Research Article

Journal of Gastroenterology & Digestive Systems

Oral Ppi VS IV Ppi in Hospitalized Patient

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Submitted: 14 Sep 2018; **Accepted**: 24 Sep 2018; **Published**: 24 Oct 2018

Abstract

Objectives: *Of this study have been produced in order to promote effective use of proton pump inhibitors (PPIs) and (H2RAs) histamine II receptor antagonists at AL-Zahraa University Hospital (ZUH) in Lebanon.*

The aims: *Of the study are to ensure PPIs use is limited to situations where there is indicated and there is a clear evidence of benefit, in order to decrease the cost when possible without affecting the patient's clinical outcome.*

Setting: *Medical and surgical in-patients floors at AL-Zahraa University Hospital (ZUH) were used for this study, which include 57medical and 43 surgical beds.*

Methods: *In this study 100 patients files were reviewed for appropriate IVPPIs uses in two separate time intervals, over six months period started on January 1st, 2016 and ended on June 30th, 2016 and divided into two equal separate time intervals, pre implementation and post implementation of restriction dispensing policy, in order to determine the proper indication and the cost impact of restriction procedure. The main outcomes measure the cost difference between pre and post restriction periods.*

Results: *During the pre-restriction period, the majority of IVPPIs vials were dispensed to patients able to tolerate oral medications with no proper indications to IVPPIs use, the daily consumption of IVPPIs were 48 vials (960 $) in the pre-restriction period as compared to only 2 vials (40$) in the post restriction period, therefore the associated daily cost was reduced from 960$ to 40$.*

Conclusion: *This study highlighted the impact of proper use of PPIs based on implantation of the dispensing authorization restriction form of IVPPIS use which based on the international protocols for peptic ulcer drugs uses, leading to statistically significant in hospital patient's daily cost reduction by 24 folds.*

Introduction

The proton pump inhibitors, (PPIs) are a group of drugs that reduce the secretion of gastric acid, PPIs are substituted benzi-midazoles that covalently bind to the H+/K+ ATPase enzyme, selectively and irreversibly inhibiting this final step of acid secretion in a dose-dependent manner, PPIs are more potent than histamine H2-receptor antagonists (H2RAs), which only inhibit one of the pathways involved in acid secretion [1]. Proton pump inhibitors (PPIs) reduce the production of acid by blocking the enzyme in the wall of the stomach that produces acid. Acid is necessary for the formation of most ulcers in the esophagus, stomach, and duodenum, and the reduction of acid with PPIs prevent ulcers and allows any ulcers that exist in the esophagus, stomach, and duodenum to heal.

The introduction of the first proton-pump inhibitor (PPI), omeprazole, was in 1989, and followed by 5 or more PPIs, the use of Proton pump inhibitors (PPIs) has dramatically increased over the past few years. And become one of the most frequently prescribed drugs worldwide this escalation was associated with concerns of inappropriate use of this class of medications in hospitalized patients where IVPPIs are prescribed most [2].

The inappropriate use of IVPPIs can lead to increased cost burden, drug shortages, and potential adverse effects, as seen in a number of studies which showed that they are often prescribed without an appropriate indication [3]. This leads to widespread over prescription, which has financial and potentially adverse clinical consequences. The use of PPIs has been linked to Clostridium difficile infection as well as osteoporosis, risk of hip fracture and other complications [4-6].

In the light of this, PPIs prescription should be reserved for patients where there is a clear indication, and clinicians should consider stopping PPIs where the indication is unclear. There are data to support stopping PPIs in patients who have been taking them long term [7]. Proton pump inhibitors are used for the prevention and

treatment of acid-related conditions such as: duodenal stomach ulcers NSAID-associated ulcers, and Zollinger-Ellison syndrome [8]. They also are used in combination with antibiotics for eradicating Helicobacter pylori, a bacterium that together with acid causes ulcers of the stomach and duodenum [9, 10]. PPIs are much more effective than H2RAs in maintaining healing of patients with GORD. Based on 5 studies, remission rates for omeprazole (a PPI) after one year on maintenance doses were 70%, but were only 30% for ranitidine (an H2RA) [11]. PPIs are available in intravenous (IV) and oral forms (enteric-coated delayed release, microencapsulated beads in a capsule, powder or suspension), and unprotected drug with sodium bicarbonate. Currently, three IVPPIs are available in the USA (esomeprazole, pantoprazole and lanzoprazole). IV omeprazole is available in Europe and Asia. IVPPIs should be administered through a dedicated IV line and flushed with compatible solutions pre- and post-administration [12]. Intravenous (IV) proton-pump inhibitors (PPIs) are potent gastric acid suppressing agents and their use is popular in clinical practice. Both IV and oral PPIs have similarly short half-lives, and their effects on acid secretion are similar, thus their dosing and dosage intervals appear to be interchangeable. The possible exception is when sustained high pH is required to promote clot stabilization in bleeding peptic ulcers. Continuous infusion appears to be the only form of administration that reliably achieves this high target ph. IVPPIs are indicated in the treatment of high-risk peptic ulcers, complicated gastro esophageal reflux, stress-induced ulcer prophylaxis, Zollinger–Ellison syndrome (ZES), and whenever it is impossible or impractical to give oral therapy. The widespread use of PPIs has been controversial. IVPPIs have been linked to the development of nosocomial pneumonia in the intensive care setting and to spontaneous bacterial peritonitis in cirrhotic patients [13].

Currently, IVPPIs is approved by the US Food and Drug Administration (FDA) for treating patients who are unable to tolerate oral medications due to complicated erosive esophagitis, and in patients with Zollinger–Ellison syndrome (ZES) with pathological hyper secretory states. In real life practices, the use of IVPPIS is much more widespread. The decision to administer IVPPIs depends on several factors such as the ability of the patient to swallow, gastric motility, intestinal transport and permeability, and cytochrome p450 activity. These factors often come into play in critically ill patients, who may require IV PPIs either to treat acid-secreting disorders, or as prophylaxis against stress-related mucosal injury. IVPPIs play a synergistic role in the treatment of bleeding peptic ulcers requiring endoscopic hemostasis, although its cost-effectiveness requires further study. The widespread use of IVPPIs has caused controversy, this is particularly important against growing epidemiological evidence that PPI use is associated with an increased risk of Clostridium difficile infection, both in hospitals and in the community and including concern over its association with respiratory complications in the critically ill patients, and with spontaneous bacterial peritonitis (SBP) in cirrhotic patients [5]. IV PPIs have been reported to be commonly used inappropriately which, if true, represent a misuse of healthcare resources [14].

Safety issues of PPIs

PPIs have very few reported side effects. These do not appear to be an issue. The long-term consequences of their direct effects, however, are at this stage still unknown, as very few patients have taken a PPI for more than ten years. This is a short time in terms of human carcinogenesis. A standard daily oral dose of a PPI causes in most patients almost complete inhibition of acid secretion by the stomach that continues for 24 hours until the next dose under normal circumstances, neither the doctor nor the patient can measure the effect of a PPI on acidity. Hence, both are unaware of the profound changes in gastric physiology caused by this treatment, Pounder state: that this degree of drug-induced lack of gastric acidity has predictable results Such as bacterial overgrowth of the stomach and duodenum by pharyngeal and enteric organisms (15-17). This may have a mutagenic effect on the gastric mucosa, 24-hour rise of plasma gastrin [18, 19].

