An-Najah National University

Faculty of Graduate Studies

COMPARISON OF THE NEUROLOGICAL ADVERSE EVENTS AND CHANGES IN ELECTROLYTES LEVELS BETWEEN PANTOPRAZOLE AND FAMOTIDINE: A PROSPECTIVE OBSERVATIONAL STUDY

By

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This Thesis was Defended Successfully on 13/06/2023and approved by

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Dedication

I dedicate this work to:

My dear father, who has been nicely my supporter until my research was fully finished,

My beloved mother who has encouraged me attentively with her fullest and truest attention to accomplish my study,

My wonderful wife, who leads me through the valley of darkness with light of hope and support,

My beloved kids: Nawwaf, Elaf, Omar and Areen, Who I look forward to seeing their bright future, InsyaAllah.

My beloved brothers and sisters,

My friends who encourage and support me.

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It would not be possible to achieve this without the support of my family, especially my parents, my wonderful wife. This accomplishment would have been impossible without them.

Thanks To everyone who gave me moral support for the completion of this task.

Declaration

I, the undersigned, declare that I submitted the thesis entitled:

COMPARISON OF THE NEUROLOGICAL ADVERSE EVENTS AND CHANGES IN ELECTROLYTES LEVELS BETWEEN PANTOPRAZOLE AND FAMOTIDINE: A PROSPECTIVE OBSERVATIONAL STUDY

I declare that the work provided in this thesis, unless otherwise referenced, is the researcher's own work, and has not been submitted elsewhere for any other degree or qualification.

Student's Name: ______________________________

Signature: ______________________________

Date: ______________________________

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COMPARISON OF THE NEUROLOGICAL ADVERSE EVENTS AND CHANGES IN ELECTROLYTES LEVELS BETWEEN PANTOPRAZOLE AND FAMOTIDINE: A PROSPECTIVE OBSERVATIONAL STUDY

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Abstract

Background: Proton-pump inhibitors (PPIs) have recently become more commonly used in patients with functional gastrointestinal illnesses or for primary prophylaxis of drug-related gastro duodenal damage, despite the fact that their benefits for those conditions have not been thoroughly confirmed. In a few studies, significant acute neurological symptoms related to PPI-induced hypomagnesemia have been observed; and histamine-2 Receptor Antagonist (H2RAs) are more strongly associated with increased delirium than PPIs. However, severe hypomagnesaemia has not been linked to usage of H2RAs.

Aim: The study aim was to compare the effects of Pantoprazole (Proton pump inhibitor) and Famotidine (histamine-2 Receptor Antagonist) on electrolytes disturbances and other neurological adverse events among critically ill patients.

Method: A prospective observational study was conducted between August 2022 and December 2022 included 100 critically ill patients in intensive and cardiac care units of Al- Watani Hospital. The response rate was 91.75%. The data sheet consisted of several sections, including sociodemographic data, health information, data about administration of Pantoprazole and Famotidine, clinical outcomes, neurological complications including delirium degree.

Results: The highest age group for the total participants was over 60 years old (60%), and more than half of the total participants were male (57.0%). The findings pointed out that the percentage of Acute Kidney Injury was higher in Pantoprazole compared with Famotidine (38% vs. 10%, respectively). The results also showed that the blood urea nitrogen was significantly higher in Pantoprazole group compared to Famotidine group (40.0±29.6 vs. 27.8±24.3 mg/dl; P < 0.05). Similarly, creatinine was significantly higher in Pantoprazole group compared to Famotidine group (2.2±2.0 vs. 1.5±1.5 mg/dl; P < 0.05). In contrast, the average albumin in Pantoprazole group were significantly lower than that in Famotidine group (2.8±0.5 vs. 3.1±0.6 g/dl; P < 0.05). The Mean±SD of serum Magnesium (2.0±0.3 mg/dl in Pantoprazole vs. 2.1±0.2 mg/dl in Famotidine; P > 0.05). The results pointed out that the percentages of neurological complication among Pantoprazole group compared to Famotidine were agitation (12% vs. 24%, P=0.118), hallucinations (10% vs. 4%, P=0.24), dizziness (4% vs. 6%, P=0.646), nausea (4% vs. 4%, P=1.000), vomiting (2% vs. 2%, P=1.000), numbness (2% vs. 2%, P=1.000), muscle spasms (2% vs. 0%, P=0.315), seizures (0% vs. 2%, P=0.315), convulsions (2% vs. 0%, P=0.315), however, nobody has loss of consciousness, death, tetany, and tremors.

Conclusion: There was no significant association between patients who were treated by Pantoprazole and who were treated by Famotidine with regards to serum magnesium level, occurrence of neurological complications, and mean delirium degree. But the Pantoprazole group were associated with elevated levels of creatinine and blood urea nitrogen, and lower levels of albumin and hematocrit compared to Famotidine group.

Keywords: Pantoprazole; Famotidine; electrolytes; neurological adverse events.

Chapter One

Introduction and Theoretical Background

1.1 Introduction

1.1.1 Research Overview

Magnesium is considered an essential intracellular cation. It plays a role in multiple cellular activities. Low levels of serum magnesium can lead to a wide variety of adverse events (AEs), including vomiting, diarrhea, cramps, convulsions, bradycardia, confusion, muscle weakness, seizures and even death. The mechanism of Proton-pump inhibitors (PPI) associated hypomagnesaemia is yet to be established but could be related to, as has been proposed, altered intestinal absorption of magnesium with long-term PPI use (Reed & Mok, 2016).

Proton-pump inhibitors medications (such as, rabeprazole, pantoprazole, lansoprazole, esomeprazole and omeprazole) suppress gastric acid secretion, through inhibiting the gastric parietal cell's hydrogen–potassium adenosine triphosphatase enzyme system (the 'proton pump'). They're commonly prescribed to treat and prevent dyspeptic symptoms, associated with esophagitis, gastritis and peptic ulcer disease. Generally, they are well tolerated, although they may have adverse effects, and some of which have the potential to be dangerous (Mackay & Bladon, 2010).

The proton-pump inhibitors have a strong and long-lasting action on production of stomach acid, making this group of medications an excellent treatment choice for a lot of acid-related disorders. However, its usage has become very common and has expanded beyond the evidentiary basis. As a result, medicine prices have risen, and the understanding of the side effects of long-term usage has improved (Benmassaoud et al., 2015).

Long term use of proton-pump inhibitors has been linked to significant side effects such as: hypomagnesaemia (Zipursky et al., 2014), hyponatremia (Falhammar et al., 2021), community acquired pneumonia, rebound acid hypersecretion syndrome, Vitamin B12 deficiency (Lam et al., 2013), higher risk of hip fracture (Vangala et al., 2018), acute interstitial nephritis, increased mortality in older patients, increased risk of bone fractures and clostridium difficile infection (Barnsley Hospital, 2018).

Although the exact incidence of severe hypomagnesaemia in patients treated with Proton-pump inhibitors is unknown, but it has been reported infrequently (Barnsley Hospital, 2018).

The widespread use of proton pump inhibitors has led to the emergence of a rare but serious side effect known as hypomagnesemia, which can be life-threatening. This condition has been found in about 21% of patients in an internal medicine ward. Hypomagnesemia can cause various symptoms such as confusion, nausea, tremor, apathy, depression, agitation, and loss of appetite.Although not frequently reported, the neurological symptoms caused by PPIs may occur due to severe hypoparathyroidism and low calcium levels resulting from hypomagnesemia.There have been some instances reported in case studies where people using PPIs have experienced severe acute neurological symptoms and significant depression as a result of hypomagnesemia (Pasina et al., 2016).

In 2011, the Food and Drug Administration (FDA) reviewed Adverse Event Reporting System (AERS) reports, medical literature, and periodic safety updates and issued a safety communication outlining the risk for hypomagnesaemia with prolonged PPI use (Reed & Mok, 2016).

Hypomagnesaemia resolved after discontinuing the PPIs but recurs following re-administration or after one PPI is replaced with another. Hypomagnesaemia not occurring with histamine-2 Receptor Antagonists (H2RAs) (e.g., ranitidine) (Janett et al., 2015).

In a critical care unit, the treatment process is highly complicated. The gastro-intestinal system is usually impacted when a patient is in critical condition. Conditions such as patients with gastric ulcers or pre-existing gastritis, acute pancreatitis, bacteremia, severe traumas (orthopedic trauma) sepsis, and severe burn injury are extremely susceptible to intestinal bleeding induced by stress ulcers. Internal bleeding caused by the ulcer significantly worsens the patient's condition. In such cases, one of the most efficient methods to overcome the condition is pharmaceutical prophylaxis. PPIs and H2RAs are commonly used for this purpose (Kaur et al., 2017).

Proton-pump inhibitors are increasingly recognized to cause hypomagnesaemia. In addition, the hypochlorhydria related to proton-pump inhibitors lowers the magnesium salts solubility, thus may cause reducing of magnesium absorption. H2RAs like ranitidine, do not show this impact (Arulanantham et al., 2011).

Cases of severe hypomagnesaemia have not been reported with the use of H2RAs, while new research revealed that their long-term usage is linked with hypomagnesaemia (Kieboom et al., 2015).

1.1.2 Problem Statement

Electrolytes disturbances such as hypomagnesaemia is a recent complication that has emerged in the research following of many case reports in the last few years; However, the exact incidence of hypomagnesaemia related to proton-pump inhibitors usage is unclear currently (Sabbagh et al., 2016). It may cause major cardiovascular and neuromuscular problems and is frequently accompanied with hypokalemia and hypocalcemia (Gragossian et al., 2022).

Hypomagnesaemia is associated with increased incidence of complications; length of hospital stays and subsequent increase the cost of hospitalization and it is associated with an increased mortality rate (Hansen & Bruserud, 2018). Since 2006, reports have identified that hypomagnesemia may occur as a result of using PPI therapy (Mackay & Bladon, 2010).

Proton-pump inhibitors have recently become more commonly used in patients with functional gastrointestinal illnesses or for primary prophylaxis of drug-related gastro duodenal damage, despite the fact that their benefits for those conditions have not been thoroughly confirmed (Kinoshita et al., 2018).

Proton-pump inhibitors are linked to a number of uncommon but possibly dangerous side effects. When considering the tens of millions of people who take proton-pump inhibitors throughout the world, these rare adverse effects become very significant (Benmassaoud et al., 2015).

Despite case studies have link hypomagnesaemia and usage of PPI, severe hypomagnesaemia has not been linked to usage of H2RAs (Kieboom et al., 2015).

Given the expense of monitoring serum electrolytes levels such as serum magnesium in patients using PPIs and the potential hazards of hypomagnesaemia, this lack of reliable data is especially concerning (Danziger et al., 2013).

1.1.3 Significant

The study was conducted to provide decision makers, healthcare facilities, healthcare staff and those interested in the findings of this research in Palestine with a comprehensive comparison between two of the most effective drugs on serum magnesium level (Pantoprazole and Famotidine) among critically ill patients by different variables in order to take advantage of it, to enhance and improve the outcome of hospitalization, to identify the most effective and safe drug that can reduce the costs of health care and decline the duration of the patient's stay in the healthcare facilities, and to reduce the incident of electrolytes disturbances and neurological adverse events.

In addition, the study encourages and supports future research in the field of most effective drugs on serum electrolytes levels and neurological adverse events, as well as providing evidence-based guidelines on the appropriate use of these drugs.

The study aim was to compare the effects of Pantoprazole (Proton pump inhibitor) and Famotidine (histamine-2 Receptor Antagonist) on electrolytes disturbances and other neurological adverse events among critically ill patients.

1.1.4 Aim and Objectives

1.1.4.1 Aim

The main aim of this study was to compare the effects of Pantoprazole (Proton pump inhibitor) and Famotidine (histamine-2 Receptor Antagonist) on electrolytes disturbances and other neurological adverse events among critically ill patients.

1.1.4.2 Objectives

- To evaluate the clinical outcomes (such as serum magnesium, Potassium, Sodium, Calcium, Albumin, C-reactive protein, Creatinine, Blood urea nitrogen, Glucose, Hematocrit, Hemoglobin, Platelets) for patients treated with Pantoprazole or Famotidine.
- To determine the neurological complications that may occur in patients treated with Pantoprazole or Famotidine.
- To determine the delirium score in patients treated with PPIs and patients treated with Pantoprazole or Famotidine.

1.1.5 Research questions

- What are the effects of Pantoprazole or Famotidine on serum electrolytes level among critically ill patients?
- What are the clinical outcomes for patients treated with Pantoprazole or Famotidine?
- What are the neurological complications that may occur in patients treated with Pantoprazole or Famotidine?
- What is the delirium score in patients treated with Pantoprazole or Famotidine?

1.1.6 Research Hypothesis

H0: There are no significant differences at a level of 0.05 between Pantoprazole and Famotidine groups related to serum electrolytes level among critically ill patients.

H0: There are no significant differences at a level of 0.05 between Pantoprazole and Famotidine groups related to clinical outcomes among critically ill patients.

H0: There are no significant differences at a level of 0.05 between Pantoprazole and Famotidine groupsrelated to neurological complications among critically ill patients.

H0: There are no significant differences at a level of 0.05 between Pantoprazole and Famotidine groups related to delirium score among critically ill patients.

1.1.7 Conceptual Definitions

Electrolytes Disturbances

Hypomagnesemia:

Based on the data from Zhang et al. (2021), the hypomagnesemia in this study refer to the state in which a participant's blood magnesium levels are abnormally lower than 1.6 mg/dl.

Delirium:

In this study, delirium refers to is a serious change in mental abilities which includes "disorientation, inappropriate behavior, inappropriate communication, hallucination, and psychomotor retardation". It was evaluated by using the NuDESC observational screening tool for delirium.

Neurological adverse event:

The neurological adverse events in this study are several neurological complications and include dizziness, nausea, vomiting, numbness, tetany, tremors, muscle spasms, hallucinations, agitation, seizures, convulsions, and loss of consciousness. These events were evaluated daily for 14 days.

1.2 Theoretical framework

1.2.1 Proton Pump Inhibitors

1.2.1.1 Definition

"It is any medication that reduces gastric acid secretion by suppressing an enzyme in the stomach's parietal cells that exchanges acid for potassium ions. The PPIs are used to treating peptic ulcer and erosive esophagitis. These medications can lower acid secretion by more than 95% when administered in adequate doses. Examples of PPIs involve rabeprazole, lansoprazole, and omeprazole" (Rogers, 2013).

1.2.1.2 Medical uses

PPIs are utilized to treat and prevent disorders related to gastric acid. The Food and Drug Administration has approved the use of PPIs for several purposes, including the treatment of gastroesophageal reflux disease (GERD), the healing and maintenance of erosive esophagitis (EE), short-term treatment and maintenance of duodenal ulcers (DU), treatment of pathological hypersecretory conditions such as Zollinger-Ellison (ZE) syndrome, treatment of pathological hypersecretory conditions such as Zollinger-Ellison (ZE) syndrome, and the reduction of the risk of gastric ulcer (GU) associated with NSAIDs, the eradication of helicobacter pylori (H. pylori) to decrease the risk of duodenal ulcer recurrence when used alongside antibiotics (Centers for Medicare & Medicaid Services, 2015).

1.2.1.3 Types of PPIs

There are several brands and names of PPIs. The majority of them work equally well. Side effects may possibly differ from drug to drug. These types are "Zegerid (omeprazole with sodium bicarbonate), Dexlansoprazole (Dexilant), Pantoprazole (Protonix), Rabeprazole (AcipHex), Lansoprazole (Prevacid), Esomeprazole (Nexium), and Omeprazole (Prilosec)" (Phillip, 2019).

1.2.1.4 Mechanism of action

PPIs work by binding to *H+, K+-ATPase*, an enzyme responsible for pumping acid (also called H+, or protons) onto the surface of the gastrointestinal (GI) mucosa. This binding process is irreversible and ultimately leads to a decrease in acid secretion in the stomach.PPIs are more effective than H2-receptor antagonists in reducing acid secretion and also have a longer-lasting effect. The positive effects of PPIs persist for up to 3-5 days even after the medication has been discontinued (Adams et al., 2013).

