by SUP medication.

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CHAPTER 1

INTRODUCTION

Significance

Critically ill patients are at risk for stress-related mucosal damage (SRMD) due to acutely increased physiological demands of the body. A landmark trial by Cook et al. identified especially those on mechanical ventilation for greater than 48 hours or with coagulopathy to more frequently develop gastrointestinal (GI) ulcers and/or bleeding (Cook, et al. 1994; ASHP, 1999). Ulcerations may be superficial and confined to the mucosa or may cause diffuse oozing of blood into submucosal vessels, producing frank hemorrhage. This process can occur within hours of major trauma or serious illness. As hospitalization stay increases, deeper and more distal lesions develop and perfusion of GI mucosa decreases. Specifically in intensive care unit (ICU) patients, the presence of multiple systemic inflammatory abnormalities and changes in hemodynamics lead to decreased cardiac output, vasoconstriction, cytokine release, and splanchnic hypoperfusion. Furthermore, they develop an imbalance between the protective layers of mucous and bicarbonate versus gastric acid production (Marik, et al. 2010; Mohebbi, et al. 2009; Spirt, 2006; Weinhouse, 2014). It has been established that patients with central nervous system (CNS)-related injuries are at an even higher risk for developing stress ulcers due to increased gastric acid secretion possibly from vagal stimulation (Burgess, et al. 1995; Hatton, et al. 1996). There is an overall lack of studies examining the efficacy of SUP in neurosurgical patients as well as constant debate over superiority of certain pharmacologic agents over others. This study is the first to compare the clinical efficacies of two widely used SUP agents in neurosurgical patients at a large, tertiary, academic medical center.

Background – Pharmacologic agents

Pharmacologic agents available for stress ulcer prophylaxis include histamine-2-receptor antagonists (H2RA's), proton pump inhibitors (PPI's), cytoprotectants (i.e. sucralfate), antacids, and prostanoids (i.e. misoprostal). However, H2RA's and PPI's have been the mainstay for maintaining a higher intragastric pH and preventing the incidence of overt GI bleeding in ICU patients (ASHP, 1999; Weinhouse, 2014). Both classes act on the gastric parietal cells, although by different mechanisms. H2RA's prevent binding of histamine-2 molecules that normally stimulate acid secretion with food ingestion. On the other hand, PPI's work further upstream by blocking the H^+/K^+-ATPase pump and the secretion of H^+ ions into the gastric lumen (Love, et al. 2014). Ultimately, gastric acid production is reduced, and GI ulcers and bleeds are prevented.

Choosing appropriate prophylactic therapy has been controversial. Various studies have repeatedly proven that H2RA's are more effective than antacids, sucralfate, and placebo (Spirt, 2006; Weinhouse, 2014). Specifically in patients with severe head injury, ranitidine significantly prevented upper GI bleeding versus placebo versus no ranitidine (Burgess, et al. 1995). However, in regards to the efficacy between H2RA's and PPI's, there is a constant debate on whether PPI's are more effective than H_2-antagonists. Recent systematic reviews suggest that there may be a clinical advantage in using PPI's over H_2-antagonists. However, there was no difference in incidence of nosocomial pneumonia, ICU length of stay, or ICU mortality, and most of the studies had a high or unclear risk of bias. On the other hand, other studies have not shown superiority of PPI's in reducing gastric pH or preventing GI bleeds (Alhazzani, et al. 2013; Barkun, et al. 2012; Devlin, et al. 2005; Lin, et al. 2010).

If a patient is no longer intubated or coagulopathic, stress ulcer prophylaxis may be discontinued. Furthermore, if gastric feeds are initiated, SUP may not be necessary. Dhandapani,

et al. studied the timing of enteral nutrition in patients with traumatic brain injury and saw that those who were fed within three days had overall better outcomes than those fed later (Weinhouse, 2014; Dhandapani, et al. 2012).

Background – Current literature

Current literature regarding the use of stress ulcer prophylaxis in neurosurgical patients is limited. There have been no original studies published in the last 10 years regarding efficacy of H2RA's as SUP agents in neurosurgical patients. Findings regarding the efficacy famotidine and ranitidine in various ICU's are summarized in **Table 1.**

Table 1 – Summary of literature

Reference	Year	Population	Intervention & Outcome	Results
Al-Quorain, et al.	1994	Intensive care unit King Fahd University Hospital, Al-Khobar, Saudi Arabia	Famotidine IV 20mg every 12 hours vs. ranitidine IV 50mg every 8 hours Gastric pH	Famotidine raised gastric pH more effectively than ranitidine
Wang, et al.	1995	General intensive care unit Chang Gung Memorial Hospital, Taipei, Taiwan	Famotidine IV 20mg every 8 hours vs. cimetidine IV 200mg every 4 hours vs. cimetidine IV 400mg every 4 hours Gastric pH	• No significant improvements in gastric pH in cimetidine 400mg every 4 hours vs. cimetidine 200mg every 4 hours • Famotidine more effective than both cimetidine groups
Burgess, et al.	1995	Surgical intensive care unit with GCS ≤ 10 University of Louisville, Louisville, KY	Ranitidine continuous infusion at 6.25mg/hr vs. placebo Gastric pH & incidence of upper GI bleeding	• No GI bleeding in the ranitidine group • 28% in placebo group developed bleeding • Mean intragastric pH in placebo group significantly lower than ranitidine group
Olsen, et al.	1995	Medical intensive care unit University of Nebraska Medical Center, Omaha, NE	Single dose - cimetidine IV 300mg vs. famotidine IV 20mg vs. ranitidine IV 50mg Gastric pH	• Famotidine had the longest duration of acid suppression • Ranitidine maintained higher gastric pH longer than cimetidine

After the landmark trial by Cook, et al. was published regarding the use of SUP in critically ill patients, several more studies were conducted to compare the efficacy of various pharmacologic agents.