This may have a mitogenic effect on the growth of gut-derived tumors [20]. Proliferation of ECL cells in the gastric mucosa which may cause rebound hyper secretion of acid after stopping a PPI [21, 22]. Accelerated development of atrophic gastritis, if H. pylori positive [23]. These changes are unlikely to be obvious in routine clinical practice, but they may become important if patients continue long-term PPI therapy.

Rational and objectives of the study

The objectives of this study have been produced in order:

To promote effective use of proton pump inhibitors (PPIs) and or (H2RAs) histamine II receptor antagonists at AL-Zahraa University Hospital (ZUH) in Lebanon.

To decrease the in hospital patient's cost by using oral PPIs instead of IVPPIs whenever possible with providing the same level of care quality to those patients.

To ensure IVPPIs use is limited to situations where there is clear evidence of benefit only, and to decrease the cost when possible.

To compare current practices concerning indication of IVPPIs at AL-Zahraa University Hospital (ZUH) in Lebanon to the international standards practices and Guidelines for Prescribing Proton Pump Inhibitors (PPIs) in Adults (excluding ICU and renal unit October 2009(Appendix I).

To develop Continuous Quality improvement system in the field of clinical practices, by implement corrective actions and prove the ability of medical staff to assess their practices. This research study is interested in the cost effectiveness of IVPPIs use, in abuse and miss use of IVPPIs in the hospital, and in applying the proper use protocols of IVPPIs according to national standard of IVPPIs use in order to decrease the in hospital patient's cost.

As the cost of IVPPIs is high in comparison with oral forms, it is likely that the cost differences between oral and IVPPIs will become more significant (20$ for IV, 4 $ for oral). If we add to it, a decrease in the length of hospitalization associated with giving oral PPI post endoscopic homeostasis, or even avoiding hospitalization altogether in selected patients who can be managed in an outpatient setting.

Risk stratification tools such as the Blatchford score. Baylor was rebleeding and the Rockall scores may be valuable in determining the risk of adverse outcomes in patients with UGIH, and in turn help the decision making process of which form, and what dosage of PPI to use [24-26].

Problems statement and Research questions

The use of PPIs has dramatically increased over the past few years; this escalation was associated with concerns of inappropriate use of

this class of medications in hospitalized patients where intravenous IVPPIs are prescribed most [27]. Inappropriate use of IVPPIs can lead to increased cost burden, drug shortages and potential adverse effects [28].

Charts review during 2014 demonstrates that overuse of IVPPIs therapy is quite frequent at this institution, over 88% of adults patients in non- intensive care settings had received a PPI during their admission, with 77% receiving at least one dose by intravenous route. This leads to widespread over prescription, which has financial and potentially adverse clinical consequences this increased consumption of PPIs vials dispensed by the pharmacy department at a single teaching hospital in Lebanon raised the concern that this drug might be inappropriately used. Especially in terms of route of administration, this led us to study the proper and improper use of IVPPIs at AL-Zahraa University Hospital (ZUH). Medical and surgical floors, based on the right indications of use according to the international standards practices and Guidelines for Prescribing Proton Pump Inhibitors (PPIs) in Adults (excluding ICU and renal unit October 2009(Appendix I)In order to reach this problems statement, several research questions should be asked to the target people.

The target readers of this study will be the medical staff including, doctors, pharmacists, registered nurse and the third party payers who take care of patient's health and hospitalization costs.

These Research questions are:

RQ1: Are parenteral PPI (ampoule) more effective than oral PPI (capsules)? 70 questioners (Appendix II) were distributed to medical staff (doctors and training residents) at AL-Zahraa University Hospital (ZUH) and we received back only 55 answered questioner. The previous studies showed IVPPIs has similar safety and efficacy profiles to the oral formulation in patients with erosive esophagitis [29].

RQ2: Is there a significant price difference between the oral and IVPPIs? Which PPI formula or route is more costly? The doctors and Pharmacists answered this question (Appendix II) based on legal ministry of health pricing structures for both formula, The cost of IVPPIs was 20$ which includes the cost of the IV vial, 100 mg solution bag, 5ml syringe, IV line, angiocath and local anesthetic cream in comparison to oral PPI price which was 3 $ per capsule [30].

RQ3: which PPIs route has more side effects? The IV route has more side effects compared with oral PPIs, this include IV site phlebitis, severe allergic reactions, and possible arrhythmias if given IV push, While the Oral route is less or no side effects related to IV site, and seen in the results of the questioner (Appendix II) [31].

RQ4: which route is more time consuming (nurses interview) the IV route is more time consuming for both nurse and patient than the oral route which needs less time as mentioned in previous studies and seen in the results of the questioner (Appendix II) [32]

RQ5: Is it possible to reduce the costs if we applied oral route when possible instead of parenteral route? (Interview with the responsible pharmacists confirmed that, knowing the big price difference between the IV and oral route) [30].

RQ6: How is it important to use corrective actions (Appendix III) and applying dispensing authorization restriction form (Appendix IV) to change the IV route to oral route? Both are essential to achieve this goal.

RQ7: Is it possible to convince the doctors to use oral PPI when possible? This can be achieved by applying dispensing authorization restriction form (Appendix IV) to the parenteral PPI route, and convincing the medical staff to restrict the IVPPIs use, based on international protocols for oral PPIs use (Appendix VI) [33]

Hypothesis

The dramatic increase in IVPPIs prescribing patterns over the past several years has raised concerns relating to their appropriate utilization and associated cost [34].

To assess the appropriateness of the indication and route of administration of proton pump inhibitors(PPIs)and their associated cost impact .Many health care centers have raised concerns related to the inappropriate use of the intravenous route of administration and unsuitable indications and to a lesser extent incorrect doses and length of therapy which led to increase treatment costs [35].

The previous studies showed that there are no statistical difference between IVPPIs and oral PPIs concerning the safety and efficacy profiles, both IVPPIs and oral formulation has similar safety and efficacy in patients with erosive esophagitis [29].

A standard daily oral dose of a PPI causes in most patients almost complete inhibition of acid secretion by the stomach that continues for 24 hours until the next dose under normal circumstances, neither the doctor nor the patient can measure the effect of a PPI on acidity. Hence, both are unaware of the profound changes in gastric physiology caused by this treatment [15, 16].

There is significant statistical difference between IVPPIs and oral PPIs cost, the IVPPIs calculated cost was 20$ per ampule, which includes the cost of the IV vial, 100 mg solution bag, 5ml syringe IV line, angiocath, and local anesthetic cream in comparison to oral PPI price which was 3 $ per capsule [30]. This also confirmed in the questioner results of this study (Appendix II).

The IV route has more side effects compared with oral PPIs include IV site phlebitis, severe allergic reactions, and possible arrhythmias if given IV push, While the Oral route is less or no side effects related to IV site [36].