1.2.1.5 Adverse effects

PPIs can cause adverse effects such as upper respiratory infections, back pain, diarrhea, abdominal pain, skin rash, dizziness, and headaches. At this time, the Food and Drug Administration has not approved any antidote for overdosage (Ahmed & Clarke, 2022). The PPIs are commonly well tolerated. Even though the impact on clinical outcomes is debatable, concomitant utilization of these PPIs with clopidogrel is not advised due to a potential raised in risk of cardiovascular events.PPIs may raise the likelihood of fractures, especially if utilized for a year or more. Persistent acid suppression with PPIs could lead to low vitamin B12, as the acid is essential for its absorption in a complex with intrinsic factor. Clostridium difficile colitis and Diarrhea could happen in patients receiving PPIs. Other side effects could involve hypomagnesemia and higher incidence of pneumonia (Whalen & Panavelil, 2014).

Additional important adverse effects related to PPIs involves reduced liver function, reduced kidney function, stevens-Johnson syndrome, serious allergic reactions, pancreatitis, erythema multiforme, and toxic epidermal necrolysis (Ogbru & Marks, 2022).

1.2.1.6 Contraindications and cautions

The contraindications of PPI involve individuals with reported hypersensitivity to that category of medications. Also, PPIs should be used with caution in individuals suffering from severe hepatic disease. (Ahmed & Clarke, 2022).

Also, in order to prevent hypersensitivity responses, these medications are contraindicated in cases where there is a known allergy to either the medication itself or its constituent parts. Caution must be used in lactating or pregnant mothers because of the possibility for harmful effects on the newborn or fetus. The effectiveness and safety of these medications have not been demonstrated for individuals under the age of 18 years, except for lansoprazole, which is the PPI of choice for children (Karch, 2009).

1.2.1.7 Monitoring

There is evidence suggested that magnesium should be monitored (particularly in patients with kidney transplantation). Monitoring vitamin B12 levels in individuals who are receiving PPIs for an extended period of time is a topic of debate. However, in certain cases, it may be appropriate to consider. At present, there is not enough evidence to endorse bone density scanning and/or calcium supplementation as a viable means of preventing osteoporosis in individuals who are receiving PPIs for long time(Ahmed & Clarke, 2022).

1.2.2 Histamine-2 Receptors Antagonist

1.2.2.1 Definition

Histamine-2 Receptor Antagonist are sometimes called H2 blockers. They lower the quantity of acid produced by the stomach. This can aid in the treatment of a variety of common health problems, such as gastro esophageal reflux disease (GERD), occasional heartburn, and stomach ulcers (Villines, 2020).

1.2.2.2 Medical uses

These medications are extremely well tolerated, and the majority of the wide-rangingpeople uses them to treat esophagitis, heartburn, peptic ulcer disease, and various other mild symptoms of upper gastrointestinal (Bethesda MD, 2012), as well as for acute stress ulcers and gastroesophageal reflux disease (GERD) (Whalen & Panavelil, 2014).

1.2.2.3 Types of H2RAs

Commonly used H2RAs include famotidine (Fluxid, Pepcid), cimetidine (Tagamet, Leader Heartburn Relief), nizatidine (Axid, Tazac), and ranitidine (Villines, 2022).

1.2.2.4 Mechanism of action

H2 –Receptor antagonists competitively block H2- receptors on parietal cell and inhibit the production of gastric acid. They suppress acid secretion at all phases (basal, cephalic, and gastric). They primarily work to reduce nocturnal acid secretion. H2 blockers also lessen the secretion of acid that is induced by ach, gastrin, food, etc. (Shanbhag & Shenoy, 2015).

1.2.2.5 Side Effects or Adverse effects

H2 receptor antagonists are generally well-tolerated. Mild side effects may include headache, drowsiness, fatigue, abdominal pain, constipation, or diarrhea. The use of H2RAs in patients who are over 50 years of age has correlated with central nervous system side effects such as headache, dizziness, delirium, confusion, hallucinations, or slurred speech. Cimetidine is generally considered the most frequent cause of these symptoms, although similar effects have also occurred with famotidine. Compared to proton pump inhibitors, H2RAs pose a minor risk for developing bacterial overgrowth and infections (Nugent et al., 2022).

1.2.2.6 Contraindications and Cautions

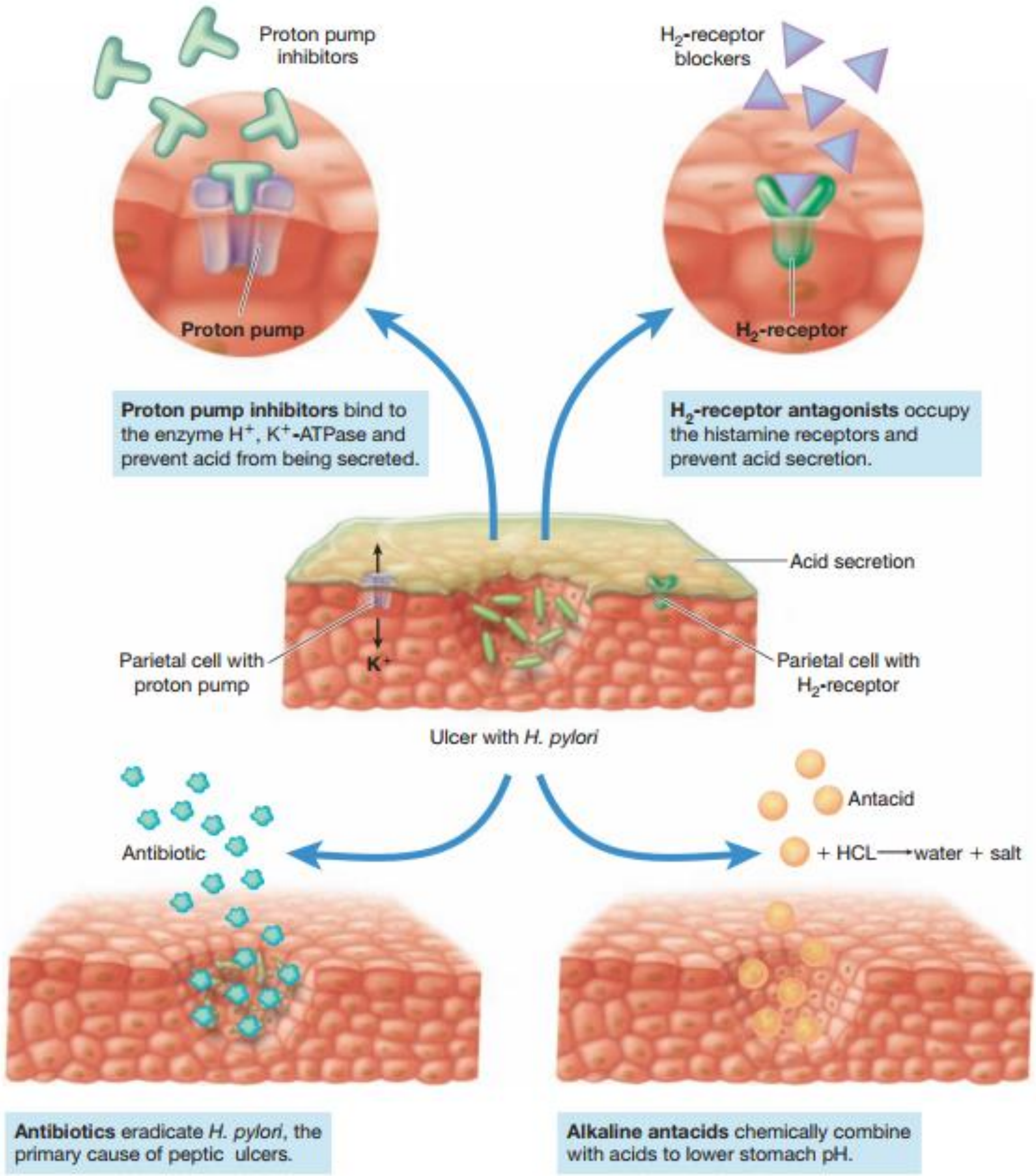
H2 antagonists shouldn't be taken by anyone who have a known allergy to any medication in this class to avoid hypersensitivity reactions. Caution must be used in lactating or pregnant mothers because of the possibility for harmful effects on the newborn or fetus and with renal or hepatic dysfunction, which may interfere with drug metabolism and excretion (Hepatic dysfunction is not as much of a problem with nizatidine). If these medications must be used for an extended period of time, caution should be exercised since they may disguise significant underlying illnesses (Karch, 2009).

1.2.2.7 Mechanisms of Action of Antiulcer Drugs.

The mechanisms of action of histamine-2 receptor antagonist and proton pump inhibitors are displayed in Figure 1.

Figure 1

Mechanisms of Action of Antiulcer Drugs



Note. (Adams et al., 2013).

1.3 Literature review

1.3.1 Background

The researcher reviewed several studies that focus on the topic the effects of proton pump inhibitors and histamine-2 receptor antagonist on serum electrolytes levels and neurological adverse events among critically ill patients.

The researcher noted a large number of mostly observational studies on a wide variety of potential relations with the usage of proton-pump inhibitors that had been published. Furthermore, a number of meta-analyses on the same topic have nearly increased the number of papers reporting on the long-term impact of proton-pump inhibitors usage in different patient groups.

1.3.2 Related studies

When reviewed the literature, the researcher read several articles and published paper. One of these papers is a case report of a 55-year-old woman was seen by various clinicians, with a variety of clinical presentations, over the space of a couple of years. During each visit, she had electrolyte disturbances and was on proton pump inhibitor therapy, which were either continued or changed to a different proton pump inhibitor. She had presented variously with diarrhea and weight loss due to microscopic colitis, confusion, and grand mal seizures on separate occasions. Changing the proton pump inhibitor did not alleviate her profound electrolyte disturbances, which completely resolved shortly after stopping drug therapy. They concluded that Electrolyte disturbances are more likely to arise in patients who are prescribed concomitant diuretic treatment or who overuse alcohol (Tagboto, 2022).

Another study investigated the rate of PPI-associated with hypomagnesaemia in a veteran population at a facility where the majority of PPIs were by prescription, not over the counter (OTC). The study results identified an association of PPI use and hypomagnesaemia in a veterans Affairs (VA) patient population of older men (Reed & Mok, 2016).

Likewise, there is a prospective cohort study conducted by Kieboom et.al (2015) to determine if the hypomagnesaemia is linked with the usage of proton-pump inhibitors in the general population and if it linked with the usage of H2RA. A total of 9,818 individuals from the general population. It showed that proton-pump inhibitor users had a lower serum magnesium level by 0.022 mEq/L than those with no use. There is an association between taking PPIs and an elevated risk of hypomagnesemia compared to not taking them. The heightened risk associated with PPIs was observed only in cases where the medication was used for an extended period. The outcomes were unaffected by the inclusion of dietary magnesium intake in the model. Individuals who used H2RAs had a higher likelihood of hypomagnesemia and lower serum magnesium levels when compared to those who did not use this medication.

Another study conducted by John Danziger et.al (2013) to examine the serum magnesium level and the possibility of hypomagnesaemia (Lower than 1.6 mg/dl) in patients who have used proton-pump inhibitor or H2RA used to decrease stomach acid among 11,490 consecutive adult admissions to a tertiary medical center's intensive care unit. Of these, 2632 participants reported using proton-pump inhibitor before admission, whereas 657 participants used H2RA. Proton pump inhibitor usage was related to 0.012 mg/dl lower adjusted serum magnesium level when compared to non-acid-suppressive drug users, however this impact was limited to diuretic users. Proton-pump inhibitor usage was related to a substantial increase in hypomagnesaemia and a 0.028 mg/dl lower serum magnesium level among the 3286 participants taking diuretics concurrently. Proton-pump inhibitor usage was unrelated to serum magnesium levels in those who did not use diuretics, while the usage of H2RA had no significantly influence on magnesium level with or without usage of diuretics.

Also, in research of AEs associated with PPIs reported to the FDA, Luk et al., (2013) estimated that 1% of patients who experienced an AE reported hypomagnesaemia and concluded that all PPIs are associated with hypomagnesaemia, but the risk varies. Of the 6 PPIs that have been FDA approved, esomeprazole was associated with the lowest risk, pantoprazole with the most. Results also suggested that the risk was higher for elderly and male patients.

In another study of prior PPI use and its effects on serum magnesium levels among 11,490 intensive care unit admissions, Danziger and colleagues found that the association of PPI use, and hypomagnesaemia was limited to patients who concomitantly received a diuretic, and H2RAs usage was not related to hypomagnesaemia (Danziger et al., 2013).

Also, there is a nested case-control study. Retrospective data were gathered from a tertiary acute-care center. The study includes 402 people who had hypomagnesemia at the time of hospital admission and 402 controls who had normal serum magnesium levels, the age and sex were matched between the two groups. It came to the conclusion that in an adult hospital population, PPI usage outside of hospitals is not linked to hypomagnesemia at the moment when an individual is admitted to the hospital for medical treatment (Koulouridis et al., 2013).

Moreover, a case-control study on a population basis was conducted in Ontario, Canada to investigate the potential association between the usage of PPIs and hypomagnesemia. Using multiple healthcare databases, they identified 366 patients aged $\geq$ 66 years hospitalized with hypomagnesaemia and 1464 control patients matched 4:1 to cases on age, gender, renal disease, and usage of several diuretic classes. Current proton-pump inhibitor usage was linked to an increased the risk of hypomagnesaemia in the general population and among diuretics users but not in non-diuretic users. The use of H2RAs was not related to hospitalization with hypomagnesaemia. The authors expected that among 76591 outpatients treated with a proton pump inhibitor for 90 days, one extra hospitalization for hypomagnesaemia would occur (Zipursky et al., 2014).

Moreover, Ströker et.al (2014) report a case of a 51-year-old female experienced severe symptomatic hypomagnesaemia afterwards receiving long time treatment with a proton pump inhibitor for recurrent peptic ulcer. And showed that the hypomagnesemia could only be partly remedied through replacement therapy, but it was fully corrected after the proton pump inhibitor was withdrawn. After retreatment with proton pump inhibitors, hypomagnesaemia recurred, supporting the causative link. After two-year period of follow-up, it was strongly suspected that the patient had an underlying condition of excessive stomach acid secretion (known as Zollinger-Ellison syndrome), which was subsequently treated using a combination of octreotide andH2RAs, with no need for additional proton pump inhibitor medications.

As well as Agarwal et al., (2008) reported a 43-year-old male developed symptomatic hypomagnesaemia and hypocalcemia after using high-dose omeprazole for reflux oesophagitis for three years. Oral and parenteral magnesium replacement failed to resolve the issue, yet discontinuation of proton pump inhibitor medications resulted in normalization of his biochemistry in 6 weeks and symptom relief in 12 weeks.

Also, Cundy and Dissanayake (2008) reported 2 patients with severe hypomagnesaemia who experienced with hypocalcemic seizures and had been using proton pump inhibitors for a long time. Their investigations revealed that these individuals were profoundly magnesium deficient, with ardent renal magnesium retention following intravenous magnesium infusions. The hypomagnesaemia was partially treated using high-dose oral magnesium supplements and resolved when the proton pump inhibitor medication was discontinued. They concluded that proton pump inhibitor medication can inhibit magnesium absorption in the intestine.

On the other hand, Ala I. Sharara et.al (2016) used a large health maintenance organization database to determine the presence of hypomagnesaemia among long-term proton pump inhibitor patients. They gathered data from 10,167 individuals who were eligible to receive prescriptions for chronic medication between 2008 to 2013. The study specifically included adult participants who had received continuous proton pump inhibitor therapy for at least 6 months between the years 2008 and 2013, and at least one serum magnesium determination(s). The study selected individuals whose magnesium levels were below 1.6 mg/dL, while excluding those who had identifiable reasons for altered magnesium homeostasis. In this study, 590 individuals received long-term proton pump inhibitors, and 414 (70.2%) of them fit the inclusion criteria for a total exposure of 2293 proton pump inhibitor-years (an estimated, 5.7 years/subject). Of these individuals, 57 (13.8%) had ≥1 low serum magnesium level; 5 were no longer using proton-pump inhibitors, and 44 had other identified reasons for hypomagnesemia (3 with malignancies, 8 with chronic kidney disease, 8 with chronic diarrhea, and 25 receiving diuretics). It found that in the absence of recognized precipitating factors, prolonged proton pump inhibitor usage doesn’t appear to be related with hypomagnesaemia.

Moreover, according to B. C. T. Kieboom et al. (2018), a cross-sectional study within 9820 individuals from the prospective Rotterdam Study revealed that thiazide diuretic usage waslinked with decreased levels of serum magnesium and an increased possibility of hypomagnesaemia. However, individuals using a combination of thiazide diuretics with a potassium-sparing agent do not exhibit this increased risk of hypomagnesemia. Also, there is no association between the usage of loop diuretics and an increased risk of hypomagnesemia.