Al-Quorain, et al. compared the efficacy of famotidine to ranitidine when administered as an intermittent IV bolus injection in raising gastric pH above 4.0 – the optimal level considered for the prevention of stress ulcers. The study included 32 patients randomly divided to receive either of the agents and only included patients admitted to the ICU, 50% of which had head injury. Appropriate exclusions were applied based on the patients' comorbidities. There were no differences between the two groups on day 1 of the study. However, starting day 2 and onwards, famotidine reached higher gastric pH levels than ranitidine ($p<0.05$) and gradually increased the total percentage of patients with $pH > 4.0$ to 100% by day 7 compared to a decline to 13% in the ranitidine group. On average, famotidine maintained $pH > 4.0$ in 79.4% of samples versus 32.6% with ranitidine (Al-Quorain, et al. 1994).

As the use of famotidine continued to increase in ICU's, another comparative study was conducted by Wang, et al. to examine cimetidine versus famotidine. Cimetidine had long stood as the H2RA agent of choice, however its adverse effects of hepatotoxicity, neutropenia, confusion, and antiandrogenic effects made it an undesirable drug. Wang, et al. studied two dosing regimens of cimetidine (200 mg every 4 hours, 400 mg every 4 hours) versus famotidine 20 mg every 8 hours in the general intensive care unit and monitored gastric pH levels. 48 patients were randomly allocated in crossover design to receive one of six different sequences. Their results showed that there was no significant improvement between the 200 mg and 400 mg cimetidine groups. However, the famotidine group had significantly higher pH than both cimetidine groups ($p=0.0009$ for 200-mg dose, $p=0.019$ for 400-mg dose). Also, the percentage

of time during which pH remained greater than 4.0 during famotidine treatment was significantly higher than both cimetidine regimens ($p<0.0001$ for 200-mg dose, $p=0.019$ for 400-mg dose). Furthermore, famotidine required less frequent bolus dosing injections than cimetidine, which can reduce nursing demand. It was noted that clearance seems to be faster in critically patients, thus requiring more frequent dosing in general (Wang, et al. 1995).

Ranitidine was introduced to the market the same year as famotidine and since then has been widely used because of its favorable pharmacodynamics profile and lack of adverse effects that were associated with cimetidine. Burgess, et al. conducted a double-blind, placebo-controlled study that compared continuous ranitidine infusion at 6.25 mg/hour versus placebo in 34 head injury patients with a Glasgow coma score ≤ 10, all of whom were mechanically ventilated. Intragastric pH levels were recorded for 72 hours. For the ranitidine group, no GI bleeding occurred and no blood transfusions were required. In contrast, 28% of the placebo group developed GI bleeding and 40% of them required blood transfusions following study withdrawal. pH levels of the placebo group were significantly lower overall than the ranitidine group.

Lastly, Olsen, et al. published the first crossover study on cimetidine, ranitidine, and famotidine and their impact on intragastric pH. They enrolled 12 adult patients admitted to the medical ICU who were mechanically ventilated. All patients were initially given sucralfate 1 gram every 6 hours for the first 24 hours of admission, but not within 6 hours of H2RA administration. Then, they were randomized to receive either cimetidine IV 300 mg, famotidine IV 20 mg, or ranitidine IV 50 mg. Each drug was given in crossover fashion on consecutive days after pH returned to baseline. To confirm washout in between doses, blood samples were collected to make sure there was no H2RA present in the plasma before dosing. Famotidine

maintained pH ≥ 4 longer than both cimetidine and ranitidine ($p<0.01$ for both drugs), and ranitidine maintained pH ≥ 4 than cimetidine ($p<0.05$). Mean onset of action was longest in the famotidine group and was able to maintain pH ≥ 6 in 70% of measurements. On the other hand, only 38.5% and 55.6% of pH readings were ≥ 4 for cimetidine and ranitidine, respectively. Furthermore, there were large variations in pH response for those two H2RA's (Olsen, et al. 1995).

At our institution

In an effort to reduce costs, ranitidine IV, tablets, and suspension were added to the formulary in 2010 to use in preference over famotidine, especially the suspension formulation. **Table 2** describes average whole sale prices of different formulations of the two drugs as reported by Lexicomp (Wolters Kluwer, Hudson, OH). Incidentally, clinicians in the neuroscience ICU (NSICU) noticed an increase in GI ulcers and/or bleeds. Therefore, a retrospective chart review was conducted to determine the true incidence of GI injury from a famotidine versus ranitidine standpoint. Patients suspected of GI injury were examined via esophagogastroduodenoscopy (EGD). We hypothesized that patients who were prophylactically given ranitidine or switched from famotidine to ranitidine developed more GI ulcers and/or bleeds compared to those who received famotidine or PPI's. Secondary endpoint was mortality.