The IV route is more time consuming for both nurse and patient than the oral route which needs less time as mentioned in previous studies and also seen in the questioner results of this study (Appendix II) [32].

Reinforcing the appropriate utilization route of this medication can lead to significant cost reduction, and the oral forms has been associated with several advantages over the IV route including lower cost, less utilization of hospital resources, similar clinical outcomes for most indications and less IV related complications [3]. Applying a dispensing authorization restriction form (Appendix IV), which was approved by the pharmacy and therapeutic committee, and the physicians were requested to fill this form with every order for IVPPIs justifying the route of administration which made the physicians reconsider ordering the IV dosage form of this medication for their patients [33].

Methodology

The methodology used depends on the descriptive method were the content analysis and the case study (as shown below) applied using the mixed methods both qualitative and quantitative.

The qualitative is based on questioners distributed on 70 doctors at AL-Zahraa University hospital (ZUH) as purpose sample (Appendix II) also the researcher carried oral interviews with the responsible pharmacist and registered nurses at (ZUH)

The quantitative is based on secondary data from the available database of AL-Zahraa university hospital (ZUH), Using audit check list tool form (Appendix VII).

A total of 100 patients files were reviewed for appropriate IVPPIs uses in two separate time intervals, over six months period started on January 1st, 2016 and ended on June 30th, 2016 and divided into two equal separate time intervals, pre implementation and post implementation of dispensing authorization restriction form, and two audits were done in order to determine the proper indication and the cost impact of restriction procedure. The main outcomes measure the cost difference between pre and post restriction periods.

Subject: Intravenous PPI cost / indications

Audit Period: First audit was in the last week of March 2016, and the second audit was in the last week of June 2016, Using audit check list tool form. (Appendix VII). Neither the nurses nor the physicians were aware of the audit time in this study in order to minimize bias.

Auditors: All the study conducted by the project leader Dr Mahmoud Hallal.

Concerned Departments: Medical and surgical in-patients floors at AL-Zahraa University Hospital (ZUH) were used for this study, which include a total of 100 beds, 57medical and 43 surgical beds.

Progress

The first 3 months of the study was observational based on chart reviews, without intervening or application of any restriction policy, the first audit was during the last week of March 2016, a total of 100 medical records were reviewed, which were all the patients admitted to regular medico-surgical floors at AL-Zahraa University Hospital (ZUH) during this period, 57 at medical floors and 43 at surgical floors. IVPPIs were prescribed in 41of them; the main outcome measure was the appropriateness of IVPPIs use including indications, dosage, interval and duration. Additional data abstracted from the medical charts included socio-demographic characteristics (age, sex); in hospital stay data (Distribution of patients by Units, Length of stay, third party Payers.

Those patients who admitted to the intensive or cardiac care units were excluded from this study, since they are known to be higher risk patients and stress ulcer prophylaxis are frequently used in these populations; in addition they are not target of this study.

The second 3 months post restriction period was interventional using a dispensing authorization restriction form which was approved by the quality department, and a dispensing authorization restriction form (Appendix IV) was applied and the physicians were requested to fill this form with every IVPPIs order justifying the indication for this route of administration, then the clinical pharmacist reviewed this form prior to approval, and contacting the prescribing physician if further clarification was needed.

The second audit was during the last week of June 2016, a total of 100 medical records, were reviewed, which were all the patients admitted to regular medico-surgical floors at AL-Zahraa University Hospital (ZUH) during this period, 57 at medical floors and 43 at surgical floors , Those patients who admitted to the intensive or cardiac care units were excluded from this study, since they are known to be higher risk patients and stress ulcer prophylaxis are frequently used in these populations; in addition they are not target of this study, there were 22 dispensing authorization restriction forms for IVPPIs use completed by the treating physicians and only two of them were approved based on the dispensing authorization restriction form (Appendix IV) the main outcome measure was the appropriateness of IVPPIs use including indications, dosage, interval and duration. Additional data abstracted from the medical charts included socio-demographic characteristics (age, sex), in hospital stay data Distribution of patients by Units, Length of stay, third party Payers. And we calculate the total cost of IVPPIs in these two periods and compare the proper indications and the different in the cost and the clinical outcome difference if present. Statistical analysis was performed using SPSS software and the data were entered into the computer, frequencies, percentages and means were calculated.

Literatures Reviews and Overview of Previous Studies

The use of IVPPIs is perhaps best established in the treatment of complicated peptic ulcer disease, and has largely replaced the use of H2RA. A meta-analysis of 24 randomized controlled trials with 4373 patients, comparing IV or oral PPI with placebo or H2RA in bleeding peptic ulcers, reported that PPI treatment in peptic ulcer bleeding reduces rebreeding and surgery compared with placebo or H2RA, All-cause mortality was not affected [37].

Intra-Gastric Ph Studies-Oral versus Intravenous Ppi

Endoscopic hemostasis plays a pivotal role in the treatment of bleeding peptic ulcers, and although this is successful >90% of the time, rebreeding still occurs within 72 h in up to 25% of cases [38].

Several studies have looked at the efficacy of PPIs, given in a combination of oral, IV bolus (defined as administration with an IV push at regular intervals) and high dose IV continuous infusion forms (usually preceded by an 80 mg bolus IV push, followed by an infusion at 8 mg/h), in achieving and maintaining this pH target goal of >6 [39]. Theoretically, high-dose IV continuous infusion should provide the most potent acid suppression. PPIs only inhibit stimulated parietal cells with active proton pumps and this is most successfully and rapidly achieved by administering a bolus dose intravenously (providing 100% bioavailability theoretically); continuous infusion then provides a steady state of the drug to inactivate any newly synthesized proton pumps, as well as any newly recruited proton pumps on parietal cells which continue to be stimulated by gastrin, histamine and food [40]. In one study, oral and IV pantoprazole were equipotent in raising intra-gastric pH, when administered at the same dose and intervals [41].

In another intra-gastric pH study on 90 patients, who had received endoscopic therapy for a bleeding peptic ulcer, IV infusion was compared against the oral forms of omeprazole, pantoprazole and rabeprazole [42].

All groups achieved a mean 72 h intra-gastric pH of >6, and there were no significant differences between the oral and infusional IV arms of each drug. Similar results were obtained with infusional IV and oral lansoprazole, although IV lansoprazole was more rapid in raising intragastric pH initially [43].

The debate between infusional IV and oral PPI becomes more complicated when one wonders whether achieving an intra-gastric pH of >6 is truly a key variable.

Some intra-gastric pH studies reported achieving a pH of >6 less than 30% of the time with infusional IV PPI [44].