Furthermore, Shiddapur et al. (2021) conducted retrospective observational study aimed at investigating the differential relationships between the administration of H2RAs or PPI and the development of delirium in individuals who were admitted to a medical ICU.The study enrolled 6,645 individuals who were critically ill. Among them, 1,899 individuals (29%) required mechanical ventilation, 3,022 individuals (45%) were aged 65 years or more, and 1,487 individuals (22%) died while in the medical ICU. Of the 6,645 individuals, 2,057 individuals (31%) received H2RAs and no PPI, 2,648individuals (40%) receivedPPI and no H2RAs, and 3,076 individuals (46%) had delirium. The H2RAs group had a higher relationship with delirium than the PPI group compared with controls receiving neither medication, afterward controlling for mechanical ventilation and age. The researchers came to conclude that H2RAs are more strongly relatedto increased delirium than PPIs.

Finally, according to Gragossian et al. (2022), the hypomagnesaemia may cause major cardiovascular and neuromuscular problems and is frequently accompanied with hypokalemia and hypocalcemia. As well as according to Pasina et al. (2016), the hypomagnesemia-related symptoms involve confusion, agitation, depression, apathy, tremor, nausea, and anorexia. PPI-induced neurological symptoms are a possible result of profound hypoparathyroidism with hypocalcemia caused by hypomagnesemia; however, they are infrequently reported. In a few case studies, significant acute neurological symptoms and major depression related to PPI-induced hypomagnesemia have been observed.

1.3.3 Summary

The majority of literature that focused on investigating the potential adverse effects of PPI or H2 receptor blockers use is composed of retrospective, observation studies.

Proton pump inhibitor usage has been linked to cause hypomagnesaemia, perhaps due to reduced magnesium absorption in the small intestine. A recent systematic reviews and meta-analysis of observational research showed a statistically significant relationship between hypomagnesaemia and usage of proton-pump inhibitor. Otherwise, several studies didn’t find a link between the usage of proton pump inhibitors and hypomagnesaemia.

Also, there are a numerous studies, discussion and publications regarding the use of PPIs and H2RAs. But the majority of them failed to point out the superior group. Both have roughly identical impacts on hospitalization duration and end results.

Results from investigations of PPI or H2RAs associated hypomagnesaemia have been inconclusive.

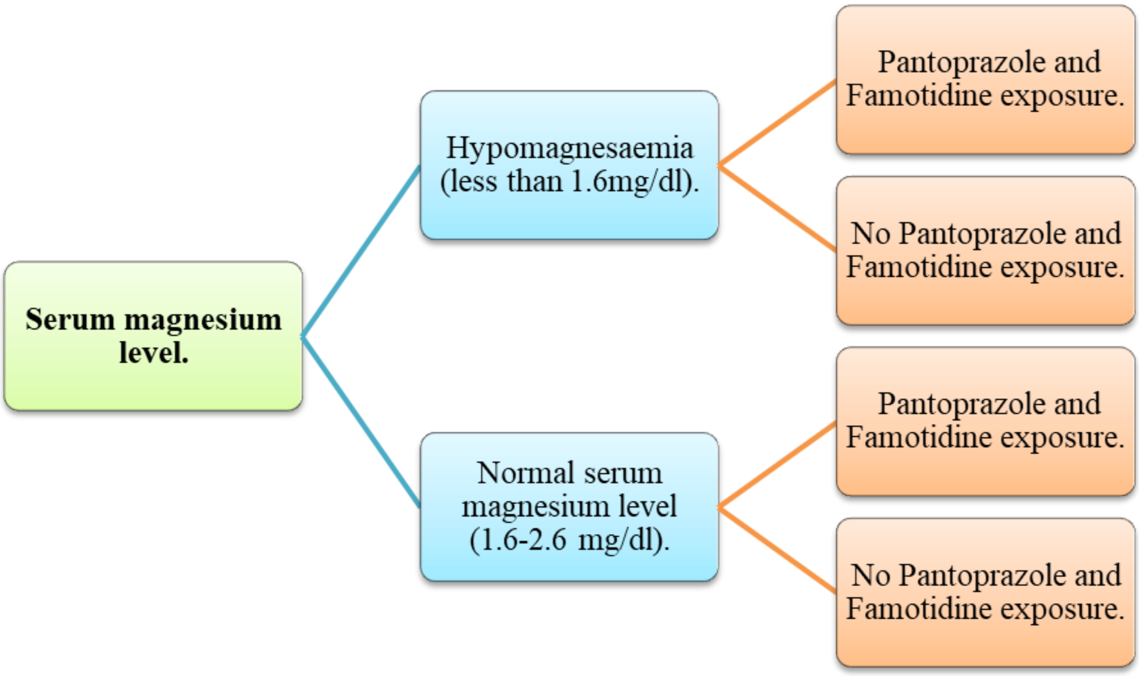
Other studies designed to investigate PPI or H2RAs associated hypomagnesaemia were limited by short-term use, small samples, concurrent diseases, and confounding variables (e.g., history of alcoholism).

1.3.4 Conceptual framework

Since the conceptual framework describes the related variables for research and shows how they relate to each other. In this study the conceptual framework was created based on a review of existing published articles, studies and theories regarding the subject. Figure (2) presents the criteria for assessing the level of serum magnesium and its relationship to the use of pantoprazole and famotidine.

Figure 2

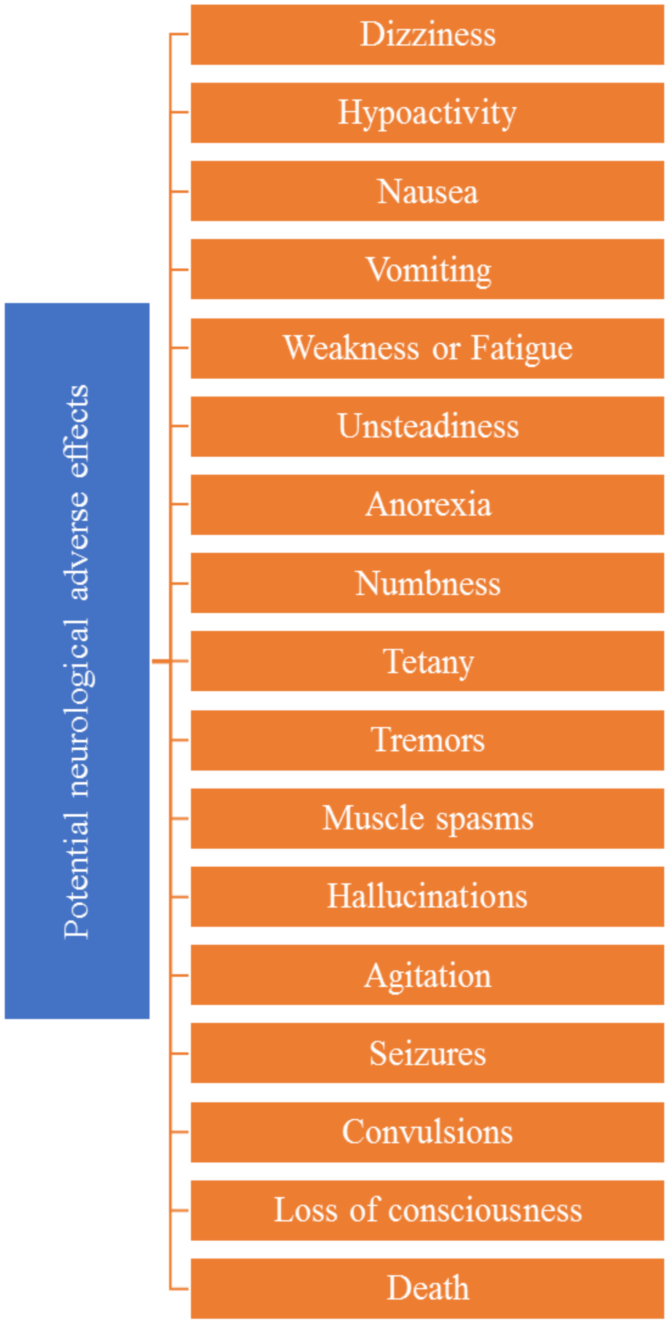
Criteria for assessing the serum magnesium level among pantoprazole and famotidine users



Also, Figure (3) represents numerous potential neurological adverse effects, including: dizziness, hypoactivity, nausea, vomiting, weakness or fatigue, unsteadiness, anorexia, numbness, tetany, tremors, muscle spasms, hallucinations, agitation, seizures, convulsions, loss of consciousness and death.

Figure 3

Potential neurological adverse effects



Chapter Two

Methods

2.1 Research design

A prospective observational design was used in this study.

The researcher chose this design because of a prospective is a type of observational study focused on following a group of people over a period of time, collecting data on their exposure to a factor of interest. Their outcomes are then tracked, in order to investigate the association between the exposure and the outcome (George, 2023).

2.2 Study Population

The study population was all critically ill patients who admitted to the intensive and cardiac care units of the Al- Watani Hospital at Nablus city. Based on the data from Al-Watani hospital, the average number of those patients is about 30 patients monthly in each unit, with an average of 60 patients per month. The study population was consisting of two groups: (I) Critically ill patients who treated by using intravenous Pantoprazole 40 mg/daily and (II) critically ill patients who treated by using intravenous Famotidine 40 mg/daily. Each participant was followed for 14 days.

2.3 Study setting

The study was carried out in intensive and cardiac care units of Al- Watani hospital at Nablus city. The researcher chose the Al- Watani hospital because it has two critical care units (intensive and cardiac care units). And, because the hospital is a government teaching hospital that provides education and healthcare, in addition to providing space for medical research and training and providing students with the optimum scientific environment and the latest infrastructure for learning and development.

2.4 Study period

The study was conducted between August 2022 and December 2022. Data collection was started on August to December 2022.

2.5 Sample size

The study's required sample size was 109 participants as determined by using the G Power program (Appendix A). These participants were then divided into the Pantoprazole and Famotidine groups.

2.6 Inclusion & Exclusion Criteria

Inclusion Criteria

- All critically ill patients who admitted to the intensive and cardiac care units of the Al- Watani hospital at Nablus city.

Exclusion Criteria

- Patients who are currently using magnesium supplements.
- Patients who have recently been using PPIs or H2RAs.
- Patients who have serum magnesium level less than 1.6 mg/dL or more than 2.6 mg/dL (the normal range of serum magnesium level is 1.6 - 2.6 mg/dL (Zhang et al., 2021)).
- Patients who have upper gastrointestinal bleeding (UGIB) or history of UGIB.
- Patient who are have problem in coagulation profile.
- Patients who have thrombocytopenia, pancytopenia.
- Patients who are recently treated by thiazide diuretic, aminoglycosides, amphotericin B, antineoplastic drugs (cisplatin and cetuximab), and calcineurin inhibitors.
- Patients who are treated by using the maximum recommended dose of a non-steroidal anti-inflammatory drugs (NSAIDs).
- Patients who have diabetic ketoacidosis or acute pancreatitis.
- Hemodialysis patients.

2.7 Sampling technique

A convenience sampling technique was used in this study. It is often referred to as availability sampling, which considered one of the types of non-probability sampling method that focuses on collection of the data from members of the population that are conveniently available to participate in study. The researcher chose this technique because it has several advantages, including simplicity of sampling and the ease of research; Helpful for pilot studies and for hypothesis generation; Data collection can be facilitated in short duration of time; and Cheapest to implement that alternative sampling methods (Dudovskiy, 2020).

2.8 Study tool

In order to achieve the research's objectives, a data sheet (Appendix B) was used in the current study for data collection. It was developed with the help of the researcher's supervisor and with the involvement of critical care professionals, after viewing, reading, and modifying numerous questions and questionnaires from many prior literatures and studies.

The data sheet was divided into several sections, including sociodemographic data, health information, data about administration of Pantoprazole or Famotidine, clinical outcomes, neurological complications such as delirium.

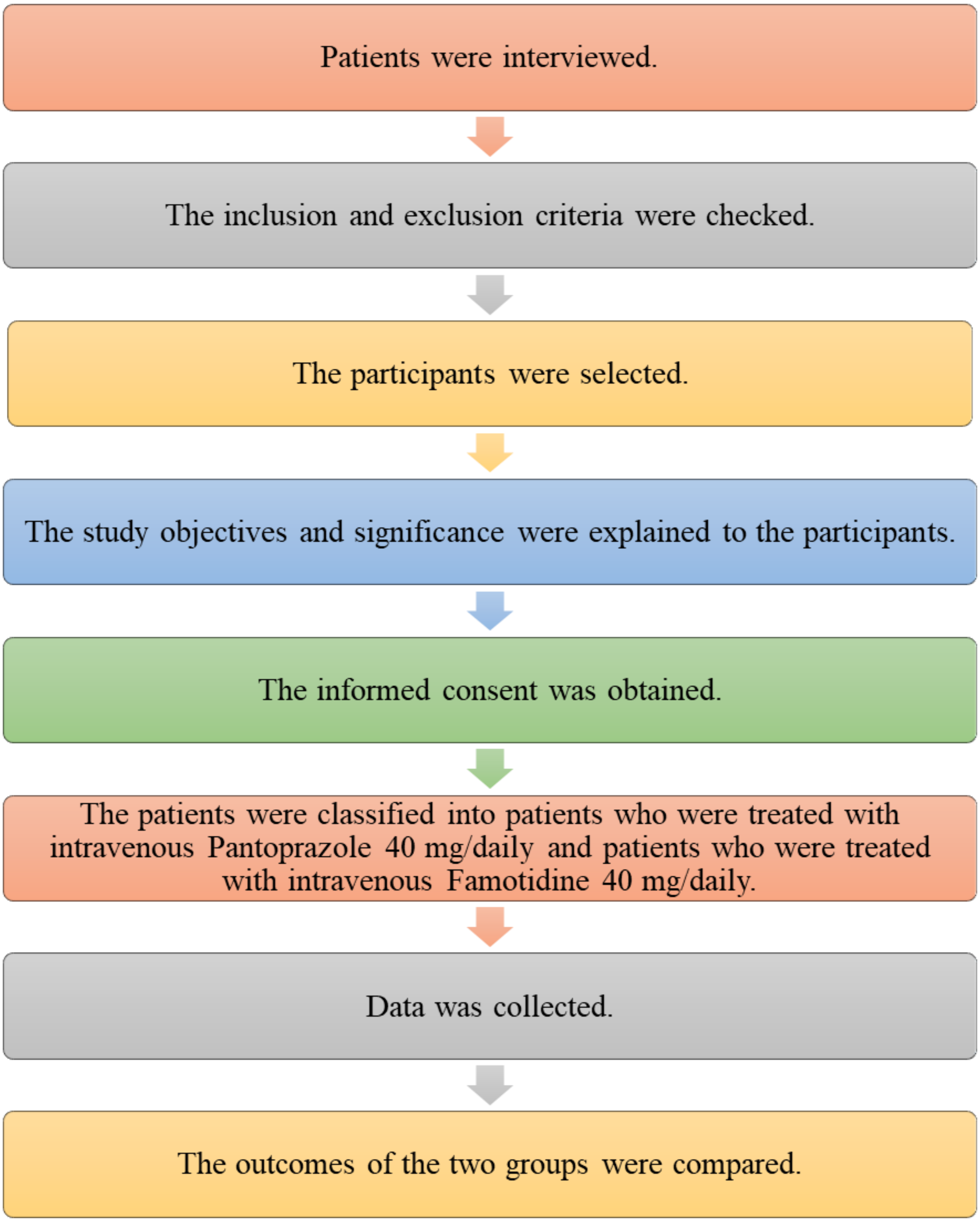
The Nursing Delirium Screen Scale (NuDESC) was utilized to evaluate the degree of delirium. This is an observational tool that evaluates five distinct characteristics associated with delirium: disorientation, inappropriate behavior, inappropriate communication, hallucinations, and psychomotor retardation. Each characteristic is rated based on its severity, ranging from 0 (absent) to 2 (severe). The evaluation is based on a composite of observations over a 12-hour period (Krupa et al., 2021). The NuDESC is designed to be used by nursing staff with slight training. It has been found to be consistently sensitive (85.7%) and specificity (86.8%) in detecting delirium. It allows nurses to assess patients easily in the moment, rather than having to determine if an acute change from baseline has occurred (Heidenreich & Gresbach, 2018).

2.9 Data Collection

Data was collected by the researcher using a data sheet from critically ill patients in intensive and cardiac care units of the Al- Watani hospital at Nablus city. Data was collected after obtained needed permissions from the MOH and IRB approval from An-Najah National University. Participants were interviewed and asked to participate in the study. The purpose of the study was explained, and appropriate instruction was given to the participants before conducting the study.