Table 2 – Cost information for famotidine and ranitidine

Formulation	Famotidine	Ranitidine
IV	40 mg dose = $2.14	50 mg dose = $3.74
Tablet	40 mg dose = $1.73	150 mg dose = $1.56
Suspension/Syrup	40 mg dose = $19.60	150 mg dose = $7.90

Research questions

The following questions were considered for the patients identified:

- What agent of stress ulcer prophylaxis was used?
- What was the result of the EGD?
- Was the patient mechanically ventilated for more than 48 hours?
- Was the patient coagulopathic upon admission?
- What high-risk medications was the patient taking before and during admission?
- What was the length of stay and mortality result of the patient?

CHAPTER 2

METHODOLOGY

This chapter will discuss in detail the methods used to conduct this study.

Institutional review board approval

All research was approved by the boards at Memorial Hermann-Texas Medical Center and the University of Houston before collecting data.

Research design

This project is a non-experimental, retrospective chart review that reviewed pre-existing inpatient data of patients admitted to the neuroscience intensive care unit (NSICU) at Memorial Hermann-Texas Medical Center from January 2013 to June 2014. A paper data collection sheet was used to collect all relevant data for the study. Then, all data was transferred to an electronic spreadsheet. For purposes of security and auditing, date of electronic access for each patient by name and medical record number was recorded in a separate spreadsheet that was securely encrypted and not used for any other purposes. All other patient data was coded to maintain confidentiality.

Sample selection

A database containing all adult patients between January 2013 and June 2014 who received an esophagogastroduodenoscopy (EGD) during their admission was created based on ICD-9 codes for EGD (45.11, 45.12, 45.13, 45.14, 45.16). From there, only patients who were initially admitted to the NSICU were selected for review of their electronic medical records.

Furthermore, patients must have had received some form of stress ulcer prophylaxis during their hospitalization. Exclusion criteria included past medical history of peptic ulcer disease or active GI bleeding. If the patient's past medical history was not available due to lack of information at time of admission, they were considered as not having a history of peptic ulcer disease or active GI bleeding.

Data collection

All potential direct and indirect variables were identified based on clinical experience as well as parameters defined in previous literature. The data collection sheet can be found in **Appendix 1**.

Variables related to admission status were: diagnosis, coagulopathy at time of admission, APACHE II score, significant labs on admission, length of stay, mortality, disposition, inpatient SUP and non-SUP medications, total number of days on mechanical ventilation, fecal occult blood test (FOBT) date and results, and EGD date and results. Diagnoses were categorized as: intracranial hemorrhage (ICH), acute ischemic stroke (AIS), subarachnoid hemorrhage (SAH), arteriovenous malformation (AVM), tumor, seizure, spinal cord injury (SCI), traumatic brain injury (TBI), and other. Admission lab values recorded were: hemoglobin, hematocrit, aPTT, platelet count, INR, and serum creatinine. Patients were considered coagulopathic on admission if INR > 1.5, aPTT > twice the normal range of values, platelet count < 50,000/m^3, or clinically indicated by the admitting physician as such. Further initial admission lab values and vitals were examined to calculate the APACHE II score, courtesy of MedCalc 3000, which was provided by Medscape. Disposition post-hospitalization was defined as transfers to: rehabilitation, skilled nursing facility (SNF), long term acute care facility (LTAC), outside hospital, hospice, or death.

Variables related to clinical characteristics and past medical history were: gender, age, history of peptic ulcer disease or active GI bleeding, and home medications.

For both at home and inpatient medications, only those that are known risks for developing GI injury were surveyed: NSAIDs, antiplatelets, anticoagulants, corticosteroids, and vasopressors. Also, use of H2RA's, PPI's, and sucralfate was recorded. A list of high-risk non-SUP medications may be found in **Appendix 3**.

Patients were assigned to SUP treatment groups based on what agent(s) they first received upon admittance to the NSICU. If a patient received multiple SUP drugs, only those that were administered for at least 48 hours were considered. If switched between agents, a switching variable was defined to reduce confounding. Grouping assignments may be found in **Appendix 2.**

For record-keeping and auditing purposes as requested by the IRB at Memorial Hermann-Texas Medical Center, dates of access for every patient were recorded by medical record number (MRN) in an encrypted spreadsheet. Efforts were made to limit visits to each patient's record to one time.

Data analysis

All data was coded (**Appendix 2**) into an Excel 2011 spreadsheet (Microsoft, Redmond, WA). Analysis was performed using SAS version 9.3 (SAS Institute Inc., Cary, NC). The level of significance for all analyses was set at $p<0.05$. Descriptive statistics (frequencies, percentages, means, standard deviations) were reported for applicable variables. Bivariate analyses were performed to see the individual effects of each independent variable with dependent variables (number of GI bleeds/ulcers and mortality). Lastly, logistic regression models were applied to

assess predictive factors for the development of GI ulcers/bleeds or mortality while controlling for confounding factors. **Table 3** describes the methods of analysis used for this study.