Post-endoscopic intravenous PPI

IVPPIs infusion, in combination with endoscopic hemostasis, has been shown to achieve the lowest rebleeding rates in ulcers with high risk bleeding stigmata [45]. In a landmark study by patients who underwent successful endoscopic hemostasis of peptic ulcers with high risk stigmata, were subsequently randomized to receive either 80 mg bolus of IV omeprazole followed by a continuous infusion of 8 mg/h for 72 h, or a bolus followed by a placebo infusion. Patients who received the high dose PPI infusion had significantly lower rebleeding rates, when compared to those who received a placebo (6.7% versus 22.5%, $p < 0.001$) [45]. The importance of endoscopic hemostasis, in combination with high dose IV PPI, was reinforced in a study by in which patients with ulcers with nonbreeding visible vessels and clots were randomized to infusional IV omeprazole alone, or to endoscopic hemostasis first, followed by infusional IV omeprazole [46]. Patients receiving the combination treatment had significantly lower rebleeding rates compared to those who received infusional IV omeprazole alone (1.1% versus 11.6%, $p = 0.009$). Although the use of IVPPIs post-endoscopic hemostasis has now become standard of care, The above studies have limitations of being single center reports, consisting mainly of Southeast Asians. The apparent efficacy of this approach has been challenged by studies with inconsistent conclusions in Western Europe and North America [47]. Moreover, mortality which is probably the most important clinical outcome, has never been shown to be affected by the use of IVPPIs [48]. Racial differences in genetic polymorphisms of the CYP450 system, parietal cell mass and the prevalence of Helicobacter pylori have challenged the external validity of the efficacy of high-dose infusional IVPPI. This controversy appears to have been laid to rest with a recent randomized, double-blinded, placebo-controlled trial by the Peptic Ulcer Bleed Study Group, consisting of 767 patients (mainly Caucasians) from 16 countries [49].

This study reinforced the efficacy of IVPPIs infusion post-endoscopic hemostasis (5.9% rebleeding within 72 hours in the IV esomeprazole infusion bolus group versus 10.3% in the placebo group; $p = 0.026$). The difference remained significant at 7 and 30 days, suggesting that the benefits of the drug is unlikely race-specific, and appears to be unequivocal, when compared to placebo.

The conventional dosage of infusional IVPPIs (80 mg bolus followed by 8 mg/h for 72 h), used in several studies and endorsed by consensus statements have been challenged by studies which have found no difference between high dosage and low dosage IVPPI [41, 50, 51]. Conducted a study across 11, Italian centers, and found no difference in in-hospital rebleeding and overall mortality rates, in patients who were given the conventional high dose PPI infusion, compared with those who had a standard dose of 40 mg IV daily for 72 h [52].

Pre-endoscopic intravenous PPIs

The next logical question is whether IVPPIs given pre-endoscopic ally in patients with bleeding peptic ulcers would further improve patient outcomes. First studied the pre-endoscopic use of omeprazole (IV bolus followed by intermittent IV and oral PPI) in 1992 in 1147 patients with UGIH, and reported a significant decrease in endoscopic signs of hemorrhage in patients who received omeprazole (33% omeprazole versus 45% placebo, $p = 0.0001$) [53]. Similar findings were reported in a study by which randomized 638 patients with UGIH to receiving either a high dose IV omeprazole infusion or a placebo prior to receiving an esophagogastroduodenoscopy (EGD) the following morning (54). The need for endoscopic therapy was lower in the omeprazole group compared with the placebo group (19.1% versus 28.4%, $p = 0.007$), suggesting that high dose PPI infusion may hasten the resolution of bleeding stigmata and the healing of the bleeding lesions. Patients in the omeprazole group had shorter hospital stays, but there were no differences in 30-day rebleeding rates, need for surgery, or 30-day mortality. This could possibly be attributed to the use of IVPPIs infusion post-endoscopic hemostasis, which may have reduced the rates of the aforementioned clinical outcomes to such a point, that small differences could no longer be detected even with their relatively large sample size. Although high dose IVPPIs in stable patients waiting for an esophagogastroduodenoscopy (EGD) appears to accelerate the healing of bleeding lesions and reduce the need for endoscopic therapy, it should not replace early endoscopy and prompt resuscitation, which remain vital in preventing adverse outcomes in patients with UGIH.

Cost-effectiveness of intravenous PPI in bleeding peptic ulcers

In the post-endoscopic hemostasis setting, the administration of IVPPIs has been shown to be more cost-effective than giving oral PPI, which in turn dominates over giving a placebo [42, 43]. Another single center study compared the strategies of oral and IVPPIs, in the context of performing diagnostic or therapeutic endoscopies in patients requiring hospitalization with acute peptic ulcer bleeding, and reported high dose IVPPIs with therapeutic endoscopy to be the most cost-effective approach [55]. With regard to giving IVPPIs pre-endoscopic ally, an analysis modeled on the results of the Lau et al. study concluded that the preemptive use of infusional IVPPIs is cost-effective, as it reduces the cost of the endoscopic procedure and the length of hospitalization [56].

The drug-related costs are offset by the overall savings in the management of UGIH. The same conclusion was reached in a similar study in a Canadian setting where the administration of pre-emptive IVPPIs is already common practice. The overall savings will be made even more significant as the cost of IVPPIs comes down with the introduction of its generic forms [57].

Intravenous PPI in the prevention of stress-related mucosal injury

Stress, defined as a response to the severe demands on the human body resulting in a disruption of homeostasis through physiological and psychological stimuli, and has long been recognized to cause gastric mucosal damage [58]. The pathophysiology remains poorly understood, and is thought to include the disruption of normal mucosal barrier defenses due to hypo perfusion, ischemia and

reperfusion, resultant oxidative stress, and gastric microcirculatory disturbances [58]. The prevalence of gastric lesions in critically ill patients is estimated to be 75% to 100% in the first 1–3 days of illness [59, 60]. It is estimated that up to 25% of patients in critical care will develop clinically overt bleeding (61 defined as hematemesis, melena, gross blood or 'coffee grounds' in the nasogastric tube. Clinically significant bleeding, defined as bleeding associated with hemodynamic instability or a drop in hemoglobin requiring transfusion, occurs in 3–4% of patients only [61].

The strongest risk factors associated with stress-induced ulcer bleeding are respiratory failure (odds ratio [OR] 15.6) and Coagulopathy (OR 4.3) amongst patients with one or both of these risk factors, 3.7% developed clinically important bleeding. This was associated with a mortality rate of 48.5%, compared to 9.1% in patients without gastrointestinal bleeding ($p < 0.001$). Other less significant risk factors include hypotension, sepsis, acute liver failure, chronic renal failure, prolonged nasogastric tube placement and alcoholism [62, 63].

This suggests that an initial 80 mg every 8 or 12 h for the first 24 h, followed by 40 mg every 12 h from the second day onwards, may obtain the best acid suppressing results [64]. However, it is not clear if high-level acid suppression is truly required, and the benefits must be weighed against the possible complications and side effects of administering IV PPI.

It is well established that PPI therapy is one of the most effective therapies available for healing erosive esophagitis [65, 66]. Although it is uncommon for this condition to cause death, when severe enough, it is associated with significant morbidity such as bleeding ulcers, strictures and malignancy. It can also occasionally cause a patient significant dysphagia and odynophagia. IVPPIs therapy in these settings may be useful.

With regard to the potency in suppressing gastric acid, there appears to be little difference between oral and IV PPIs and the decision to administer IV bolus PPI probably rests on a patient's ability to swallow oral PPIs [67-69].