Figure 4

Flow chart of data collection



Interventions for data collection

After the patient was admitted to the intensive or cardiac care units based on the doctors' decision, a screening was carried out based on the inclusion and exclusion criteria. A meeting was held with the patient, or his family and they were given an idea about the subject of the study, its importance and objectives, and they were assured that the information will remain confidential and will not be used except for the purposes of scientific research and it will not cause any harm to the patient. Then the patient or his family was asked to sign a consent form to participate in the study. The patients were classified into patients who treated by using intravenous Pantoprazole 40 mg/daily, and patients who treated by using intravenous Famotidine 40 mg/daily. At first the sociodemographic data, health information, and data about usage of Pantoprazole and Famotidine were evaluated for participants in two groups. Then the clinical outcomes (including Magnesium (mg/dl), Potassium (mEq/L), Sodium (mEq/L), Calcium (mg/dL), Albumin (g/dL), C-reactive protein (mg/dL), Creatinine (mg/dL), Blood urea nitrogen (mg/dL), Glucose (mg/dl), Hematocrit (%), Hemoglobin (g/dL), and Platelets 103/µl) were evaluated daily, for a maximum of two weeks for participants in two groups. When taking blood samples from the patient to evaluate clinical outcomes, the correct methods for taking blood samples were followed, such as sterilization and pressure on the place where blood samples were taken, to ensure that no infection or complications occurred at the place where blood samples were taken. Also, the neurological complications (including dizziness, nausea, vomiting, numbness, tetany, tremors, muscle spasms, hallucinations, agitation, seizures, convulsions, and loss of consciousness), death, any other complications and delirium score were evaluated daily, for a maximum of two weeks for two groups.

2.10 Variables

Independent variables: Age, gender, marital status, level of education, medical & surgical history, history of receiving diuretics, type and dose of Pantoprazole and Famotidine, and history of using diuretics.

Dependent variable: Clinical outcomes (including serum Magnesium, Potassium, Sodium, Calcium, Albumin, C-reactive protein, Creatinine, Blood urea nitrogen, Glucose, Hematocrit, Hemoglobin, and Platelets), the neurological complications (including dizziness, nausea, vomiting, numbness, tetany, tremors, muscle spasms, hallucinations, agitation, seizures, convulsions, and loss of consciousness), death, any other complications and delirium score.

2.11 Statistical Analysis

The data obtained from the study was analyzed using the Statistical Package for Social Sciences (SPSS) software version 25. Several statistical tests were employed to explore the relationships between the variables and address the research questions. For quantitative data, the mean and standard deviation were computed. To evaluate the association between two categorical variables, the researcher utilized the chi-square test to determine if there was a statistically significant relationship. To assess whether there was a statistically difference between the means of two independent groups, the researcher employed the student’s t-test. In the study, a significance level of $P \leq 0.05$ was applied, indicating that findings were considered statistically significant if the p-value was equal to or less than 0.05.

2.12 Ethical Consideration

To conduct the study, all research ethics guidelines and general ethical values were adhered by the researcher. IRB approval was obtained from An-Najah National University; in addition, a permission letter was acquired from the Palestinian Ministry of Health (Appendix C) to allow the researcher to collect data. Participants were informed about the study's goals, importance, potential risks and benefits of participating in the trial. Furthermore, each participant provided a researcher with informed written consent (Appendix D) in order to participate in the study. Participation was entirely voluntary, and the participants have the right to withdraw from the study at any time, and the outcomes have been protected in such a way as to ensure that all participants are not named. The data was collected in appropriate time. Credibility in writing the findings of the study. Ensure that participants were treated with respect and dignity throughout the trial. Ensure that the trial was conducted in accordance with the ethical principles of autonomy, beneficence, non-malfeasance, and justice. Participants was not subjected to any physical or moral harm.

Chapter Three

Results

3.1 Introduction

This chapter discusses the outcomes of the statistical analysis conducted on the data, which encompasses descriptive analysis that introduces the study and provides solutions to the study's research questions. The total sample number was 109 critically ill patients in intensive or cardiac care units of Al- Watani Hospital (55 patients received Pantoprazole and 54 patients received Famotidine), but during the study, 9 participants dropped out from the study, then the sample size reached 100 participants. The response rate was 91.75%. The researcher employed a convenience sampling method to allocate the patients for the study, and subsequently distributed the participants into two groups; the first group was 50 critically ill patients received intravenous Pantoprazole 40 mg/daily, and the second group was 50 critically ill patients who received intravenous Famotidine 40 mg/daily). The researcher utilized appropriate statistical calculations, involving mean and standard deviation, for numerical data. Additionally, the independent t-test (Student's t-test) was utilized to assess whether there was a statistically significant difference between Pantoprazole and Famotidine regarding magnesium, potassium, sodium, calcium, albumin, c-reactive protein, creatinine, blood urea nitrogen, glucose, hematocrit, hemoglobin, platelets and delirium score; furthermore, the Pearson's chi-squared test was employed to evaluate whether there was a statistically significant difference between the expected frequencies and the observed frequencies in one or more categories of a contingency table, such as the comparison between Pantoprazole and Famotidine in relation to the diagnosis of cases in critically ill patients, past medical history, having a past surgical, the history of receiving diuretics, usage of Pantoprazole and Famotidine, neurological complications and delirium score … etc. Multivariate analyses of factors identifying factors affected by Pantoprazole compared to Famotidine group among the study participants. P-value is significant at $P \leq 0.05$.

3.2 Distribution of the participants according to socio-demographic characteristics

The results illustrates that the highest age group for the total participants is over 60 years old (60%) followed by the group between the ages of 39 to 59 years old (29%). The results show that the lowest age group for the total participants is between 18 to 38 years old (11%). More than half of total participants were males (57.0%) and 43.0% were females. The majority of participants are married (67%) which considered the highest group of the study participants; followed by 15% are divorced; 10% are widowed; and 8% are single which considered the lowest group of the study participants. The majority of the participants have an educational level less than Tawjihi (56%) which considered the highest educational level of the study participants; followed by 17% have a Tawjihi level; 16% have a diploma level; and 11% have a bachelor level. On the other hand, the results showed that the nobody of participants have a higher education level.

In details, regarding to age, the age group from 18-38 years old included 5/50 participants from Pantoprazole versus 6/50 from Famotidine; the age group from 39-59 years old included 15/50 participants from Pantoprazole versus 14/50 from Famotidine; and the age group more than 60 years old included 30/50 participants from Pantoprazole versus 30/50 from Famotidine. As for gender [28/50 (56%) males and 22 (44%) females in Pantoprazole versus 29/50 (58%) males and 21/50 (42%) females in Famotidine, $P>0.05$]. Furthermore, the study includes 67 participants (34 from Pantoprazole versus 33 from Famotidine) are married; 15 participants (9 from Pantoprazole versus 6 from Famotidine) are divorced; 10 participants (3 from Pantoprazole versus 7 from Famotidine) are widowed; and 8 participants (4 from Pantoprazole versus 4 from Famotidine) are single. Finally, the study includes 56 participants (30 from Pantoprazole versus 26 from Famotidine) have an educational level less than Tawjihi; 17 participants (8 from Pantoprazole versus 9 from Famotidine) have a Tawjihi level; 16 participants (7 from Pantoprazole versus 9 from Famotidine) have a diploma level; and 11 participants (5 from Pantoprazole versus 6 from Famotidine) have a bachelor level. There are no statistically significant differences between Pantoprazole and Famotidine cases regarding age, gender, marital status and education level.

Table 1

Distribution of participants according to socio-demographic characteristics

Socio-demographic characteristics	Total (n=100) n (%)	Cases		Statistical test	
		Pantoprazole (n=50)	Famotidine (n=50)	Chi-square (χ^2)	P-value
Age					
18-38	11 (11%)	5 (10)	6 (12)	0.125	0.939
39-59	29 (29%)	15 (30)	14 (28)		
60+	60 (60%)	30 (60)	30 (60)		
Gender					
Male	57 (57%)	28 (56)	29 (58)	0.041	0.839
Female	43 (43%)	22 (44)	21 (42)		
Marital status					
Single	8 (8%)	4 (8)	4 (8)	2.215	0.529
Married	67 (67%)	34 (68)	33 (66)		
Divorced	15 (15%)	9 (18)	6 (12)		
Widowed	10 (10%)	3 (6)	7 (14)		
Education					
Less than tawjihi	56 (56%)	30 (60)	26 (52)	0.685	0.877
Tawjihi	17 (17%)	8 (16)	9 (18)		
Diploma	16 (16%)	7 (14)	9 (18)		
Bachelor	11 (11%)	5 (10)	6 (12)		
High education	0 (0%)	0 (0)	0 (0)		

3.3 Distribution of participants according to diagnosis information

The results show that septic shock is the highest diagnosis for the total participants (n=43, 43%), the second one was acute kidney injury (AKI) with percentage 24% followed by type 2 respiratory failure (n=17, 17%) followed by cerebrovascular accident (CVA) (n=12, 12.0%), sepsis (n=5, 5%), chronic obstructive pulmonary disease (COPD) (n=4, 4%), cardiogenic shock (n=4, 4%), snake bite (n=3, 3%), brain hemorrhage (n=3, 3%), neutropenic fever (n=1, 1%), and deep vein thrombosis (DVT) (n=1, 1%). The number of cases with other diagnoses was 12 cases (12%). Note that other diagnoses included 3 participants with type 1 respiratory failure, 1 participant with pulmonary embolism (PE), 4 participants with non-ST segment elevation myocardial infarction (NSTEMI), 1 participant with aspiration pneumonia, 1 participant with epilepsy, 1 participant with pulmonary edema, 1 participant with plural effusion.

The finding pointed out that the percentage of AKI was higher in Pantoprazole compared with Famotidine (38 % vs. 10 %, respectively), and statistically significant (P = 0.001). In contrast, there is no significant difference between Pantoprazole case and Famotidine case regarding having septic shock (46% vs. 40%, P=0.544), type 2 respiratory failure (24% vs. 10%, P=0.062), CVA (10% vs. 14%, P=0.538), neutropenic fever (0% vs. 2%, P=0.315), DVT (0% vs. 2%, P=0.315), sepsis (6% vs. 4%, P=0.646), COPD (6% vs. 2%, P=0.307), snake bite (2% vs. 4%, P=0.558), cardiogenic shock (4% vs. 4%, P=1.000), brain hemorrhage (0% vs. 6%, P=0.079) respectively. In brief, the results showed that no significant differences at 0.05 level between Pantoprazole and Famotidine cases regarding diagnosis information in critically ill patients (the p-values of the chi-square test are higher than 0.05). While AKI was significant differences at 0.05 level between Pantoprazole and Famotidine cases regarding diagnosis information in critically ill patients (the p-values of the chi-square test are less than 0.05).

Table 2

Distribution of participants according to diagnosis information

Diagnosis		Total (n=100) n (%)	Cases n (%)		Statistical test	
			Pantoprazole (n=50)	Famotidine (n=50)	Chi-square (χ^2)	P-value
Septic shock	Yes	43 (43%)	23 (46)	20 (40)	0.367	0.544
	No	57 (57%)	27 (54)	30 (60)		
AKI	Yes	24 (24%)	19 (38)	5 (10)	10.746	0.001*
	No	76 (76%)	31 (62)	45 (90)		
Type 2 respiratory failure	Yes	17 (17%)	12 (24)	5 (10)	3.473	0.062
	No	83 (83%)	38 (76)	45 (90)		
CVA	Yes	12 (12%)	5 (10)	7 (14)	0.379	0.538
	No	88 (88%)	45 (90)	43 (86)		
Neutropenic Fever	Yes	1 (1%)	0 (0)	1 (2)	1.010	0.315
	No	99 (99%)	50 (100)	49 (98)		
DVT	Yes	1 (1%)	0 (0)	1 (2)	1.010	0.315
	No	99 (99%)	50 (100)	49 (98)		
Sepsis	Yes	5 (5%)	3 (6)	2 (4)	0.211	0.646
	No	95 (95%)	47 (94)	48 (96)		
COPD	Yes	4 (4%)	3 (6)	1 (2)	1.042	0.307
	No	96 (96%)	47 (94)	49 (98)		
Snake bite	Yes	3 (3%)	1 (2)	2 (4)	0.344	0.558
	No	97 (97%)	49 (98)	48 (96)		
Cardiogenic shock	Yes	4 (4%)	2 (4)	2 (4)	0.000	1.000
	No	96 (96%)	48 (96)	48 (96)		
Brain hemorrhage	Yes	3 (3%)	0 (0)	3 (6)	3.093	0.079
	No	97 (97%)	50 (100)	47 (94)		
Others	Yes	12 (12%)	6 (12)	6 (12)	0.001	0.999
	No	88 (88%)	44 (88)	44 (88)		

3.4 Distribution of participants according to past medical history

The results show that 82 participants (82%) having a past medical history, while 18 participants (18%) did not have a past medical history. The results showed that the highest past medical history for the participants who have past medical histories is hypertension (n=48, 58.5%) followed by diabetes (n=39, 47.6%), heart diseases (n=29, 35.4%), renal diseases (n=15, 18.3%), liver diseases (n=6, 7.3%) and osteoporosis (n=1, 1.2%). Also, the least past medical histories are metastatic (n=0, 0%), chronic diarrhea (n=0, 0%), and gastric hemorrhage (n=0, 0%). The number of participants with other diagnoses was 12 participants (14.6%). Note that the other diagnoses include 2 participants with CVA, 3 participants with COPD, 2 participants with COVID, 2 participants with breast cancer, 2 participants with testicular cancer, and 1 participant with DVT.

The finding pointed out that there is no significant difference between Pantoprazole case and Famotidine cases regarding having past medical history (84% vs. 80%, P=0.602), hypertension (57.1% vs. 60%, P=0.792), diabetes (50% vs. 45%, P=0.65), heart diseases (40.5% vs. 30%, P=0.321), liver diseases (11.9% vs. 2.5%, P=0.102), renal diseases (23.8% vs. 12.5%, P=0.185), metastatic cancer (0.0% vs. 0.0%, P=1), osteoporosis (2.4% vs. 0.0%, P=0.326), chronic diarrhea (0% vs. 0%, P=1.000), gastric hemorrhage (0% vs. 0%, P=1.000) and others (9.5% vs. 20%, P=0.179), respectively.In brief, the results showed that no significant differences at 0.05 level between Pantoprazole and Famotidine cases regarding past medical history in critically ill patients (the p-values of the chi-square test are higher than 0.05).

Table 3

Distribution of participants according to past medical history

Past medical history		Total (n=100) n (%)	Cases n (%)		Statistical test	
			Pantoprazole (n=50)	Famotidine (n=50)	Chi-square (χ^2)	P-value
Having past medical history	Yes	82 (82%)	42 (84)	40 (80)	0.271	0.602
	No	18 (18%)	8 (16)	10 (20)		
If yes, Specify			(n=42)	(n=40)		
Hypertension	Yes	48 (58.5%)	24 (57.1)	24 (60)	0.069	0.792
	No	34 (41.5%)	18 (42.9)	16 (40)		
Diabetes	Yes	39 (47.6%)	21 (50)	18 (45)	0.205	0.650
	No	43 (52.4%)	21 (50)	22 (55)		
Heart diseases	Yes	29 (35.4%)	17 (40.5)	12 (30)	0.984	0.321
	No	53 (64.6%)	25 (59.5)	28 (70)		
Liver diseases	Yes	6 (7.3%)	5 (11.9)	1 (2.5)	2.672	0.102
	No	76 (92.7%)	37 (88.1)	39 (97.5)		
Renal diseases	Yes	15 (18.3%)	10 (23.8)	5 (12.5)	1.753	0.185
	No	67 (81.7%)	32 (76.2)	35 (87.5)		
Osteoporosis	Yes	1 (1.2%)	1 (2.4)	0 (0)	0.964	0.326
	No	81 (98.8%)	41 (97.6)	40 (100)		
Others	Yes	12 (14.6%)	4 (9.5)	8 (20)	1.800	0.179
	No	70 (85.4%)	38 (90.5)	32 (80)		

3.5 Distribution of participants according to past surgical history

The results show that 22 participants (22%) having a past surgical history, while 78 participants (78%) did not have a past surgical history. The results showed that the highest past surgical history for the participants who have past surgical histories is coronary artery bypass graft (CABG) (n=5, 22.7%), followed by appendectomy (n=4, 18.2%), cardiac Cath (n=3, 13.6%), mastectomy (n=2, 9.1%), hysterectomy (n=2, 9.1%), and laparotomy (n=2, 9.1%). The lowest past surgical histories were hip replacement (n=1, 4.5%), rectal bleeding (n=1, 4.5%) and lumber disk (n=1, 4.5%).