Patients were assigned into three different treatment groups based on the initial SUP agent given upon admission. However, if switched to a different drug, the medication had to have been administered for at least 48 hours prior to the switch in order to assign it to that treatment group. If given for less than 48 hours, the initial medication was disregarded and the subsequent drug was assigned as the treatment group.

Table 3 – Types of analyses used

Type of analysis	***Purpose of test***	***Variables involved***
Descriptive analysis	Description of independent variables	Frequency (%): Gender, age, treatment group
Bivariate Analysis	Association of each independent variable with the dependent variable.	To test effect of independent variables on incidence of GI ulcers or bleeds.
Logistic Regression	Association of primary independent variable with the dependent variable controlling for possible confounders	To test the effect of SUP on GI ulcers or bleeds while controlling for confounding variables

CHAPTER 3

RESULTS & ANALYSES

Study population

A total of 97 patients received an EGD after being admitted to the NSICU from 2012 to 2014. After applying exclusion criteria, 72 patients were included for analysis. Reasons for exclusion consisted of: history of PUD, active GI bleeding at admission, missing EGD report, or no SUP used.

Descriptive analysis of patient characteristics

Patient demographics and clinical profile information are presented in **Table 4**. Mean age of the patients was 59.3 (± 17) days, with a range of 19 to 89 years. Gender was distributed to 55.56% males and 44.44% females. Mean length of stay was 23.1 (± 13.4) days, with a range of 6 to 89 days. The majority of patients (98.61%) survived admission, while only 1.39% died. Upon admission, only 6 patients were coagulopathic (8.33%). During their hospital stay, 20 (27.78%) patients had a fecal occult blood test (FOBT) performed. All patients received at least one EGD while admitted. Findings consisted of 73.61% total incidence of GI ulcers and 75% incidence of GI bleeds.

Table 4 – Descriptive analysis of patients' demographics and clinical profiles

Variable	Categories	Frequency (%) or Mean +/- SD (n = 72)
Age (years)		59.3 ± 17
Gender	Male	40 (55.56%)
	Female	32 (44.44%)
Length of stay (days)		23.1 ± 13.4
Coagulopathy on admission	Yes	6 (8.33%)
	No	66 (91.67%)
Received FOBT	Yes	20 (27.78%)
	No	52 (72.22%)
Positive EGD	GI ulcer	53 (73.61%)
	GI bleed	54 (75%)
Mortality	Alive	71 (98.61%)
	Dead	1 (1.39%)

Table 5 describes the frequency of use of home medications associated with a high risk of developing GI ulcers or bleeds as well as documented home use of H2RA's and PPI's. More than 94% of patients did not use H2RA's, PPI's, NSAID's, corticosteroids, or anticoagulants. However, 25% were on antiplatelets and 12.5% were on anticoagulants before admission.

Table 5 – Descriptive analysis of home medication use

Medication	Categories	Frequency (%)
Home H2RA	Yes	1 (1.39%)
	No	71 (98.61%)
Home PPI	Yes	4 (5.56%)
	No	68 (94.44%)
Home NSAID	Yes	2 (2.78%)
	No	70 (97.22%)
Home corticosteroids	Yes	1 (1.39%)
	No	71 (98.61%)
Home anticoagulants	Yes	9 (12.5%)
	No	63 (87.5%)
Home antiplatelets	Yes	18 (25%)
	No	54 (75%)

Patients were grouped according to the initial SUP drug they received upon admission. However, if the medication was switched to a different drug before 48 hours of administration had passed, the subsequent medication was assigned as the treatment group. For instance, if patient A was given ranitidine for 72 hours and then had SUP discontinued, then patient A would be assigned into the "ranitidine" group. If patient B was started on ranitidine, but after 24 hours switched to famotidine, patient B would be grouped into the "famotidine" group since ranitidine was given for less than 48 hours. If patient C was started on ranitidine, then after 24 hours switched to famotidine for another 24 hours, then switched to a PPI, patient C would be grouped into the "PPI" group. In order to account for multiple medication switches that occurred post-48

hours, once the treatment group was defined for each patient, a SWITCH variable was coded to see if the effect of switching would influence the primary outcome. **Table 6** describes the distribution of patients into each treatment group.

Table 6 – Descriptive analysis of patient distribution in treatment groups

Treatment Group	Frequency (%) N = 72
Ranitidine	36 (50%)
Famotidine	18 (25%)
PPI	18 (25%)

Bivariate analysis of primary outcome with each independent variable

Bivariate analyses of each independent variable were performed to see the frequencies and probabilities of developing GI ulcers or bleeds.

Table 7 shows the probability (odds ratio) of developing a GI ulcer or bleed depending on various factors. No factors were statistically significant. However, this analysis was used to identify variables appropriate for logistic regression analysis.