Pattern of Intravenous PPIs Use in ICU and Non-ICU Setting: A Prospective Observational Study

Background/Aim: The use of intravenous acid-suppressive therapy for stress ulcer prophylaxis in critically ill patients with specific risk factors has been recommended for over a decade. However, there is a lack of supporting data regarding the extension of such therapy to non-critically ill patients (non-ICU). The aim of this study was to compare appropriate indications with current practicing patterns in adult non-ICU and ICU patients, contributing factors and financial impact of inappropriate use [70].

Materials and Methods: A prospective cross-sectional study was carried out at a tertiary teaching Hospital in Riyadh, Saudi Arabia. For a period of 4 consecutive months, all hospitalized patients on IV PPIs, aged 18 and above, were identified. A concise listing of indications considered appropriate for the use of IV PPIs was pre-defined based on material from available literature and guidelines.

Results: A total of 255 patients received IV PPI. Inappropriate use of IV PPI was significantly higher in non-ICU (71.7%) than in ICU (19.8%) patients (P=0.01). The most common cause for inappropriate use in non-ICU patients was stress ulcer prophylaxis (SUP). In ICU patients, appropriate indicators for IV PPI were SUP (47.9%), PUD (11.5%), and the UGIB (20.8%). There was a high association between appropriate uses of IV PPI with respect to endoscopic procedure and also between appropriate uses of IV PPIs to subsequent discharge with oral PPI in non-ICU patients. The total estimated direct cost (drug acquisition cost) for inappropriate use of IV PPIs, during the study period was 11,000 US dollars.

Conclusion: Inappropriate IV PPIs utilization was predominant in non-ICU patients, mostly for stress ulcer prophylaxis that leads to a waste of resources.

Applying appropriate policies, procedures and evidence-based guidelines, educated physicians and surgeons can clearly limit inappropriate IV PPIs use.

Clinical and cost impact of intravenous proton pump inhibitor use in non-ICU patients

Abstract

Aim: To assess the appropriateness of the indication and route of administration of proton-pump-inhibitors (PPIs) and their associated cost impact [71].

Methods: Data collection was performed prospectively during a 6-mo period on 340 patients who received omeprazole intravenously during their hospital stay in non-intensive care floors. Updated guidelines were used to assess the appropriateness of the indication and route of administration.

Results: Complete data collection was available for 286 patients which were used to assess intravenous (IV) PPIs utilization. Around 88% of patients were receiving PPIs for claimed stress ulcer prophylaxis (SUP) indication; of which, only 17% met the guideline

Criteria for SUP indication, 14% met the criteria for non-steroidal-anti-inflammatory drugs-induced ulcer prophylaxis, while the remaining 69% were identified as having an unjustified indication for PPI use. The initiation of IV PPIs was appropriate in 55% of patients. Half of these patients were candidates for switching to the oral dosage form during their hospitalization, while only 36.7% of these patients were actually switched. The inappropriate initiation of PPIs via the IV route was more likely to take place on the, Medical floor than the surgical floor (53% vs. 36%, P = 0.003). The cost analysis associated with the appropriateness of the indication for PPI use as well as the route of administration of PPI revealed a possible saving of up to $17 732.5 and $14 571, respectively.

Conclusion: This study highlights the over-utilization of IV PPIs in non-intensive care unit patients. Restriction of IV PPIs use for justified indications and route of administration is recommended.

Outlines of study and the field work

In order to satisfy objectives of the study the research was divided into introduction and four chapters, the introduction describe the PPIs molecule discovery, indication for uses, side effects, the cost burden and the reason why we choose this study.

Chapter I include the literature reviews, articles and previous national and international studies related to this study.

Chapter II describes the outlines and the field work of the study describing the characteristic of Al-Zahraa university hospital (ZUH).

Chapter III contains all the results both qualitative and quantitative results, statistical analysis in tables and figures in addition to conclusions.

Chapter IV mentioned the study limitations, suggestions, recommendations and corrective actions.

The space of research was at AL-Zahraa university hospital (ZUH) in Beirut, Lebanon, medical and surgical floors excluding the cardiac and intensive care units, knowing that AL-Zahra university hospital (ZUH) is a general teaching hospital in Beirut area established in 1975, and attracts patients from all over the country (Lebanon territory).

AL-Zahraa university hospital (ZUH) consists of 220 beds distributed as medical, surgical, pediatric, (ICU) intensive care unit, (CCU) coronary care unit, obstetrics and gynecology floors in addition to outpatients and paramedical departments laboratory, radiology, pathology, emergency, GI endoscopy, chemotherapy, operating rooms and other hospital related departments.

The research time period is conducted over 6 months started on Jan, 1st, 2016 and ended on June 30th, 2016 and divided in two equal separate time intervals, the pre restriction period was the first 3 months and the post restriction period was the second 3 months after implementation of dispensing authorization restriction form (Appendix IV) and used to determine cost impact of this study. The main outcome measures were the cost difference between pre and post restriction periods.

Results and Recommendations

The data were collected from the answered questioners (Appendix II) and from the first and second audit (audit tools, Appendix VII), statistical analysis was performed using SPSS software, and the data were entered into the computer, frequencies, percentages and means were calculated.

Data from the 55 questioner answers were analyzed and we compare these results with the results in literature reviews and it was as fellows

Table 1: Demographic data of the doctors who answered the questioner

Age (In years)	Frequency	Percent
<35	15	27.27
36-45	10	18.18
46-55	26	47.27
>55	4	7.27
Total	55	100.00

The ages of answered doctors were distributed as mentioned above in table 1 and 47.27% of them were between the age of 46-55 yrs.

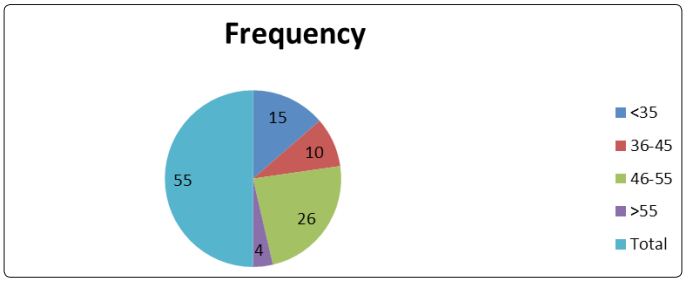

Figure 1: Demographic data of the doctors who answered the questioner

Table 2: Gender of the doctors who answered the questioner

Sex	Frequency	Percent
Female	22	40.00
Male	33	60.00
Total	55	100.00

60 % of the answered doctors were male and 40 % were female doctors.

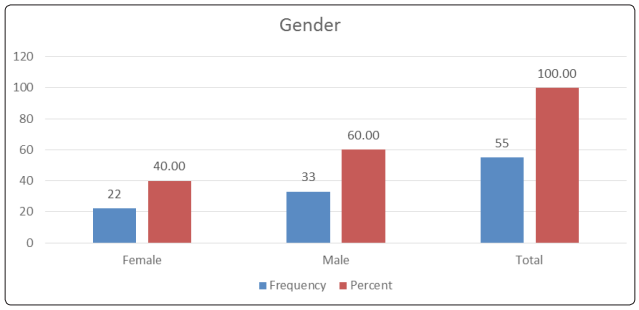

Figure 2: Gender of the doctors who answered the questioner

Table 3: Rank of the doctors who answered the questioner per level of education

Doctor Rank	Frequency	percent
Resident	15	27.27
General practitioner	4	7.27
specialized doctor	36	65.45
Total	55	100.00

Total of 15 training residents, 4 general practitioner and 36 specialized doctors were answered the questioner, the specialized doctor were equal to 65% of the answered doctors.