The finding pointed out that there is no significant difference between Pantoprazole and Famotidine groups regarding to having past surgical history (22% vs. 22%, P=1.000). Also, the results showed no significant difference between Pantoprazole and Famotidine groups regarding having orchiectomy (0% vs. 9.1%, P=0.306), hip replacement (9.1% vs. 0%, P=0.306), mastectomy (0% vs. 18.2%, P=0.138), rectal bleeding (0% vs. 9.1%, P=0.306), hysterectomy (9.1% vs. 9.1%, P=1), CABG (36.4% vs. 9.1%, P=0.127), cardiac Cath (9.1% vs. 18.2%, P=0.534), laparotomy (18.2% vs. 0%, P=0.138), lumber disk (9.1% vs. 0%, P=0.306), and appendectomy (9.1% vs. 27.3%, P=0.269), respectively. In brief, the results showed that no significant differences at 0.05 level between Pantoprazole and Famotidine groups regarding to having a past surgical among critically ill patients (the p-values of the chi-square test are higher than 0.05).

Table 4

Distribution of participants according to having past surgical history

Past surgical history		Total (n=100) n (%)	Cases n (%)		Statistical test	
			Pantoprazole (n=50)	Famotidine (n=50)	Chi-square (χ^2)	P-value
Having past surgical history	Yes	22 (22%)	11 (22)	11 (22)	0.000	1..000
	No	78 (78%)	39 (78)	39 (78)		
If yes, specify			n=11	n=11		
Orchiectomy	Yes	1 (4.5%)	0 (0)	1 (9.1)	1.048	0.306
	No	21 (95.5%)	11 (100)	10 (90.9)		
Hip Replacement	Yes	1 (4.5%)	1 (9.1)	0 (0)	1.048	0.306
	No	21 (95.5%)	10 (90.9)	11 (100)		
Mastectomy	Yes	2 (9.1%)	0 (0)	2 (18.2)	2.200	0.138
	No	20 (90.9%)	11 (100)	9 (81.8)		
Rectal Bleeding	Yes	1 (4.5%)	0 (0)	1 (9.1)	1.048	0.306
	No	21 (95.5%)	11 (100)	10 (90.9)		
Hysterectomy	Yes	2 (9.1%)	1 (9.1)	1 (9.1)	0.000	1.000
	No	20 (90.9%)	10 (90.9)	10 (90.9)		
CABG	Yes	5 (22.7%)	4 (36.4)	1 (9.1)	2.329	0.127
	No	17 (77.3%)	7 (63.6)	10 (90.9)		
Cardiac Cath	Yes	3 (13.6%)	1 (9.1)	2 (18.2)	0.386	0.534
	No	19 (86.4%)	10 (90.9)	9 (81.8)		
Laparotomy	Yes	2 (9.1%)	2 (18.2)	0 (0)	2.200	0.138
	No	20 (90.9%)	9 (81.8)	11 (100)		
Lumber Disk	Yes	1 (4.5%)	1 (9.1)	0 (0)	1.048	0.306
	No	21 (95.5%)	10 (90.9)	11 (100)		
Appendectomy	Yes	4 (18.2%)	1 (9.1)	3 (27.3)	1.222	0.269
	No	18 (81.8%)	10 (90.9)	8 (72.7)		

3.6 Distribution of participants according to history of receiving diuretics and usage of Pantoprazole and Famotidine

The results show that 24 participants (24%) have a history of receiving diuretics, while 76 participants (76%) don't have a history of receiving diuretics. The results showed that the highest received diuretic is loop (n=20, 83.3%), followed by combination (received 2 or more types of diuretics) (n=2, 8.3%), and potassium-sparing (n=2, 8.3%). The results show that half of participants received PPIs (n=50, 50.0%) and another half of participants received H2RAs (n=50, 50.0%). The only received type of PPIs was Pantoprazole; while the only received type of H2RAs was Famotidine. Both Pantoprazole and Famotidine patients received a dose of 40 mg/day intravenously.

The findings illustrated that there is no significant difference between Pantoprazole case and the Famotidine case regarding to history of receiving diuretics (28% vs. 20%, P=349). Also, the results showed no significant difference between Pantoprazole case and the Famotidine case regarding the type of diuretics (P=0.665); The p-values of the chi-square test are higher than 0.05.

Table 5

Distribution of participants according to history of receiving diuretics and usage of Pantoprazole and Famotidine

History of receiving diuretics		Total (n=100) n (%)	Cases n (%)		Statistical test	
			Pantoprazole (n=50)	Famotidine (n=50)	Chi-square	P-value
History of receiving diuretics	Yes	24 (24)	14 (28)	10 (20)	0.877	0.349
	No	76 (76)	36 (72)	40 (80)		
If yes, specify type of diuretics	Loop	20 (83.3)	11 (78.6)	9 (90)	1.577	0.665
	Potassium-sparing	2 (8.3)	2 (14.3)	0 (0)		
	Combination	2 (8.3)	1 (7.1)	1 (10)		

Table 6

Usage of PPIs and H2RAs

Usage of PPIs and H2RAs		N	%
PPIs (n=50)	Pantoprazole	50	100.0%
	Omeprazole	0	0%
	Esomeprazole	0	0%
	Rabeprazole	0	0%
	Lansoprazole	0	0%
	Dexlansoprazole	0	0%
Dose of PPIs	40 mg/day	50	100%
H2RAs (n=50)	Famotidine	50	100.0%
	Ranitidine	0	0%
	Cimetidine	0	0%
	Nizatidine.	0	0%
Dose of H2RAs	40 mg/day	50	100.0%

3.7 Hematological and biochemical parameters

The results show that the frequencies and percentages for the qualitative variables and means and standard deviations for the quantitative variables for study participants.

The results showed that the under normal levels of calcium for most of the patients (n=66, 66%), under normal levels of albumin for most of the patients (n=82, 82%), under normal levels of hematocrit for most of the patients (n=77, 77%) and under normal levels of hemoglobin for most of the patients (n=52, 52%). From the other hand, the results showed that the above normal levels of magnesium for the most of the patients (n=3, 3%), above normal levels of potassium for the most of the patients (n=6, 6%), above normal levels of sodium for the most of the patients (n=15, 15%), above normal levels of C-reactive protein for the most of the patients (n=97, 97%), above normal levels of platelets for most of the patients (n=5, 5%). Finally, the normal levels of magnesium for most of the patients (n=96, 96%), normal levels of creatinine for most of the patients (n=39, 39%), normal levels of blood urea nitrogen for most of the patients (n=39, 39%), normal levels of glucose for most of the patients (n=29, 29%).

Independent t-test showed that the blood urea nitrogen was higher statistically significant in Pantoprazole cases compared to Famotidine cases (40.0±29.6 vs. 27.8±24.3 mg/dl; & $P < 0.05$). Also, the creatinine was higher statistically significant in Pantoprazole cases compared to Famotidine cases (2.2±2.0vs. 1.5±1.5 mg/dl; & $P < 0.05$). In contract, the average of albumin in Pantoprazole cases was lower statistically significant than Famotidine cases (2.8±0.5 vs. 3.1±0.6 g/dl & $P < 0.05$). At the same way, the average of hematocrit in Pantoprazole cases was lower statistically significant than Famotidine cases (31.4±6.5 vs. 35.5±7.3%; & $P < 0.05$). Independent t-test showed that are no statistically significant differences between Pantoprazole and Famotidine cases regarding the average magnesium, potassium, sodium, calcium, c-reactive protein, glucose, hemoglobin, and platelets (the p-values of the chi-square test are higher than 0.05).

The results show that there are significant differences at 0.05 level between the Pantoprazole and Famotidine cases regarding laboratory results groups such as Albumin, Creatinine, Blood urea nitrogen and Hematocrit (The p-values of the chi-square test are less than 0.05).

Regarding the Sodium, the results show that the percentage of the above-normal Sodium patients (>145) among Pantoprazole cases (n=12, 12/50=24%) is significantly higher than the percentage of the above-normal Sodium patients among Famotidine cases (n=3, 3/50=6%), the p-value of the test is 0.040<0.05. Therefore, it can be concluded that Pantoprazole dose increased the risk of having higher Sodium level (hypernatremia).

Regarding Albumin, the results show that the percentage of the lower-normal Albumin patients (<3.5) among Pantoprazole cases (n=46, 46/50=92%) is significantly higher than the percentage of the lower-normal Albumin patients among Famotidine cases (n=36, 36/50=72%), the p-value of the test is 0.009<0.05. Therefore, it can be concluded that Pantoprazole dose increased the risk of having lower Albumin level (hypoalbuminemia).

Regarding the creatinine, the results show that the percentage of the above-normal Creatinine patients (>1.2) among Pantoprazole cases (n=27, 27/50=54%) is significantly higher than the percentage of the above-normal Creatinine patients among Famotidine cases (n=15, 15/50=30%), the p-value of the test is 0.049<0.05. Therefore, it can be concluded that the Pantoprazole dose increased the risk of having higher Creatinine level.

Regarding Blood urea nitrogen, the results show that the percentage of the above-normal Blood urea nitrogen patients (>20) among Pantoprazole cases (n=34, 34/50=68%) is significantly higher than the percentage of the above-normal Blood urea nitrogen patients among Famotidine cases (n=22, 22/50=44%), the p-value of the test is 0.029<0.05. Therefore, it can be concluded that Pantoprazole dose increased the risk of having higher blood urea nitrogen level.

In brief, the results indicated that sodium, albumin, creatinine, blood urea nitrogen, and hemoglobin were both statistically and clinically significant. However, hematocrit was found to be statistically significant but not clinically significant (P>0.05).

Table 7

Means, and standard deviations for the hematological and biochemical parameters of study participants (n = 100)

Clinical outcomes	Total Mean±SD	Cases Mean±SD		Statistical test	
		Pantoprazole (n=50)	Famotidine (n=50)	t	P-value
Magnesium (mg/dl)	2.05 ±0.26	2.0±0.3	2.1±0.2	-0.888	0.377
Potassium (mEq/L)	4.09±0.6	4.1±0.5	4.1±0.7	0.015	0.988
Sodium (mEq/L)	137.87±5.68	138.9±6.2	136.9±5	1.775	0.079
Calcium (mg/dL)	8.41±0.83	8.4±0.9	8.5±0.8	-0.610	0.544
Albumin (g/dL)	2.92±0.58	2.8±0.5	3.1±0.6	-2.623	0.010*
C-reactive protein (mg/dL)	10.2±15.49	11.5±20.5	8.9±7.8	0.838	0.404
Creatinine (mg/dL)	1.88±1.8	2.2±2.0	1.5±1.5	2.000	0.048*
Blood urea nitrogen (mg/dL)	33.88±27.61	40±29.6	27.8±24.3	2.257	0.026*
Glucose (mg/dl)	143.09±44.53	142.8±42	143.3±47.3	-0.055	0.956
Hematocrit (%)	33.49±7.21	31.4±6.5	35.5±7.3	-2.953	0.004*
Hemoglobin (g/dL)	11.27±2.57	11.1±4.4	11.9±2.6	-1.066	0.289
Platelets 10^3/µl	240.11±98.81	242.5±105.9	237.8±92.2	0.236	0.814

Table 8

Frequencies, percentages, and the chi-square test of comparison between Pantoprazole and Famotidine cases regarding laboratory results groups (n = 100)

Clinical outcomes		Total n (%)	Cases n (%)		Statistical test	
			Pantoprazole (n=50)	Famotidine (n=50)	Chi-square	P-value
Magnesium	<1.6 mg/dl	1 (1%)	1 (2)	0 (0)	1.375	0.503
	1.6–2.6 mg/dl	96 (96%)	47 (94)	49 (98)		
	>2.6 mg/dl	3 (3%)	2 (4)	1 (2)		
Potassium	<3.5 mEq/L	4 (4%)	2 (4)	2 (4)	0.000	1.000
	3.5–5.0 mEq/L	90 (90%)	45 (90)	45 (90)		
	>5.0 mEq/L	6 (6%)	3 (6)	3 (6)		
Sodium	<136 mEq/L	30 (30%)	14 (28)	16 (32)	6.424	0.040*
	136–145 mEq/L	55 (55%)	24 (48)	31 (62)		
	>145 mEq/L	15 (15%)	12 (24)	3 (6)		
Calcium	<8.6 mg/dL	66 (66%)	36 (72)	30 (60)	1.670	0.434
	8.6–10.2 mg/dL	32 (32%)	13 (26)	19 (38)		
	>10.2 mg/dL	2 (2%)	1 (2)	1 (2)		
Albumin	<3.5 g/dL	82 (82%)	46 (92)	36 (72)	6.775	0.009*
	3.5–5.5 g/dL	18 (18%)	4 (8)	14 (28)		
	>5.5 g/dL	0 (0%)	0 (0)	0 (0)		
C-reactive protein	≤0.8 mg/dL	3 (3%)	2 (4)	1 (2)	0.344	0.558
	>0.8 mg/dL	97 (97%)	48 (96)	49 (98)		
Creatinine	<0.7 mg/dl	19 (19%)	7 (14)	12 (24)	6.001	0.048*
	0.7–1.2 mg/dl	39 (39%)	16 (32)	23 (46)		
	>1.2 mg/dl	42 (42%)	27 (54)	15 (30)		
Blood urea nitrogen	<8 mg/dL	5 (5%)	3 (6)	2 (4)	7.105	0.029*
	8–20 mg/dL	39 (39%)	13 (26)	26 (52)		
	>20 mg/dL	56 (56%)	34 (68)	22 (44)		
Glucose	<70 mg/dl	0 (0%)	0 (0)	0 (0)	0.049	0.826
	70-110 mg/dl	29 (29%)	15 (30)	14 (28)		
	>110 mg/dl	71 (71%)	35 (70)	36 (72)		
Haematocrit	Low	77 (77.8%)	41 (82)	36 (73.5)	1.042	0.307
	Normal	22 (22.2%)	9 (18)	13 (26.5)		
	High	0 (0%)	0 (0)	0 (0)		
Haemoglobin	Low	52 (52%)	32 (64)	20 (40)	5.769	0.016*
	Normal	48 (48%)	18 (36)	30 (60)		
	High	0 (0%)	0 (0)	0 (0)		
Platelets	<150	20 (20%)	9 (18)	11 (22)	0.413	0.813
	150-450	75 (75%)	38 (76)	37 (74)		
	>450	5 (5%)	3 (6)	2 (4)		

3.8 Distribution of participants according to occurrence of neurological complications

The results show that the distribution of participants according to occurrence of neurological complications, which includes dizziness, nausea, vomiting, numbness, tetany, tremors, muscle spasms, hallucinations, agitation, seizures, convulsions, loss of consciousness, and death. The results show that the highest complication is agitation (n=18, 18.0%), followed by hallucinations (n=7, 7.0%), dizziness (n=5, 5.0%), nausea (n=4, 4.0%), vomiting (n=2, 2.0%), and numbness (n=2, 2.0%). while the lowest complications are muscle spasms (n=1, 1%), seizures (n=1, 1.0%) and convulsions (n=1, 1.0%). however, nobody has loss of consciousness (n=0, 0.0%), death (n=0, 0.0%) tetany (n=0, 0.0%) and tremors (n=0, 0.0%) complications.

The results pointed out that there is no significant difference between Pantoprazole case and Famotidine case regarding neurological complications such as dizziness (4% vs. 6%, P=0.646), nausea (4% vs. 4%, P=1.000), vomiting (2% vs. 2%, P=1.000), numbness (2% vs. 2%, P=1.000), tetany (0% vs. 0%, P=1.000), tremors (0% vs. 0%, P=1.000), muscle spasms (2% vs. 0%, P=0.315), hallucinations (10% vs. 4%, P=0.24), agitation (12% vs. 24%, P=0.118), seizures (0% vs. 2%, P=0.315), convulsions (2% vs. 0%, P=0.315), loss of consciousness (0% vs. 0%, P=1.000), and death (0% vs. 0%, P=1.000), respectively. In summary, the results showed no significant differences at 0.05 level between Pantoprazole and Famotidine cases regarding a history of neurological complications among critically ill patients (the p-values of the chi-square test are higher than 0.05).

Table 9

Distribution of participants according to occurrence of neurological complications.