Table 7 – Odds ratio of independent variables on primary outcome

Outcome	Variable	Odds Ratio
GI Ulcer	Switch	0.43
	Ranitidine vs. PPI	1.92
	Famotidine vs. PPI	2.50
	Home antiplatelets	1.35
	Home PPI	1.08
	Home anticoagulant	0.89
	Positive FOBT	2.52
	Coagulopathy on admission	1.88
	Positive EGD2	1.08
GI Bleed	Home antiplatelets	1.23
	Home anticoagulants	0.82
	Home PPI	1.0
	Coagulopathy on admission	1.74
	Positive FOBT	2.29
	Positive EGD2	1.0
	Switch	0.48

** Results were statistically significant at $\alpha = 0.05$. None were significant at this time.*

Table 8 – Incidence of GI ulcers by treatment group

Treatment Group	Frequency (%)
Ranitidine N=36	26 (72.22%)
Famotidine N = 18	12 (66.67%)
PPI N=18	15 (83.33%)

Table 9 – Incidence of GI bleeds by treatment group

Treatment Group	Frequency (%)
Ranitidine	27 (75%)
Famotidine	12 (66.67%)
PPI	15 (83.33%)

Table 8 reports the frequency of GI ulcers depending on the treatment group. The "ranitidine" group had an incidence of GI ulcers at 72.22% while the famotidine group had an incidence of 12 (66.67%). Similarly, **Table 9** shows the frequency of GI bleeds depending on the treatment group. Of the patients who received ranitidine, 75% developed GI bleeds in contrast to 66.67% of patients who received famotidine. Of note, patients who received any PPI had 83.33% rate of developing both GI ulcers and bleeds.

Next, the frequency of medication switch was analyzed by treatment group. Both "ranitidine" and "famotidine" groups had the same frequency of switches at 16.67%. Patients started on PPI's had less medication switches at 6.94%. Results are in **Table 10**.

Table 10 – Frequency of SUP medication switch by treatment group

Treatment Group	Frequency (%) N = 72
Ranitidine	12 (16.67%)
Famotidine	12 (16.67%)
PPI	5 (6.94%)

Table 11 shows the incidence of GI bleeds according to whether the patient had medication switch or not. Those who had a switch had less frequent bleeds than those who did not (33.33% vs. 41.67%).

Table 11 – Incidence of GI bleeds in patients with medication switch

Switch?	Frequency (%) N = 72
Yes	24 (33.33%)
No	30 (41.67%)

A final bivariate analysis was done to see the incidence of any GI injury (GI ulcer or bleed) when given an H2RA (famotidine or ranitidine) versus when given a PPI. Patients given H2RA's had higher incidences of GI injury (75%) than those on PPI's (25%) (**Table 12)**.

Table 12 – Incidence of GI ulcer or bleed between H2RA vs. PPI

Treatment Group	Frequency (%) N = 72
H2RA	54 (75%)
PPI	18 (25%)

Bivariate analysis of secondary outcome with each independent variable

The secondary endpoint that was analyzed was mortality. Variables correlated with the probability of mortality are presented in **Table 13**. No factors were significant. Overall mortality rate was 1.39%, which occurred in the famotidine group (**Table 14)**.

Table 13 – Probability of mortality

Variable	P value
Home H2RA	0.99
Home PPI	0.98
Home NSAIDs	0.98
Home anticoagulants	0.97
Home antiplatelets	0.95
Home corticosteroids	0.99
Positive FOBT	0.94
Coagulopathy on admission	0.97
Switch medications	0.95

**Statistical significance was set at $\alpha = 0.05$.*

Table 14 – Mortality by treatment group

Treatment Group	Frequency (%) N = 72
Ranitidine	0
Famotidine	1 (1.39%)
PPI	0

Logistic regression of GI ulcers and bleeds

An explanatory analysis was conducted to predict the factors associated with GI ulcers and GI bleeds separately. **Table 15** shows the results of logistic regression of factors predictive

for GI ulcers. Although no factors were statistically significant, "famotidine" treatment group had a p value of 0.07. Also, switching medications had a p value of 0.15. **Table 16** describes the results of logistic regression of factors predictive for GI bleeds. No factors were statistically significant, however the "ranitidine" treatment group had a p value of 0.09. Switching medications had a p value of 0.08.

Table 15 – Logistic regression of factors predictive for GI ulcer

Risk factor	P value
Home H2RA	0.99
Home PPI	0.41
Home anticoagulants	0.78
Home antiplatelets	0.53
Coagulopathy on admission	0.48
Switch medications	0.15
Mechanical ventilation ≥ 48 hours	0.26
Ranitidine	0.82
Famotidine	0.07

**Statistical significance was set at $\alpha = 0.05$.*

Table 16 – Logistic regression of factors predictive for GI bleed

Risk factor	P value
Home H2RA	0.98
Home PPI	0.45
Home anticoagulants	0.79
Home antiplatelets	0.57
Coagulopathy on admission	0.50
Medication switch	0.08
Famotidine	0.87
Ranitidine	0.09

**Statistical significance was set at $\alpha = 0.05$.*

Logistic regression of mortality

An exploratory analysis using logistic regression was performed to predict factors associated with in-hospital mortality. No factors were statistically significant.

Table 17 – Logistic regression of factors predictive for mortality

Risk factor	P value
Home H2RA	0.99
Home PPI	0.93
Home anticoagulants	0.81
Home antiplatelets	0.99
Coagulopathy on admission	0.76
Switch medications	0.98
GI bleed	0.99

**Statistical significance was set at $\alpha = 0.05$.*

Hosmer-Lemeshow test for goodness-of-fit

The Hosmer-Lemeshow test for goodness-of-fit is used for logistic regression models. The test assesses how well the data fits the model based on a null hypothesis. If $p > 0.05$, the results are considered statistically significant, and the data is considered to fit the model well. For GI ulcers the p value was 0.78 and for GI bleeds the p value was 0.91, which shows that both sets of data from logistic regression analysis were appropriate.