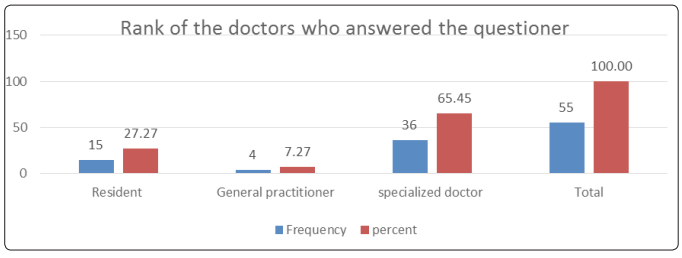

Figure 3: Rank of the doctors who answered the questioner

Table 4: the efficacy of IVPPIs compared with oral PPIs

IV PPIs efficacy	Frequency	percent
more effective than oral PPIs	32	58.18
same effects as oral PPIs	20	36.36
less effective than oral PPIs	3	5.45
Total	55	100.00

A total of 58.18 % doctors believe that IVPPIs is more effective than oral, in contrast to the previous studies which showed no difference in efficacy ,(29) Schneider H, Van rensburgC ,Schmidt S, et al.Digestion,2004:70:250-6).

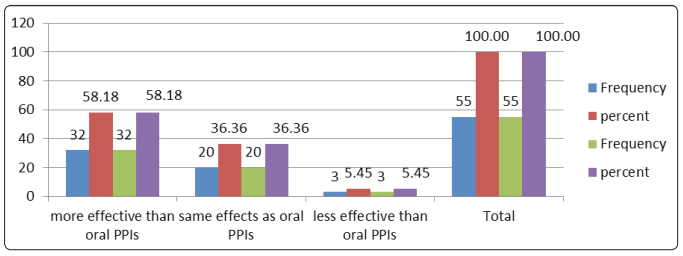

Figure 4: The efficacy of IVPPIs compared with oral PPIs

Table 5: The cost of IVPPIs compared with oral PPIs

IVPPIs Cost	Frequency	Percent
More expensive than oral PPIs	48	87.27
same price as oral PPIs	6	10.91
Less expensive than oral PPIs	1	1.82
Total	55	100.00

Most of the doctors (87.27%) answered that IVPPIs is more expensive than oral which is true as seen in other studies.

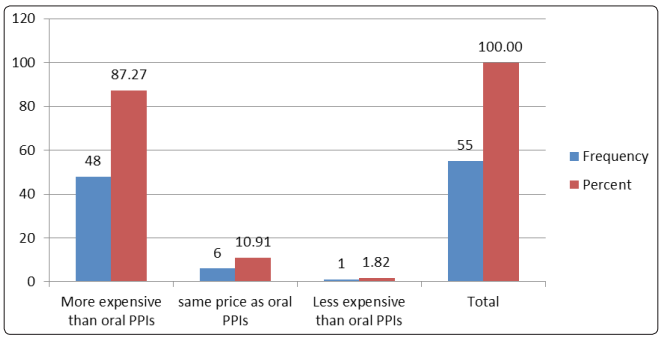

Figure 5: The cost of IVPPIs compared with oral PPIs

Most of the doctors (63.64%) answered that IVPPIs has more side effects when compared with oral PPIs, which is true as seen in other studies.

Table 6: The side effects of IVPPIs compared with oral PPIs

IV PPIs side effects	Frequency	Percent
More side effects than oral PPIs	35	63.64
same side effects as oral PPIs	15	27.27
Less side effects than oral PPIs	5	9.09
Total	55	100.00

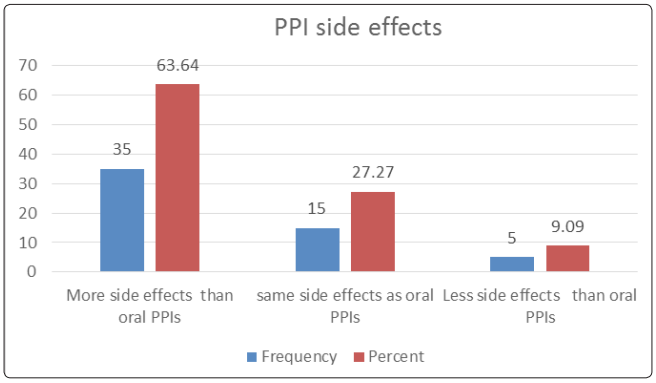

Figure 6: The side effects of IVPPIs compared with oral PPIs

49 % of the answering doctors released that IVPPIs is more time consuming than oral PPIs.

Table 7: The time difference when using IVPPIs compared with oral PPIs

Time consuming when using IVPPIs	Frequency	Percent
More time consuming than oral PPIs	27	49
No time difference	11	20
Less time consuming than oral PPIs	17	31
Total	55	100

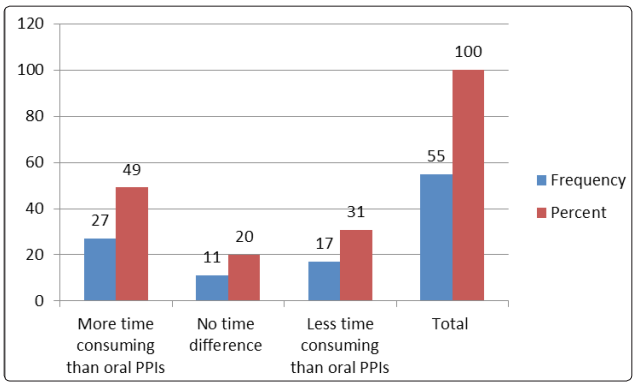

Figure 7: The time difference when using IVPPIs compared with oral PPIs

The answers distributed as follow 43 % agree with uses of the dispensing authorization restriction form of IVPPIs use, while 29% didn't agree with and 27 % didn't know the answer.

Table 8: The dispensing authorization restriction form of IVPPIs use

Using restriction form for IVPPIs	Frequency	Percent
Do you agree with it	24	43.64
I don't know the answer	15	27.27
I don't agree with it	16	29.09
Total	55	100.00

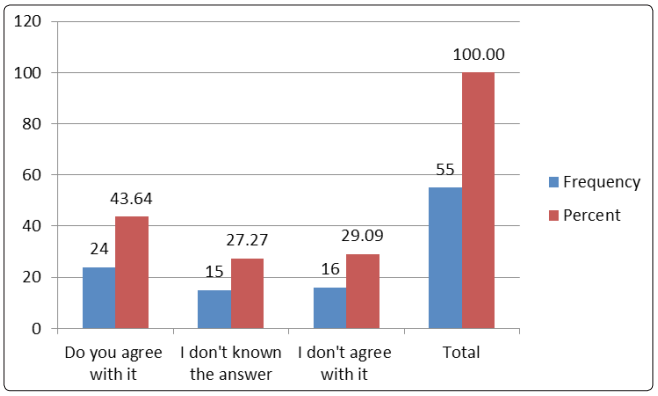

Figure 8: The IVPPIs use restriction policy applications

The data from first audit showed: that 41patients were using IVPPIs and zero patient was taking oral PPIs, total numbers of ampoule used for those patients as seen in the (Table19) and it was 48 ampoules per day, the total daily cost was 960 $ and the total cost based on long of stay of these 41 patients were 5000 $ as seen in the (Table 20).