Neurological complications		Total n (%)	Cases n (%) Pantoprazole (n=50)	Famotidine (n=50)	Statistical test χ^2	P-value
Dizziness	Yes	5 (5%)	2 (4)	3 (6)	0.211	0.646
	No	95 (95%)	48 (96)	47 (94)		
Nausea	Yes	4 (4%)	2 (4)	2 (4)	0.000	1.000
	No	96 (96%)	48 (96)	48 (96)		
Vomiting	Yes	2 (2%)	1 (2)	1 (2)	0.000	1.000
	No	98 (98%)	49 (98)	49 (98)		
Numbness	Yes	2 (2%)	1 (2)	1 (2)	0.000	1.000
	No	98 (98%)	49 (98)	49 (98)		
Tetany	Yes	0 (0%)	0 (0)	0 (0)	0.000	1.000
	No	100 (100%)	50 (100)	50 (100)		
Tremors	Yes	0 (0%)	0 (0)	0 (0)	0.000	1.000
	No	100 (100%)	50 (100)	50 (100)		
Muscle spasms	Yes	1 (1%)	1 (2)	0 (0)	1.010	0.315
	No	99 (99%)	49 (98)	50 (100)		
Hallucinations	Yes	7 (7%)	5 (10)	2 (4)	1.382	0.240
	No	93 (93%)	45 (90)	48 (96)		
Agitation	Yes	18 (18%)	6 (12)	12 (24)	2.439	0.118
	No	82 (82%)	44 (88)	38 (76)		
Seizures	Yes	1 (1%)	0 (0)	1 (2)	1.010	0.315
	No	99 (99%)	50 (100)	49 (98)		
Convulsions	Yes	1 (1%)	1 (2)	0 (0)	1.010	0.315
	No	99 (99%)	49 (98)	50 (100)		
Loss of consciousness	Yes	0 (0%)	0 (0)	0 (0)	0.000	1.000
	No	100 (100%)	50 (100)	50 (100)		
Death	Yes	0 (0%)	0 (0)	0 (0)	0.000	1.000
	No	100 (100%)	50 (100)	50 (100)		

3.9 Comparison between Pantoprazole and Famotidine cases regarding to delirium score

The independent t-test showed no statistically significant difference between Pantoprazole cases and Famotidine cases regarding Mean±SD of delirium score (0.7±1.4 vs. 0.5±0.8 mg/dl; & P > 0.05). Also, the results showed no significant differences at 0.05 level between Pantoprazole and Famotidine cases regarding delirium score groups (0, 1, 2, more than 2) among critically ill patients (the p-values of the chi-square test are higher than 0.05).

Table 10

Comparison between Pantoprazole and Famotidine cases regarding to delirium score

Clinical outcomes	Cases Mean±SD		Statistical test	
	Pantoprazole (n=50)	Famotidine (n=50)	t-test	P-value
Delirium score	0.7±1.4	0.5±0.8	1.411	0.161
Delirium score groups n (%)				
0.00	34 (68)	31 (62)	2.9898	0.408
1.00	2 (4)	0 (0)		
2.00	8 (16)	11 (22)		
More than 2	6 (12)	8 (16)		

Chapter Four

Discussions and Conclusions

4.1 Discussion

Introduction

Discussion and conclusion chapter summarizes from the data analysis in chapter three. The use of Pantoprazole is associated with an increased risk of magnesium levels dropping below normal in some patients, which may result in neurological adverse events and delirium. Low levels of magnesium may cause symptoms such as confusion, muscle weakness, and seizures (Florentin & Elisaf, 2012).

It's important to note that while low magnesium levels can cause neurological symptoms, not all neurological symptoms are necessarily due to magnesium deficiency. Additional medical issues or elements (like medications) might also play a role in the emergence of neurological symptoms (Xue et al., 2019). In order to distinguish hypomagnesemia symptoms from other neurological symptoms in patients being administered Pantoprazole (PPIs) versus Famotidine (H2RAs), it is crucial to assess the level of magnesium in the blood and examine for potential electrolyte irregularities, such as hypocalcemia and hypokalemia (Aronson, 2016). And when the magnesium level is deficient, it indicates that the neurological symptoms arise from decreased magnesium levels (Xue et al., 2019).

Hypomagnesemia may be asymptomatic, yet when it is symptomatic, the neurological manifestations include agitation, tremor, myoclonus, seizures (rarely), confusion, coma, paresthesias, muscle fasciculations, weakness, tetany, and hyper-reflexia (Aronson, 2016). These symptoms may coincide with various other neurological disorders. Nevertheless, if a patient displays these symptoms during the course of PPI or H2RAs treatment, and no other apparent reasons for the neurological symptoms are apparent, hypomagnesemia must be evaluated and taken into account (Yamashiro et al., 2022). Furthermore, if the patient's symptoms get better through the use of magnesium supplements, it indicates that the symptoms probably stemmed from hypomagnesemia (Lewis, 2023).

Moreover, conducting an evaluation of the patient's past use of medications is essential. If the patient has been undergoing prolonged PPI treatment and exhibits neurological symptoms, it is important to contemplate the potential connection between PPI use and hypomagnesemia. Conversely, H2RAs have not shown a robust link to hypomagnesemia (Sabbagh et al., 2016).

When contrasted with H2RAs, the PPIs have been shown to carry a greater likelihood of causing magnesium deficiency (Almoussa et al., 2018). This discrepancy arises because PPIs hinder the absorption of magnesium within the digestive system (Suksridechacin et al., 2020), whereas H2RAs do not produce this effect (Fan et al., 2023). The greatest susceptibility to magnesium deficiency exists among patients undergoing prolonged PPIs usage and those with pre-existing disorders that hinder magnesium absorption, like liver or kidney disorders. Consequently, it becomes crucial for individuals receving PPIs to undergo regular monitoring of their magnesium levels to ensure they remain within the standard range. The goal of this study was to examine electrolyte abnormalities, delirium, and neurological adverse effects in Pantoprazole (PPI) patients vs Famotidine (H2RA) patients.

Comparison of patients receiving Pantoprazole and patients receiving Famotidine regarding magnesium levels

“The results revealed that there was no noteworthy association between the utilization of Pantoprazole (PPIs) and Famotidine (H2RAs) concerning magnesium levels. Based on the studies of Heidelbaugh (2013) and Thurber et al. (2023) who have investigated the connection between PPI usage and the risk of mineral and vitamin deficiency; the authors revealed that hypomagnesemia arising from prolonged PPI treatment is a documented but infrequent occurrence. However, the precise underlying cause for the link between PPI usage and hypomagnesemia remains uncertain. One study suggested that hypomagnesemia might arise among patients with impaired PPI metabolism, but subsequent research has disproven this theory. It has been demonstrated that all PPIs that are biochemically substituted pyridylmethyl sulphonyl benzimidazole derivatives can lead to hypomagnesemia.”

Danziger et al., (2013) investigated that PPIs utilize is linked to low concentrations of serum magnesium and showed no association between PPIs and H2RAs cases regarding magnesium levels. The researchers arrived at the conclusion that there was no significant association between the use of PPIs and serum magnesium concentrations.

Other studies disagree with the current study, Kieboom et.al (2015) were studied a prospective cohort study to assess the hypomagnesemia is linked with the usage of PPIs in the general population and if it is linked with the usage of H2RA and they concluded the increased risk with PPIs was only seen after prolonged use. Also, John Danziger et.al (2013) examined the serum magnesium level and showed patients who have used PPIs or H2RA used to decrease stomach acid among 11,490 consecutive adult admissions to a tertiary medical center's intensive care unit. Also, they showed PPIs usage was unrelated to serum magnesium levels in those who did not use diuretics, while the usage of H2RA had no significant influence on magnesium levels with or without usage of diuretics.

However, Singh et al., (2018) conducted a study indicating that the risk of hypomagnesemia with PPIs is slightly increased with long-term usage and when used in conjunction with medications that can cause low magnesium levels. Besides, Wee et al., (2013) conducted a study to compare the effectiveness of IV Famotidine and IV Pantoprazole for preventing stress ulcers in the ICU. The authors randomly assigned cases to either IV pantoprazole or IV famotidine and identified that the Pantoprazole was commonly associated with hypomagnesemia. the most frequent risk factors for hypomagnesemia associated with SRMB.

Pantoprazole (PPIs) and Famotidine (H2RAs) can affect the absorption of minerals such as magnesium, but the exact mechanisms involved are not fully understood. Additionally, many other factors can contribute to hypomagnesemia, such as diet, medical conditions, medications, and lifestyle. As such, it is difficult to isolate the specific effects of Pantoprazole (PPIs) and H2RAs on magnesium levels. Additionally, the current study was short-term use Pantoprazole (PPIs) and H2Ras, that maybe lead to not effect on magnesium levels.

Comparison between Pantoprazole and Famotidine cases regarding others laboratory results

The current study showed that BUN and creatinine were higher associated in Pantoprazole (PPIs) cases compared to Famotidine (H2RAs) cases. The results agree with another study by Tatsuzawa, et al., (2016). They studied influence of proton pump inhibitors and histamine H2 receptor antagonists on serum phosphorus level control by calcium carbonate and they showed that there is no statistically significant in the average of BUN and creatinine among PPIs and H2RAs cases. In contrast, Wu et al., (2021) studied the association between PPIs and H2RAs in critically ill patients and showed that there is BUN and creatinine were higher statically significant in PPIs cases compared to H2RAs cases. Also, Kim et al., (2017) showed no statistically significant in the average of BUN and creatinine among PPIs and H2RAs cases.

The exact mechanisms by which Pantoprazole (PPIs) can lead to elevated BUN and creatinine levels are not fully understood. However, there are several proposed hypotheses: Acute interstitial nephritis: PPI use has been associated with an increased risk of acute interstitial nephritis (AIN), which is an inflammatory condition affecting the kidney tubules and interstitial. AIN can lead to impaired kidney function. Renal vasoconstriction: Pantoprazole (PPIs) have been shown to inhibit the production of nitric oxide, a substance that helps dilate blood vessels. This inhibition of nitric oxide production may cause vasoconstriction (narrowing of blood vessels) in the kidneys, reducing blood flow and potentially leading to acute kidney injury (AKI). finally, Drug interactions: Pantoprazole (PPIs) can interact with other medications that are known to increase the risk of AKI, such as diuretics or nonsteroidal anti-inflammatory drugs (NSAIDs).

Regarding hematocrit and albumin, the average of hematocrit and albumin in Pantoprazole (PPIs) cases was lower associated than Famotidine (H2RAs) cases. Singh et al., (2017) showed that the average albumin in PPIs cases was lower associated than H2RAs cases while Kim et al., (2017) showed no statistically significant in the average albumin among PPIs and H2RAs cases. Danziger et al., (2013) showed the average hematocrit in PPIs cases was lower among PPIs and H2Ras. ICU patients who are given PPIs may have lower hematocrit and albumin levels than those given H2RAs.

The exact mechanism by which Pantoprazole (PPIs) reduce albumin and hematocrit levels is not fully understood. However, it is believed that Pantoprazole (PPIs) can hinder the absorption of certain nutrients, such as vitamin B12, iron, magnesium, and calcium. Prolonged use of Pantoprazole (PPIs) can potentially result in deficiencies of these nutrients, which might indirectly impact hematocrit and albumin levels. Iron deficiency, for example, can lead to anemia, which is characterized by low hematocrit levels. Furthermore, albumin is a protein synthesized in the liver, and inadequate nutrition or nutrient deficiencies can lower its production. Individuals who experience inadequate nutrient absorption due to prolonged use of Pantoprazole (PPIs) may exhibit decreased albumin levels.

The results showed that are no association between Pantoprazole (PPIs) and Famotidine (H2RAs) cases regarding the others studied parameters as potassium, sodium, calcium, c-reactive protein, glucose, hemoglobin, and platelets. The results agree with other studies by Danziger et al., (2013). They illustrated that PPI use was not associated with PPIs and H2RAs cases regarding glucose levels. There is not found to have any significant effect on glucose levels. This is because PPIs and H2RAs are primarily used to reduce the production of stomach acid, and do not directly affect the body's glucose levels.

Regarding potassium, sodium, and calcium, the study by Makunts et a., (2019) have similar results to the current study. The researchers studied the analysis of post marketing safety data for PPIs and H2RAs and showed association between PPIs and H2RAs cases regarding the other studied parameters such as potassium, sodium, and calcium. Shikata et al., (2014) studied the use of proton pump inhibitors is associated with anemia, the researcher found that levels of potassium and sodium do not significant difference between PPIs and H2RAs among ICU patients.

Potassium, sodium, and calcium levels are essential electrolytes in the body, and their regulation is primarily influenced by factors such as kidney function, hormonal regulation (e.g., aldosterone), dietary intake, certain medical conditions, and medications. However, long-term use of Pantoprazole (PPIs) and Famotidine (H2RAs) may potentially cause alterations in these electrolyte levels, as well as other minerals, due to their impact on absorption in the gastrointestinal tract. Consequently, it is important to monitor electrolyte levels if taking Pantoprazole (PPIs) or Famotidine (H2RAs) for an extended period of time.

The results showed that are no associations between Pantoprazole (PPIs) and Famotidine (H2RAs) cases regarding c-reactive protein. These results agree with another study by Kim et al., (2021) that showed no significantly differ between PPIs and H2Ras regarding c-reactive protein (0.59±0.74 vs. 0.36±0.67 mg/dl, P=0.486). Leary et al., (2014) were studied H2RAs and right ventricular morphology: the MESA right ventricle study and the researchers illustrated that no statistically significant between PPIs and H2RAs cases regarding c-reactive protein (4.3 ± 5.6 vs. 4.6 ± 5.9 mg/dl, P=0.597). C reactive protein (CRP) plays a role, as a biomarker indicating inflammation, within the human body. It is commonly used to assess the efficacy of therapies, for inflammatory medical conditions, like rheumatoid arthritis and other autoimmune disorders. Lately there has been a rise in the use of PPIs and H2RAs as a treatment for acid reflux. However, it hasn't been proven that they have substantial influence on CRP levels. This is probably due to the fact that these medications are intended to decrease the levels of stomach acid rather than to reduce the inflammation or the immunological response. In terms although PPIs and H2RAs can alleviate acid reflux symptoms, they are unlikely to have a significant impact on reducing inflammation or CRP levels (Thurber et al., 2023).

The current study pointed out that the levels of hemoglobin, and platelets are not a significant difference between Pantoprazole (PPIs) and Famotidine (H2RAs) among ICU patients. Yokota et al., (2017) showed no significant difference between PPIs and H2RAs among ICU regarding platelets (205 vs. 203 × 104 mm-3, P=0.860). Additionally, a study conducted by Robles et al., in 2020 indicated that the occurrence of thrombocytopenia in the group receiving PPIs was higher than in the group receiving H2RAs (31% vs. 26%); Furthermore, the study found no difference in thrombocytopenia percentages between PPIs and H2RAs among patients in the intensive care unit with regard to platelet levels. Also, in the study of Shikata et al., (2014) which investigated the relationship between the usage of PPIs and anemia; the researcher reported that there was no significant difference in platelet levels between PPIs and H2RAs among patients in ICU.

The results showed that there was no significant difference between Pantoprazole (PPIs) and Famotidine (H2RAs) among ICU patients in relation to the levels of hemoglobin. Shikata et al., (2014) studied the use of proton pump inhibitors as associated with anemia and the results showed that there is no statistically significantly different between PPIs and H2RAs among ICU patients regarding levels of hemoglobin (13.4±1.5 vs. 12.8±1.8 g/dl, P=0.137).

PPIs and H2RAs do not directly affect platelet levels. However, long-term use of PPIs and H2RAs has been associated with a slight reduce platelet levels and causes iron deficiency anemia, which may be due to other factors, such as changes in the gut microbiome (De Bruyne et al., 2018; Jaynes et al., 2019 & Gifford et al., 2021).

Comparison between Pantoprazole and Famotidine cases regarding to neurological complications and delirium

The current study pointed out showed no significant differences between Pantoprazole (PPIs) and Famotidine (H2RAs) cases regarding neurological complications among critically ill patients such as dizziness, nausea, vomiting, numbness, tetany, tremors, muscle spasms, hallucinations, agitation, seizures, convulsions, loss of consciousness, and death. No previous study discusses a comparison between Pantoprazole (PPIs) and Famotidine (H2RAs) cases regarding to neurological complications. Cleary, no significant differences between Pantoprazole (PPIs) and Famotidine (H2RAs) cases regarding the neurological complications among critically ill patients is that medications are effective in treating these conditions, they are not typically used to treat neurological complications. The Pantoprazole (PPIs) and Famotidine (H2RAs) does not directly affect the nervous system. Therefore, these medications are not effective at treating conditions such as seizures, migraines, or other neurological disorders.