CHAPTER 4

DISCUSSION

Stress ulcer prophylaxis has been established to be beneficial for certain critically ill patients (ASHP, 1999). GI ulcers and bleeds can clinically alter the course of a patient's inpatient progress and long-term outcomes as well (Weinhouse, 2014). Many factors contribute to the development of stress ulcers and bleeds, but it is multifactorial and complex in nature. Current literature shows the benefit of having SUP, but also highlights the possible superiority of famotidine over ranitidine over cimetidine. Efficacy of H2RA's compared to PPI's is still under debate and ultimately the choice of SUP drug may be influenced by physician preference.

This study is the first comparative analysis of two commonly used H2RA's conducted at a large, tertiary-care, academic institution involving neurosurgical and neuro-trauma ICU patients. Although sample size was limited to 72 patients, it was still a higher enrollment than previous studies.

The results of this study showed that there was a total incidence of 73.61% of GI ulcers and 75% of GI bleeds. Mortality included only 1 patient (1.39%). Most patients were not using high-risk home medications except for 9 patients (12.5%) on anticoagulants and 18 (25%) on antiplatelets. At-home use of both drugs was not significant for developing GI bleeds or ulcers. 50% of all patients received ranitidine, 25% received famotidine, and 25% received PPI's as SUP. Incidence of GI bleeds and ulcers by treatment group was almost identical: the ranitidine group (n=36) had 26 (72.22%) GI ulcers and 27 (75%) GI bleeds, the famotidine group (n=18) had 12 (66.67%) GI ulcers and 12 (66.67%) bleeds, and the PPI group (n=18) had 15 (83.33%) GI ulcers and 15 (83.33%) GI bleeds. When ranitidine and famotidine results were combined to represent use of H2RA's in total versus PPI's, incidence of any GI event was 75% in the H2RA

group and 25% in the PPI group. Factors predictive for developing GI ulcer may include use of famotidine (p=0.07). On the other hand, factors predictive for developing GI bleed may include use of ranitidine (p=0.09) and having SUP medication regimen switched (p=0.08). For mortality, no factors were considered significant in correlation to having mortality or predicting mortality, including APACHE II scores.

Strengths and limitations

Due to the small sample size, definitive conclusions and clinical implications cannot be made at this time. A *post hoc* power analysis revealed that 236 patients would have been needed to find significance. Since data only included the most recent patients from the last two years, it would be of interest to either prospectively study incoming NSICU patients or further review past admission records. Also, due to the emergent nature of some admissions, accurate past medical histories or records of home medication use were not available for those patients. They were included for analysis but were coded as not having history of PUD or active bleeding and not using the listed home medications.

Despite these limitations, there were many strengths of this project as well. As mentioned before, this project had higher enrollment than previous studies. Also, the study population was specific for neurosurgical patients- rather than any ICU patients- who are believed to be even more at risk for developing GI ulcers and bleeds. Lastly, this study compared ranitidine and famotidine from a clinical standpoint as well as an economic standpoint, which was not done in the previous studies.

Conclusion

Although the results were not statistically significant, the trend in data points shows that use of ranitidine and switching SUP medications may have predisposed patients to developing GI bleeds. Furthermore, compared to those who received PPI's, those on either famotidine or ranitidine had higher rates of GI injury. No factors were correlated closely with mortality. While the use of ranitidine was initiated from a cost-savings perspective, increases in GI injury may render the formulary interchange ineffective. Future studies with a higher sample size would be able to strengthen these findings of the incidence of GI bleeds and ulcers by SUP medication.

APPENDICES

Appendix 1 – Data Collection Sheet

Patient Number _____

Diagnosis: ICH AIS SAH AVM Tumor Seizure SCI TBI Other

Gender: Male/Female Age: _____

Admission date: _____ LOS: _____

Admission APACHE II: _____

Coagulopathy: Yes No

History of PUD/GI bleeding: Yes No

Admission labs:				
Hemoglobin (g/dL) / Hematocrit (%)	aPTT (secs)	Platelets (#/mm^3)	INR	SCr (mg/dL)
		<50 50-99 100-150 >150		

Home medications: yes/no					
H2RA	PPI	NSAID	ANTIPLATELET	ANTICOAGULANTS	CORTICOSTEROIDS

Mechanical ventilation ≥ 48 hours: Yes No

Total days on mechanical ventilation: _____

Occult blood stool date: _____ Occult blood stool result: + / -

In-Hospital Medications (first 28 days or until dc'd from ICU, whichever comes first)								
	H2RA	PPIs	Sucralfate	NSAIDs	Antiplatelets	Anticoagulants	Steroids	Vasopressor
Y/N								
Start Date								
Drug								
Dose								
Route								

EGD result:	**Date:**	**Hospital Day #:**
GI ulcer		GI bleed (overt and/or clinically significant)