We apply the dispensing authorization restriction form of IVPPIs use (Appendix IV) after completion and diffusing of the guidelines to all the active physicians at (ZUH) regarding indications of Intravenous PPI, (Appendix V).

During the last week of June 2016, second audit done and a total of 100 medical records were reviewed, at AL-Zahraa University Hospital (ZUH) 57 at medical floors and 43 at surgical floors. Only 2 patients of them IVPPIs were used due to applying the dispensing authorization restriction form, the main outcome measure was the appropriateness of IVPPIs use including indications, dosage, interval and duration. Additional data abstracted from the medical charts included socio-demographic characteristics (age, sex); in hospital stay data (Distribution of patients by Units, Length of stay, third party Payers (Table 13).

We calculate the total cost of IVPPIs in the 2 patients ,numbers of ampoule used for those patients, it was 2 ampoules per day, total daily cost was 40$ (Table 31), and the total cost based on long of stay of these 2 patients were 200$ as seen in the (Table 32).

We compare the difference between the two audit (pre and post) and calculate the expense daily reduction, which was highly significant and count for 920$ per day (960-40=920 $) which is 24 folds reductions.

The First Audit Findings

Which was done during the last week of March 2016?

Table 9: First audit demographic data, age of the patients

Age (In years)	Frequency	Percent
<25	2	4.9
26-40	5	12.2
41-65	11	24.4
>65	23	53.7
Total	41	100.0

Most of the patients (53.7%) were older than 65 yrs of age which indicate the higher admission rate of old patient in comparison to young patient at Al-Zahraa university hospital.

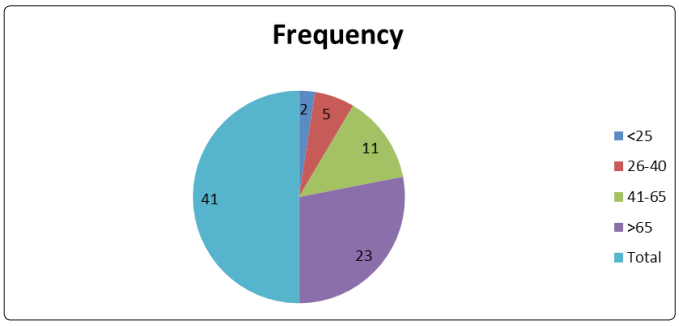

Figure 9: First audit demographic data, age of the patients

Table 10: First audit Patient gender:

51 % of the patients were male and 49 % were female

Sex	Frequency	Percent
Female	20	48.78
Male	21	51.22
Total	41	100

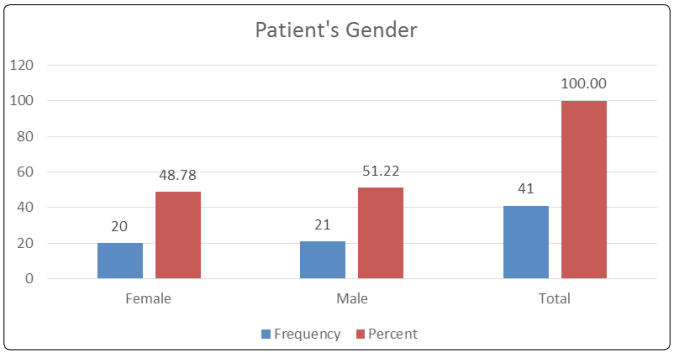

Figure 10: First audit Patient gender

Table 11: In hospital stay data Distribution of patients by Units

Unit	Frequency	percent
MED A	5	12.20
MED B	10	24.39
SURG A	6	14.63
SURG B	9	21.95
Private	11	26.83
Total	41	100.00

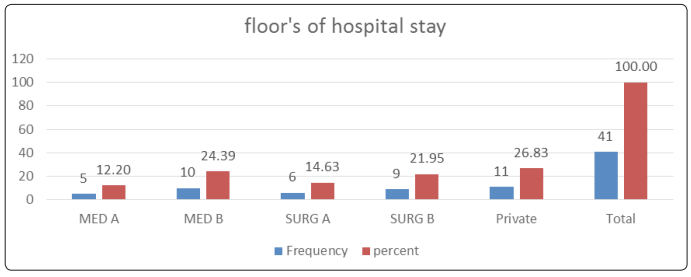

Figure 11: In hospital floor Distribution of patients by Units

Table 12: Patient's length of stay in the hospital:
where distributed only 17% stay for 48 hours , 41.46% more than 2 days and less than one week and the 41.46 % more than one week

Length of Stay	Frequency	percent
less than or equal 48 hours	7	17.07
more than 2 and less than 7 days	17	41.46
equal or more than 7 days	17	41.46
Total	41	100.00

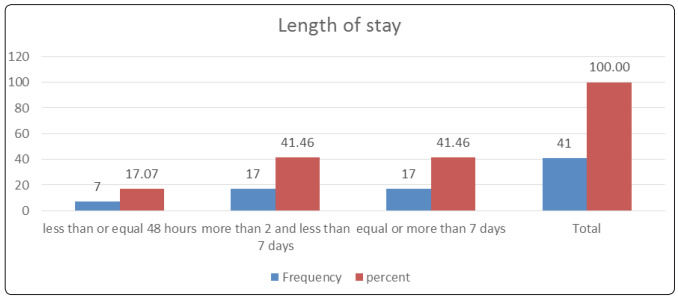

Figure 12: Patient's length of stay in the hospital

Table 13: Patient's third party Payers:
Most of the patients 41.5% were financially covered by cassee national social security (CNSS).

Third party payer	Frequency	Percent
MOH	4	9.8
CNSS	17	41.5
COOP	5	12.2
Lebanese Army	8	19.5
ISF	1	2.4
SELF	3	7.3
MUNICIPALITY of BEIRUT	2	4.9
OTHER	1	2.4
Total	41	100

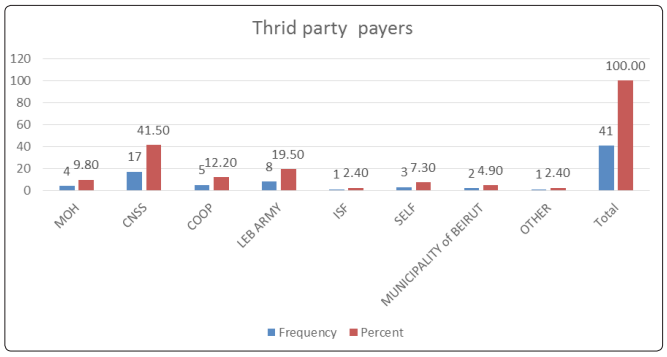

Figure 13: Patient's third party Payers

Table 14: PPI Prescription data:
Details on IVPPIs use is described in the following table as fellow 63.4 % of them were using generic molecules Risek and 36.6 using the brand molecules Nexium and 40mg doses were used in all patients.