However, the results showed no statistically significant difference between Pantoprazole (PPIs) cases and Famotidine (H2RAs) cases regarding delirium. Sogawa et al., (2022) studied the effects of anti-ulcer drugs on delirium in trauma patients in ICU and the results of this study disagree with the current study and showed significant differences between PPIs and H2RAs cases regarding delirium. As results showed there is no significant differences have been found between PPIs and Histamine H2RAs cases regarding delirium studied by Kikkawa et al., (2021) that found the risk of delirium was similar among patients who used PPIs or H2RAs. The authors concluded that PPIs and H2RAs had comparable effects on the risk of delirium. However, they cautioned against drawing firm conclusions due to the limited number of studies available and the possibility of confounding factors. The founding showed there is no significant differences between PPIs and H2RAs cases regarding a delirium among critically ill patients is that the exact mechanism is not yet known. Both drugs may affect the neurotransmitters involved in delirium, or it may be due to other factors such as dosage, drug interactions, or individual patient characteristics. Therefore, it is important for healthcare providers to consider all potential risks when prescribing either type of drug.

Comparison between Pantoprazole and Famotidine cases regarding diagnosis information

The current study pointed out that the proportion of AKI among Pantoprazole (PPIs) cases was significantly higher compared to Famotidine (H2RAs) cases. Yang et al., (2017) were studied a comprehensive meta-analysis of seven studies to assess the effect of PPIs on the risk of AKI in 2,404,236 participants. They demonstrated an AKI increase in PPIs cases (61%). The researchers concluded that there is association remains significant across sensitivity analyses. Another study showed that incident AKI elevated in PPIs cases (Hart et al., 2019 & Wu et al., 2021).

The precise mechanisms underlying the association between Pantoprazole (PPIs) and AKI have not been fully elucidated, although several hypotheses have been proposed. Firstly, the occurrence of acute interstitial nephritis (AIN), characterized by inflammation affecting the kidney tubules and interstitium, has been observed to increase in individuals using Pantoprazole (PPIs). AIN has the capacity to influence and compromise renal function, potentially resulting in AKI. Additionally, Pantoprazole (PPIs) have been observed to diminish the production of nitric oxide, a vasodilator that is crucial for blood vessel dilatation. Consequently, this reduction may induce vasoconstriction within the kidneys, reducing blood flow and fostering the possibility of AKI. Moreover, Pantoprazole (PPIs) could potentially interact with other medication categories like diuretics or non-steroidal anti-inflammatory drugs (NSAIDs), both recognized contributors to AKI risk. While the exact mechanisms are not fully elucidated, these proposed explanations offer valuable insights into the potential pathways through which Pantoprazole (PPIs) might contribute to AKI. Further investigation is imperative to enhance our comprehension of this intricate interrelation.

The findings revealed no causal relationship between Pantoprazole (PPIs) and Famotidine (H2RAs) cases with respect to diagnosis information such as septic shock, type 2 respiratory failure, neutropenic fever, deep vein thrombosis, sepsis, chronic obstructive pulmonary disease, snake bite, cardiogenic shock, and brain hemorrhage. These findings are consistent with another research by MacLaren et al., (2014), in which no significant relationship was demonstrated between PPIs and H2RA cases with respect to septic shock, type 2 respiratory failure, neutropenic fever, deep vein thrombosis, sepsis, and Chronic obstructive pulmonary disease, snakebite, cardiogenic shock, and brain hemorrhage.

It has been determined that septic shock raises the possibility of renal injury. Septic shock is a severe type of sepsis that is marked by an inflammatory response within the body to infections. The inflammatory responses, together with the production of other pro-inflammatory mediators, may lead to widespread blood vessel dilatation, low blood pressure, and impaired perfusion to important organs such as the kidneys. Ischemia and consequent renal injury may occur as a result of decreased blood flow and oxygen supply to the kidneys. Furthermore, during septic shock, the production of inflammatory cytokines and the activation of immune cells might lead to a damage to the kidneys. Therefore, septic shock represents a significant risk factor for the development of kidney injury (Messerer et al.,2021 and Zarbock et al., 2023).

Comparison between Pantoprazole and Famotidine cases regarding past medical history and past surgical history

The current study showed no significant differences between Pantoprazole (PPIs) and Famotidine (H2RAs) cases regarding past medical history in such as hypertension, diabetes, heart diseases, liver diseases, renal diseases, metastatic cancer, osteoporosis, chronic diarrhea, gastric hemorrhage and others. Also, the statistical test showed no significant differences between Pantoprazole (PPIs) and Famotidine (H2RAs) cases regarding having a past surgical such as Surgical, Orchiectomy, Hip Replacement, Mastectomy, Rectal Bleeding, Hysterectomy, CABG, Cardiac Cath, Laparotomy, Lumber Disk and Appendectomy among critically ill patients. The results agree with other studies that no significant differences between PPIs and H2RAs cases regarding past medical history and past surgical history (Wu et al., 2021) while Song et al., (2019) studied the risk of post-stroke pneumonia with proton pump inhibitors, H2 receptor antagonists and neuroprotective agents in A retrospective nationwide cohort study. The researchers showed that there are significant differences between PPIs and H2RAs cases regarding past medical history. So, no evidence to suggest that PPIs or H2RAs are significant differences between PPIs and H2RAs cases regarding past medical history and surgical history in critically ill patients.

Comparison between Pantoprazole and Famotidine cases regarding to history of receiving diuretics

The current study illustrated that there is no significant difference between the Pantoprazole (PPIs) case and the Famotidine (H2RAs) case regarding and the type of diuretics and history of receiving diuretics. The results agree with other studies by Danziger et al., (2013) which showed no significant difference between the PPIs case and the H2RAs case regarding the type of diuretics and history of receiving diuretics. The use of PPIs and H2RAs has little to do with the type of diuretics used in ICU patients. Diuretics are typically used to help reduce fluid retention in the body and are often used to treat congestive heart failure and kidney failure. Ultimately, the choice of diuretic depends on the underlying cause of the fluid retention and the patient's individual needs and medical history.

4.2 Conclusion

Based on these results, it seems that the study participants are primarily older and male and are mostly married with a lower level of education. The found was showed acute kidney injury (AKI) was the most common diagnosis among critically ill patients, and patients who treated by proton pump inhibitors had a significantly higher incidence of AKI compared patients who treated by H2 receptor antagonists. No significant differences were found between the two groups in terms of other diagnoses. The results show that about one-fourth of the participants had a past surgical history, with the highest being coronary artery bypass graft (CABG) and the lowest being hip replacement, rectal bleeding and lumber disk. The results did not show a significant difference between two cases, Pantoprazole and Famotidine, regarding having a past surgical history among critically ill patients. One quartile of the participants had a history of receiving diuretics, with loop diuretics being the most commonly received type. The results showed that there was no significant difference between the two groups in regard to their history of receiving diuretics or the type of diuretics received.

The results found that there are significant differences between patients who treated by Pantoprazole and who treated by Famotidine with respect to several laboratory results. The results indicate that Pantoprazole have higher serum creatinine and blood urea nitrogen while lowering albumin and hematocrit compared to Famotidine. In contrast no significant differences found between the two groups for the other laboratory results such as magnesium, potassium, calcium, C-reactive protein, glucose, hemoglobin, and platelets.

There was no significant difference between Pantoprazole and Famotidine cases regarding the occurrence of neurological complications such as dizziness, nausea, vomiting, numbness, tetany, tremors, muscle spasms, hallucinations, agitation, seizures, convulsions, loss of consciousness, and death.

There was no significant association between patients who treated by Pantoprazole and who treated by Famotidine with regards to their mean delirium score and their classification into different delirium score groups. The results indicate that there is no significant association between the use of Pantoprazole or Famotidine and the presence or severity of delirium in critically ill patients.

4.3 Strengths points

This study has several strengths including: It is the first study that conducted in Palestine. In addition, the prospective design follows a group of patients over time and collects data on their exposure to Pantoprazole and Famotidine, as well as their magnesium levels and incidence of delirium and other neurological adverse events; This allows for the examination of the temporal relationship between exposure and outcome and can help establish causality. Besides, this research investigates the usage of two types of acid-suppressive drugs in order to detect variations in their effects on the level of magnesium and neurologic adverse events.

The purpose of this study is to look at the association between the level of magnesium and the usage of Pantoprazole and Famotidine. This is significant since the usage of Pantoprazole may cause low magnesium levels, and the low magnesium levels have been linked to an elevated probability of cognitive decline and dementia. This study includes follow-up evaluations to assess the impact of the medications being investigated, providing an even deeper understanding about their efficacy.

4.4 Limitations

The research study had considerable constraints, that includes the following: the population in the study consisted of only patients who admitted to cardiac and intensive care units and received acid-suppressive medications. As a result, the findings could not be appropriate to different patient groups, like patients who visit outpatient settings. The follow-up period was short in this study, meaning that it might have been insufficient for identifying all probable adverse events related to the usage of acid-suppressive drugs.

4.5 Recommendations

Several recommendations are made in the study, including: According to the study, physicians ought to prescribe acid-suppressive drugs that depends on a risk-benefit evaluation, taking into account individual's specific risk factors as well as any possible negative consequences related to each drug. Furthermore, the study encourages additional studies to assess the safety of acid-suppressive drugs, which may include much larger research projects with more varied patient groups and more extended follow-up period of time. The research study additionally suggests that physicians should be aware about the possible side effects of acid-suppressive drugs, such as neurological adverse events and delirium, and they should take suitable precautions in order to monitor and manage these side effects in their patients.

In summary, the study highlights that, while Pantoprazole and Famotidine are useful in treating acid-related diseases, they ought to be taken with careful consideration and physicians ought to be aware about the possible negative consequences.

List of Abbreviations

Abbreviation	Meaning
AEs	Adverse Events
AKI	Acute Kidney Injury
CABG	Coronary Artery Bypass Graft
CNS	central nervous system
COPD	Chronic Obstructive Pulmonary Disease
CVA	Cerebrovascular Accident
DU	Duodenal Ulcer
DVT	Deep Vein Thrombosis
EE	Erosive Esophagitis
FDA	Food and Drug Administration
g/Dl	Grams per decilitre
GI	Gastrointestinal
GU	Gastric Ulcer
H	Hour
H. pylori	Helicobacter Pylori
H+, K+-ATPase	Gastric hydrogen potassium ATPase
H2RAs	Histamine-2 Receptor Antagonists
ICU	Intensive Care Unit
IRB	Institutional review board
mEq/L	Milliequivalents per litre
mg/dl	Milligrams per decilitre
MOH	Ministry of Health
N	Number of participants
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
NSTEMI	Non-ST Segment Elevation Myocardial Infarction
NuDESC	Nursing Delirium Screen Scale
OTC	Over The Counter

PE	Pulmonary Embolism
pH	Potential of Hydrogen or Power of Hydrogen
PPIs	Proton-pump inhibitors
SD	Standard Deviation
SPSS	Statistical Package for the Social Sciences
T	Independent t-test
UGIB	Upper Gastrointestinal Bleeding
µl	Microlitre
VA	Veterans Affairs
vs	Versus
χ^2	Chi-Square Test
ZE	Zollinger-Ellison

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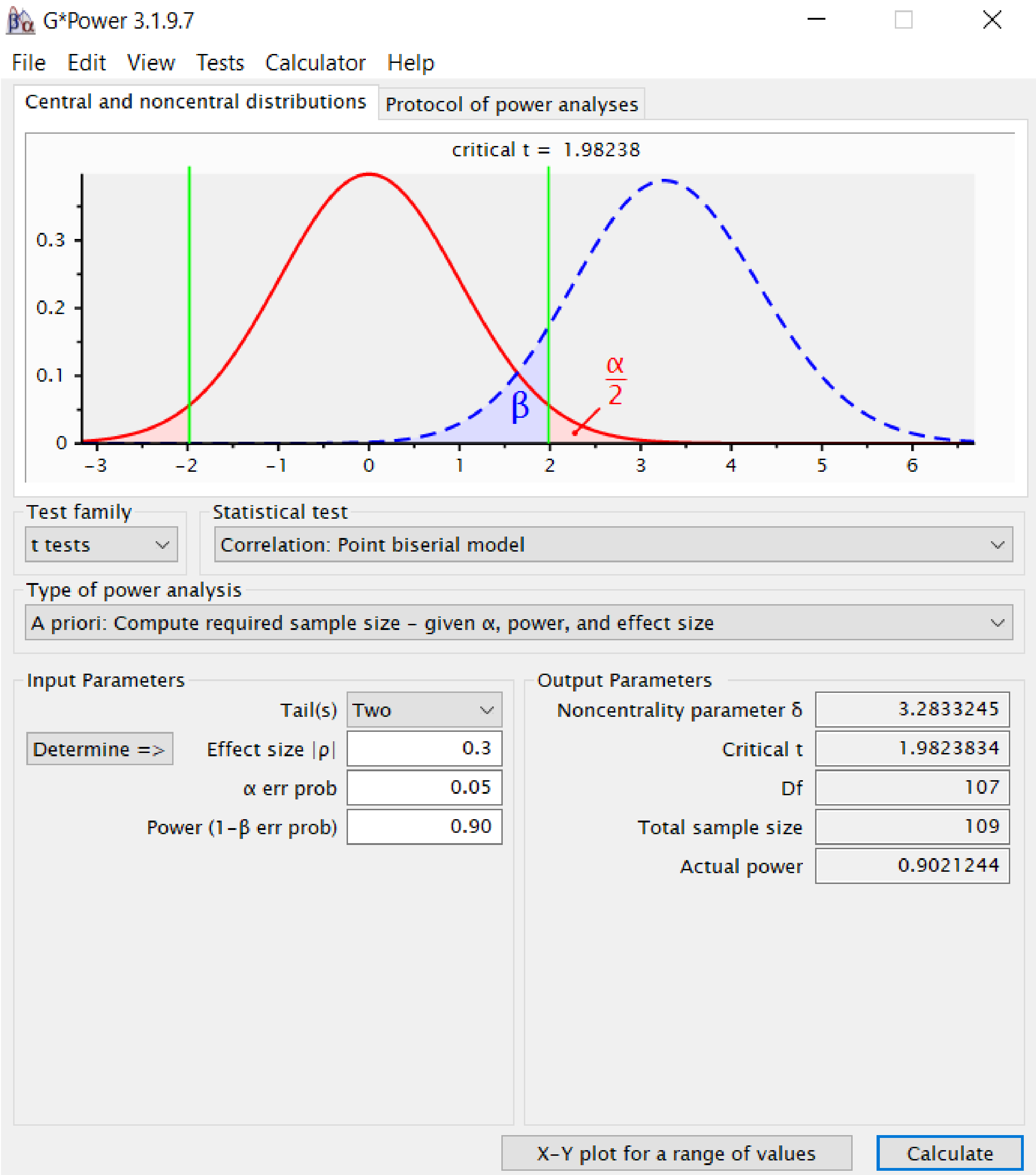
Appendices

Appendix A

Sample size calculator



Appendix B

Data sheet

An-Najah National University
Faculty of Graduate Studies
Master of Critical Care Nursing

<u>Questionnaire about:</u>

Comparison of the Neurological Adverse Events and Changes in Electrolytes levels between Pantoprazole and Famotidine: A Prospective Observational Study.

Prepared by:

Amer Nawwaf Zidan

Supervisor:

Dr. Nizar Said

Section 1: Sociodemographic data:

Patient number: ……………………………….

- **Patient:**
  - ☐ Patients who treated by using PPIs.
  - ☐ Patients who treated by using H2RAs.
- **Age group:**
  - ☐ 18-38 years old.
  - ☐ 39-59 years old.
  - ☐ More than 60 years old.
- **Gender:**
  - ☐ Male.
  - ☐ Female.
- **Marital status:**
  - ☐ Single.
  - ☐ Married.
  - ☐ Divorce.
  - ☐ Widow.
- **Level of education:**
  - ☐ Less than Tawjihi.
  - ☐ Tawjihi.
  - ☐ Diploma.
  - ☐ Bachelors.
  - ☐ Higher than bachelors.

Section 2: Health information.

- **Diagnosis:** ……………………………..…………
- **Having past medical history:**
  - ☐ Yes.
  - ☐ No.

If yes, specify:(More than one option can be selected).