Mortality: Alive Dead

Disposition: Home Rehab SNF LTAC HOSPICE OSH

Appendix 2 – Data Code Sheet

Gender (male / female)	0 = male 1 = female
Age	#
Diagnosis	1 = ICH (intercranial hemorrhage) 2 = AIS (acute ischemic stroke) 3 = SAH (subarachnoid hemorrhage) 4 = AVM (arteriovenous malformation) 5 = Tumor 6 = Seizure 7 = SCI (spinal cord injury) 8 = TBI (traumatic brain injury) 9 = OTHER
Admission date	MM/DD/YY
Length of stay (days)	#
APACHE II score	#
Coagulopathy on admission (yes / no)	0 = no 1 = yes
History of PUD or active GI bleeding (yes / no)	0 = no 1 = yes
Admission labs: - Hemoglobin (g/dL) - Hematocrit (%) - aPTT (secs) - platelets (#/m^3) - INR - SCr (mg/dL)	# Platelets: 1 = <50 2 = 50-99 3 = 100-150 4 = >150
Home medications: (yes / no) - H2RA's - PPI's - NSAID's - Antiplatelets - Anticoagulants - Corticosteroids	0 = no 1 = yes

Mechanical ventilation > 48 hours (yes / no)	0 = no 1 = yes
Total days on mechanical ventilation (days)	#
Fecal occult blood test performed (yes / no)	0 = no 1 = yes
FOBT date	MM/DD/YY
FOBT result (positive / negative)	0 = negative 1 = positive
SUP treatment group	1 = famotidine only 2 = ranitidine only 3 = famotidine to ranitidine switch 4 = ranitidine to famotidine switch 5 = famotidine to PPI switch 6 = ranitidine to PPI switch 7 = PPI to ranitidine switch 8 = PPI to famotidine switch 9 = PPI only
EGD date	MM/DD/YY
EGD hospital day	#
EGD result: - GI bleed (yes / no) - GI ulcer (yes / no)	0 = no 1 = yes
Mortality: - Dead - Alive	0 = dead 1 = alive
Disposition	1 = home 2 = rehabilitation 3 = SNF 4 = LTAC 5 = outside hospital 6 = hospice 7 = dead

Appendix 3 – Non-SUP Medications

NSAIDs	Aspirin Diclofenac Etodolac Fenoprofen Flurbiprofen Ibuprofen Indomethacin Ketoprofen Ketorolac Meclofenamate Mefenamic acid Meloxicam Nabumetone Naproxen Piroxicam Sulindac Tolmetin
Antiplatelets	Anagrelide Aspirin Aspirin/dipyridamole Cilostazol Clopidogrel Defibrotide Dipyridamole Eptifibatide Prasugrel Ticagrelor Ticlopidine Tirofiban Vorapaxar
Corticosteroids	Betamethasone Budesonide Corticotrophin Cortisone Dexamethasone Fludrocortisone Hydrocortisone Methylprednisolone Prednisolone Prednisone Triamcinolone
Anticoagulants	Acenocoumarol Antithrombin Apixaban

	Argatroban Bivalirudin Dabigatran Dalteparin Danaparoid Desirudin Enoxaparin Fondaparinux Heparin Nadroparin Rivaroxaban Tinzaparin Warfarin
Vasopressors	Dobutamine Dopamine Ephedrine Epinephrine Norepinephrine Phenylephrine Racepinephrine

Appendix 4 – References

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LIST OF TABLES

Table 1 – Summary of literature

Reference	Year	Population	Intervention & Outcome	Results
Al-Quorain, et al.	1994	Intensive care unit King Fahd University Hospital, Al-Khobar, Saudi Arabia	Famotidine IV 20mg every 12 hours vs. ranitidine IV 50mg every 8 hours Gastric pH	Famotidine raised gastric pH more effectively than ranitidine
Wang, et al.	1995	General intensive care unit Chang Gung Memorial Hospital, Taipei, Taiwan	Famotidine IV 20mg every 8 hours vs. cimetidine IV 200mg every 4 hours vs. cimetidine IV 400mg every 4 hours Gastric pH	• No significant improvements in gastric pH in cimetidine 400mg every 4 hours vs. cimetidine 200mg every 4 hours • Famotidine more effective than both cimetidine groups
Burgess, et al.	1995	Surgical intensive care unit with GCS ≤ 10 University of Louisville, Louisville, KY	Ranitidine continuous infusion at 6.25mg/hr vs. placebo Gastric pH & incidence of upper GI bleeding	• No GI bleeding in the ranitidine group • 28% in placebo group developed bleeding • Mean intragastric pH in placebo group significantly lower than ranitidine group
Olsen, et al.	1995	Medical intensive care unit University of Nebraska Medical Center, Omaha, NE	Single dose - cimetidine IV 300mg vs. famotidine IV 20mg vs. ranitidine IV 50mg Gastric pH	• Famotidine had the longest duration of acid suppression • Ranitidine maintained higher gastric pH longer than cimetidine

Table 2 – Cost information for famotidine and ranitidine

Formulation	**Famotidine**	**Ranitidine**
IV	40 mg dose = $2.14	50 mg dose = $3.74
Tablet	40 mg dose = $1.73	150 mg dose = $1.56
Suspension/Syrup	40 mg dose = $19.60	150 mg dose = $7.90