- ☐ Hypertension.
- ☐ Diabetesmellitus.
- ☐ Heart diseases.
- ☐ Liver diseases.
- ☐ Renal diseases.
- ☐ Metastatic cancer.
- ☐ Osteoporosis
- ☐ Chronic diarrhea.
- ☐ Gastric hemorrhage
- ☐ Others: ………………………………..

- ❖ **Having past surgical history:**
  - ☐ Yes.
  - ☐ No.

  If yes, specify:……………………………………………………..
- ❖ **Having history of receiving diuretics:**
  - ☐ Yes.
  - ☐ No.

  If yes, specify type of these diuretics:
  - ☐ Loop.
  - ☐ Thiazide.
  - ☐ Potassium-sparing.
  - ☐ Combination.

Section 3: Data about usage of PPIs and H2RA.

If the patients selected as PPIs user.

- ❖ **Type of PPIs medications:**
  - ☐ Omeprazole
  - ☐ Esomeprazole
  - ☐ Pantoprazole
  - ☐ Rabeprazole
  - ☐ Lansoprazole
  - ☐ Dexlansoprazole
- ❖ **Dose of PPI** ……………………….………… **mg/day**

If the patients selected as H2RAs user.

- ❖ **Type of H2RAs medications:**
  - ☐ Famotidine.
  - ☐ Ranitidine.
  - ☐ Cimetidine.
  - ☐ Nizatidine.
- ❖ **Dose of H2RAs ………………..………… mg/day.**

Section 4: Clinical Outcomes.

It will be evaluated daily, for a maximum of two weeks.

Item	1st day	2nd day	3rd day	4th day	5th day	6th day	7th day	8th day	9th day	10th day	11th day	12th day	13th day	14th day
Magnesium (mg/dl)														
Potassium (mEq/L)														
Sodium (mEq/L)														
Calcium (mg/dL)														
Albumin (g/dL)														
C-reactive protein (mg/dL)														
Creatinine (mg/dL)														
Blood urea nitrogen (mg/dL)														
Glucose (mg/dl)														
Hematocrit (%)														
Hemoglobin (g/dL)														
Platelets $10^3/\mu l$														

Section 5: Neurological complications.

Item	1st day		2nd day		3rd day		4th day		5th day		6th Day		7th day		8th day		9th day		10th day		11th day		12th day		13th day		14th day	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Dizziness																												
Nausea																												
Vomiting																												
Numbness																												
Tetany																												
Tremors																												
Muscle spasms																												
Hallucinations																												
Agitation																												
Seizures																												
Convulsions																												
Loss of consciousness																												
Death																												

Other complications:

Item	1st day		2nd day		3rd day		4th day		5th day		6th day		7th day		8th day		9th day		10th day		11th day		12th day		13th day		14th day	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
1.																												
2.																												
3.																												
4.																												
5.																												

Delirium screening:

Item	1st day	2nd day	3rd day	4th day	5th day	6th day	7th day	8th day	9th day	10th day	11th day	12th day	13th day	14th day
Delirium score														

Nursing Delirium Screening Scale-NuDESC

NURSING DELIRIUM SCREENING SCALE
Disorientation
Inappropriate Behavior
Inappropriate Communication
Illusions/Hallucinations
Psychomotor Retardation
NuDESC Score

Disorientation
0=Alert, oriented to person, place, time
1=Disoriented but easily reoriented
2=Disoriented x2 or x3 not easily oriented

Inappropriate Behavior
0=Calm Cooperative
1=Restless and cooperative
2=Agitated pulling at devices climbing over side rails

Inappropriate Communication
1=Unclear thinking or rambling speech
2=Incoherence, nonsensical or unintelligible speech

Illusions/Hallucinations
0=None Noted
1=Paranoia, fears
2=Hallucinations, distortions of visual objects

Score NuDESC every shift, every day and ifthere is a *change in mentation* that occurs*anytime*duringtheshift.

Each cell contains 3 descriptors to choosefrom.

This is an observational screening tool. Pleaseuse yourbestjudgmentastowhatthepatientisdemonstrating.

Delirium can have fluctuating behaviors, onemoment calm, and the other moment agitated.Pleasescoretoolagainif behaviorschange.

Use Family Caregiver Sheet if patient hascognitive impairment and is cared for byfamilymemberstogiveusinsighttotheirneeds.

Perceptual distortions accompanyingdeliriumareusuallyvisual.

Psychomotor Retardation

0=None
1=Delayed or slow responsiveness
2=Excessive sleeping, somnolent, lethargic

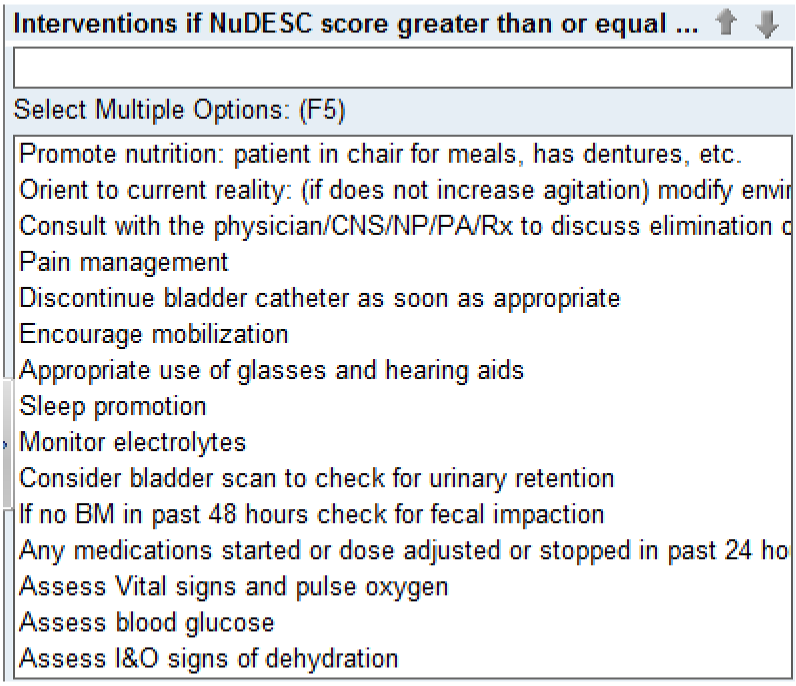
NuDESC Score

DELIRIUM INTERVENTIONS

Interventions if NuDESC score greater than or equal to 2:

Delirium can be hypoactive, hyperactive ormixed. Be aware that hypoactive is the leastdetectedbyclinicalstaff.

Score> or= to2 indicatespatient is ***screening* positive for delirium.Take action!**



Interventions if NuDESC score greater than or equal ...

Select Multiple Options: (F5)

Promote nutrition: patient in chair for meals, has dentures, etc.
Orient to current reality: (if does not increase agitation) modify envir
Consult with the physician/CNS/NP/PA/Rx to discuss elimination c
Pain management
Discontinue bladder catheter as soon as appropriate
Encourage mobilization
Appropriate use of glasses and hearing aids
Sleep promotion
Monitor electrolytes
Consider bladder scan to check for urinary retention
If no BM in past 48 hours check for fecal impaction
Any medications started or dose adjusted or stopped in past 24 ho
Assess Vital signs and pulse oxygen
Assess blood glucose
Assess I&O signs of dehydration

Updated interventions for patientsscreeningpositivefordelirium.Nursinginterventions can make a difference isrecognizingandtreatingdelirium.

Source: (Gaudreau et al., 2005).

Appendix C

Approval Letters

IRP Approval Letter

An-Najah National University
Faculty of Medicine & Health Sciences
Institutional Review Board

جامعة النجاح الوطنية
كلية الطب وعلوم الصحة
لجنة اخلاقيات البحث العلمي

Ref: Mas. June. 2022/10

IRB Approval Letter

Title of Research:

Magnesium Level and Delirium with Other Neurological Adverse Event among Patient Receiving Proton Pump Inhibitors Comparing to Histamine-2 Receptors Antagonist: A Randomized Control Trial

Submitted by:
Amer Nawwaf Jameel Zidan

Supervosor:
Nizar Said

Approved:
15th June 2022.

Your Study Title **"Magnesium Level and Delirium with Other Neurological Adverse Event among Patient Receiving Proton Pump Inhibitors Comparing to Histamine-2 Receptors Antagonist: A Randomized Control Trial"**reviewed by An-Najah National University IRB committee and was approved on 15th June 2022.

Hasan Fitian, MD

IRB Committee Chairman

IRB

Nablus - P.O Box :7 or 707 | Tel (970) (09) 2342902/4/7/8/14 | Faximile (970) (09) 2342910| E-mail : IRB@najah.edu

MoH Approval Letter

State of Palestine Ministry of Health Education in Health and Scientific Research Unit	دولة فلسطين وزارة الصحة وحدة التعليم الصحي والبحث العلمي

Ref.: ……………… الرقـم: عدد/١١٢٤/٢٠٢٢
Date: ……………… التـاريخ: ٦/٧/٢٠٢٢

الأخ مدير عام الادارة العامة للمستشفيات المحترم،،،

تحية واحترام...

<u>الموضـــوع: تسهيل مهمة بحث</u>

يرجى التكرم بتسهيل مهمة الطالب: **عامر نواف زيدان – ماجستير تمريض العناية المكثفة– جامعة النجاح**، لعمل بحث الماجستير بعنوان:

"Magnesium Level and Delirium with other Neurological adverse event among patient receiving Proton pump inhibitors comparing to histamine-2 receptors antagonist: a randomized control trial"

حيث سيقوم الطالب بجمع معلومات من الممرضين الذين يعملون في أقسام العناية المكثفة، مع العلم أن مشرف الدراسة: د. نزار سعيد.

وذلك في:

– مستشفى الوطني

على ان يتم الالتزام بالمحافظة على اخلاقيات البحث العلمي وسرية المعلومات،
على ان يتم الالتزام بجميع تعليمات واجراءات الوقاية والسلامة الصادرة عن وزارة الصحة بخصوص جائحة كورونا، وتحت طائلة المسؤولية. وابراز شهادة التطعيم قبل دخول مرافق وزارة الصحة.
على ان يتم تزويد الوزارة بنسخة PDF من نتائج البحث، التعهد بعدم النشر لحين الحصول على موافقة وزارة الصحة.

مع الاحترام...

د. عبد الله القواسمي
رئيس وحدة التعليم الصحي والبحث العلمي

نسخة: مدير دائرة التمريض والقبالة المحترمة/ جامعة النجاح

Telfax.:09-2333901 scientificresearch.dep@gmail.com تلفاكس: 09-2333901

Appendix D

Consent form

نموذج موافقة

عزيزي/تي المُشارِك/ة:

أنا الطالب عامر زيدان، أدرس ماجستير العناية المكثفة بكلية الدراسات العليا، في جامعة النجاح الوطنية.

أقوم بإعداد دراسة بعنوان:

"مقارنة الأحداث السلبية العصبية والتغيرات في مستويات عناصر أملاح الدم بين بانتوبرازول وفاموتيدين : دراسة رصدية مستقبلية".

باعتباره متطلب للتخرج والحصول على درجة الماجستير، وتم اختيارك بناءً على مطابقتك لشروط العينة.

الهدف الرئيسي من هذه الدراسة هو "مقارنة الأحداث السلبية العصبية والتغيرات في مستويات عناصر أملاح الدم بين بانتوبرازول وفاموتيدين : دراسة رصدية مستقبلية". بين المرضى المصابين بأمراض خطيرة.

بالإضافة الى ذلك، فان الدراسة تهدف إلى تقييم النتائج السريرية للمرضى الذين عولجوا باستخدام بانتوبرازول والمرضى الذين عولجوا بالفاموتيدين. ولتحديد المضاعفات العصبية التي قد تحدث في المرضى الذين عولجوا باستخدام بانتوبرازول والمرضى المعالجين بالفاموتيدين.

أشكر لك مشاركتك في هذه الدراسة، وفي حال أنّ الموعد غير مناسب الرجاء تحديد موعد آخر يناسبكم.

مشاركتك طوعية، ويمكنك رفض المشاركة أو الإجابة عن أي سؤال، وأرغب أنْ أؤكد لك أنّ المعلومات ستكون سرية ولن تستخدم إلا لغرض البحث العلمي، لذا أرجو أن تكون الإجابات دقيقة.

قبل البدء، هل تود/ين الاستفسار حول أي شيء عن الدراسة وهل من الممكن أن نبدأ المقابلة؟

(   ) نعم

(   ) لا

توقيع المشارك:

أشكرك على حسن تعاونك

جــامعـــة النجاح الوطنية
كليـــة الدراســـات العليـــا

مقارنة الأحداث السلبية العصبية والتغيرات في مستويات الكهارل بين البانتوبرازول والفاموتيدين: دراسة وصفية مستقبلية

إعداد
عامر نواف زيدان

إشراف
د. نزار سعيد

قدمت هذه الرسالة استكمالا لمتطلبات الحصول على درجة الماجستير في تمريض العناية المكثفة، من كلية الدراسات العليا، في جامعة النجاح الوطنية، نابلس– فلسطين.

2023

مقارنة الأحداث السلبية العصبية والتغيرات في مستويات الكهارل بين البانتوبرازول والفاموتيدين: دراسة وصفية مستقبلية

إعداد

عامر نواف زيدان

إشراف

د. نزار سعيد

الملخص

الخلفية: أصبحت مثبطات مضخة البروتون مؤخرًا أكثر شيوعًا في المرضى الذين يعانون من أمراض الجهاز الهضمي الوظيفية أو للوقاية الأولية من التلف المعدي الاثني عشر المرتبط بالأدوية، على الرغم من حقيقة أن فوائدها لهذه الحالات لم يتم تأكيدها بدقة. ولم يتم ربط نقص مغنسيوم الدم الشديد باستخدام مضادات مستقبلات الهستامين 2 على الرغم من دراسات الحالة التي تربط بين نقص مغنسيوم الدم واستخدام مثبطات مضخة البروتون.

الهدف: تهدف الدراسة إلى مقارنة تأثيرات بانتوبرازول وفاموتيدين على عناصر أملاح الدم والأحداث السلبية العصبية بين المرضى في وحدات العناية المركزة.

المنهجية: أجريت دراسة رقابية مستقبلية بين يوليو 2022 وديسمبر 2022، شملت 100 مريض في حالة حرجة في وحدات العناية المركزة في مستشفى الوطني (50 مريض من مجموعة بانتوبرازول و50 مريض من مجموعة فاموتيدين). وبلغ معدل الاستجابة 91.75٪. تتكون ورقة البيانات من عدة أقسام، بما في ذلك البيانات الاجتماعية الديموغرافية، والمعلومات الصحية، وبيانات حول استخدام بانتوبرازول وفاموتيدين، والنتائج السريرية، والمضاعفات العصبية، ودرجة الهذيان.

النتائج: كانت أعلى فئة عمرية لإجمالي المشاركين تزيد عن 60 عامًا (60٪)، وكان أكثر من نصف إجمالي المشاركين من الذكور (57.0٪). أشارت النتائج إلى أن النسبة المئوية لإصابة الكلى الحادة كانت أعلى في بانتوبرازول مقارنة مع فاموتيدين (38٪ مقابل 10٪ على التوالي)، وكان هذا الاختلاف ذا دلالة إحصائية (P = 0.001). أظهرت النتائج أيضًا أن نيتروجين اليوريا في الدم كان أعلى بشكل ملحوظ في حالات بانتوبرازول مقارنة بحالات فاموتيدين (40.0 ± 29.6 مقابل 27.8 ± 24.3 مجم / ديسيلتر؛ P <0.05). وبالمثل، كان الكرياتينين أعلى بشكل ملحوظ في حالات بانتوبرازول مقارنة بحالات فاموتيدين (2.2 ± 2.0 مقابل 1.5 ± 1.5 ملغ / ديسيلتر؛ P <0.05). في المقابل، كان متوسط الألبومين في حالات بانتوبرازول أقل بكثير من حالات فاموتيدين (2.8 ± 0.5 مقابل 3.1 ± 0.6 جم / ديسيلتر؛ P <0.05).

الاستنتاج: وجدت الدراسة أن مجموعة بانتوبرازول كانت مرتبطة بمستويات مرتفعة من الكرياتينين ونيتروجين اليوريا في الدم، وانخفاض مستويات الألبومين والهيماتوكريت مقارنةً بمضادات مستقبلات الهيستامين 2.

الكلمات المفتاحية: بانتوبرازول، فاموتيدين، عناصر أملاح الدم، الأحداث السلبية العصبية.