Table 3 – Types of analyses used

Type of analysis	***Purpose of test***	***Variables involved***
Descriptive analysis	Description of independent variables	Frequency (%): Gender, age, treatment group
Bivariate Analysis	Association of each independent variable with the dependent variable.	To test effect of independent variables on incidence of GI ulcers or bleeds.
Logistic Regression	Association of primary independent variable with the dependent variable controlling for possible confounders	To test the effect of SUP on GI ulcers or bleeds while controlling for confounding variables

Table 4 – Descriptive analysis of all patients

Variable	Categories	Frequency (%) or Mean +/- SD (n = 72)
Age (years)		59.3 +/- 17
Gender	Male	40 (55.56%)
	Female	32 (44.44%)
Length of stay (days)		23.1 +/- 13.4
Mortality	Alive	125 (90.6%)
	Dead	13 (9.4%)
Coagulopathy on admission	Yes	6 (8.33%)
	No	66 (91.67%)
Received FOBT	Yes	20 (27.78%)
	No	52 (72.22%)
Positive EGD	GI ulcer	53 (73.61%)
	GI bleed	54 (75%)
Mortality	Alive	71 (98.61%)
	Dead	1 (1.39%)

Table 5 – Descriptive analysis of home medication use

Medication	Categories	Frequency (%)
Home H2RA	Yes	1 (1.39%)
	No	71 (98.61%)
Home PPI	Yes	4 (5.56%)
	No	68 (94.44%)
Home NSAID	Yes	2 (2.78%)
	No	70 (97.22%)
Home corticosteroids	Yes	1 (1.39%)
	No	71 (98.61%)
Home anticoagulants	Yes	9 (12.5%)
	No	63 (87.5%)
Home antiplatelets	Yes	18 (25%)
	No	54 (75%)

Table 6 – Descriptive analysis of patient distribution in treatment groups

Treatment Group	Frequency (%) N = 72
Ranitidine	36 (50%)
Famotidine	18 (25%)
PPI	18 (25%)

Table 7 – Odds ratio of independent variables on primary outcome

Outcome	Variable	Odds Ratio
GI Ulcer	Switch	0.43
	Ranitidine vs. PPI	1.92
	Famotidine vs. PPI	2.50
	Home antiplatelets	1.35
	Home PPI	1.08
	Home anticoagulant	0.89
	Positive FOBT	2.52
	Coagulopathy on admission	1.88
	Positive EGD2	1.08
GI Bleed	Home antiplatelets	1.23
	Home anticoagulants	0.82
	Home PPI	1.0
	Coagulopathy on admission	1.74
	Positive FOBT	2.29
	Positive EGD2	1.0
	Switch	0.48

** Results were statistically significant at $\alpha = 0.05$. None were significant at this time.*

Table 8 – Incidence of GI ulcers by treatment group

Treatment Group	Frequency (%)
Ranitidine N=36	26 (72.22%)
Famotidine N = 18	12 (66.67%)
PPI N=18	15 (83.33%)

Table 9 – Incidence of GI bleeds by treatment group

Treatment Group	Frequency (%)
Ranitidine	27 (75%)
Famotidine	12 (66.67%)
PPI	15 (83.33%)

Table 10 – Frequency of SUP medication switch by treatment group

Treatment Group	Frequency (%) N = 72
Ranitidine	12 (16.67%)
Famotidine	12 (16.67%)
PPI	5 (6.94%)

Table 11 – Incidence of GI bleeds in patients with medication switch

Switch?	Frequency (%) N = 72
Yes	24 (33.33%)
No	30 (41.67%)

Table 12 – Incidence of GI ulcer or bleed between H2RA vs. PPI

Treatment Group	Frequency (%) N = 72
H2RA	54 (75%)
PPI	18 (25%)

Table 13 – Probability of mortality

Variable	P value
Home H2RA	0.99
Home PPI	0.98
Home NSAIDs	0.98
Home anticoagulants	0.97
Home antiplatelets	0.95
Home corticosteroids	0.99
Positive FOBT	0.94
Coagulopathy on admission	0.97
Switch medications	0.95

**Statistical significance was set at $\alpha = 0.05$.*

Table 14 – Mortality by treatment group

Treatment Group	Frequency (%) N = 72
Ranitidine	0
Famotidine	1 (1.39%)
PPI	0

Table 15 – Logistic regression of factors predictive for GI ulcer

Risk factor	P value
Home H2RA	0.99
Home PPI	0.41
Home anticoagulants	0.78
Home antiplatelets	0.53
Coagulopathy on admission	0.48
Switch medications	0.15
Mechanical ventilation ≥ 48 hours	0.26
Ranitidine	0.82
Famotidine	0.07

**Statistical significance was set at $\alpha = 0.05$.*

Table 16 – Logistic regression of factors predictive for GI bleed

Risk factor	P value
Home H2RA	0.98
Home PPI	0.45
Home anticoagulants	0.79
Home antiplatelets	0.57
Coagulopathy on admission	0.50
Medication switch	0.08
Famotidine	0.87
Ranitidine	0.09

**Statistical significance was set at $\alpha = 0.05$.*

Table 17 – Logistic regression of factors predictive for mortality

Risk factor	P value
Home H2RA	0.99
Home PPI	0.93
Home anticoagulants	0.81
Home antiplatelets	0.99
Coagulopathy on admission	0.76
Switch medications	0.98
GI bleed	0.99

**Statistical significance was set at $\alpha = 0.05$.*