Molecule Prescribed	Frequency	Percent
RISEK	26	63.40
NEXIUM	15	36.60
Total	41	100.00

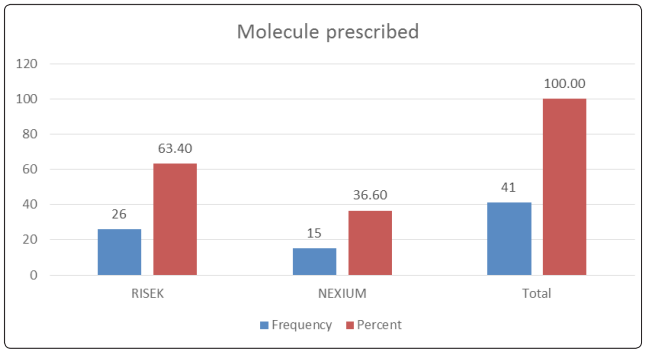

Figure 14: PPI molecules Prescribed

Table 15: PPI dosage used
40mg doses were used in all patients.

Dosage	Frequency	Percent
40 mg	41	100

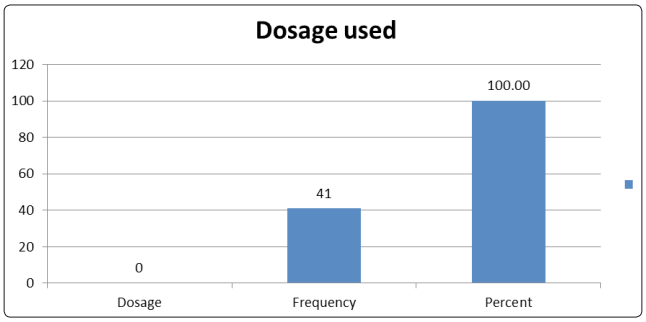

Figure 15: PPI dosage used

Table 16: PPI dosage interval
In 82.9 % of cases PPI was given once per 24 hours and only 17.1% was given once per 12 hours.

Interval	Frequency	Percent
24 hours	34	82.90
12 hours	7	17.10
Total	41	100.00

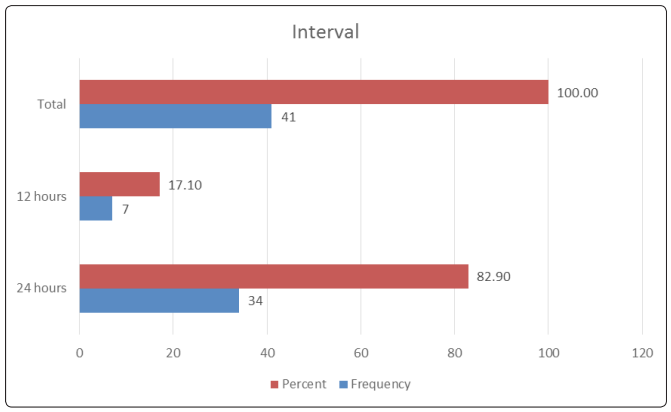

Figure 16: PPI dosage intervals

Table 17: PPI dosage duration

Only 7 patients (17.07 %) received PPIs for 48 hours, 17 patients (41.46%) received more than 2 days and less than one week and 17 patients (41.46%) received for more than one week.

INTERVAL DURATION	24 HOURS (ONCE DAILY)	12 HOURS TWICE DAILY	TOTAL	Percentage
less than or equal 48 hours	0	7	7	17.08%
More than 2 and less than 7 days	17	0	17	41.46%
Equal or more than one week	17	0	17	41.46%
Total	34	7	41	100%

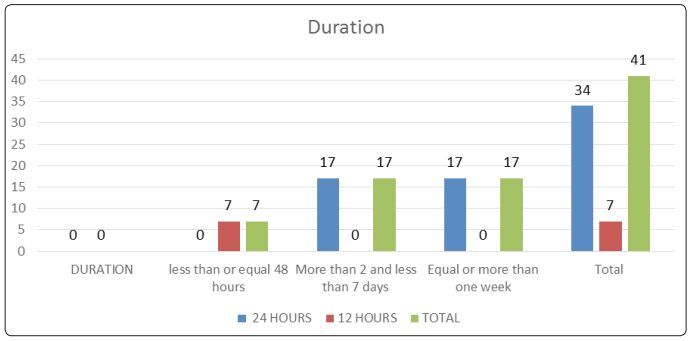

Figure 17: PPI dosage duration

Results of the first audit:

Careful data analysis showed that in only 7.3% of cases (3/41), IV PPIs were used with a proper indication, one of them duration and dosage were not appropriate.

Table 18: PPI usage indications and compliance

COMPLIANCE (N=41)	Frequency	Percent
Indications	3	7.3
Duration	2	4.9
Interval	2	4.9
Overall	2	4.9

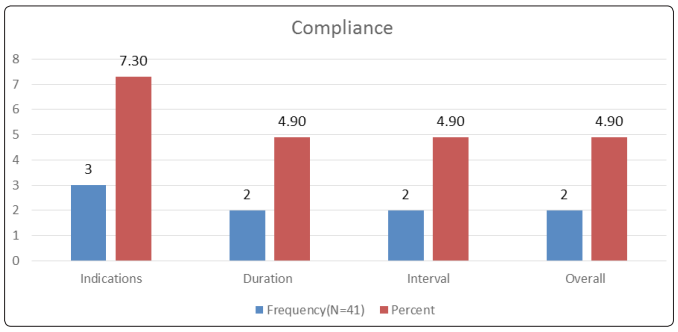

Figure 18: PPI usage indications and compliance

Table 19: IV PPIs daily cost in the first audit

Number of patient	Ampule /day	Daily cost /$
2	4	80
5	10	200
10	10	200
7	7	140
12	12	240
5	5	100
41	48	960

A total of 48 ampoules of PPI were used per day and the daily cost were 960 $.

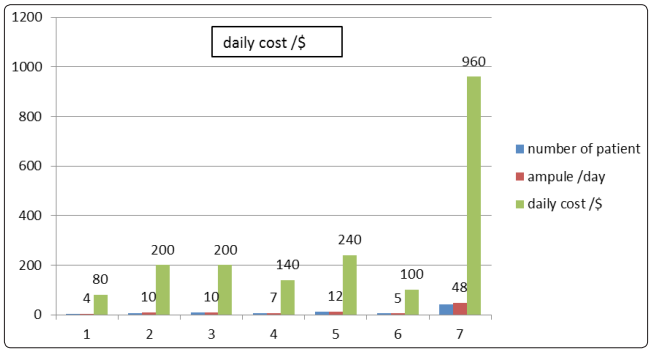

Figure 19: IV PPIs daily cost in the first audit

Table 20: The first audit total PPIs cost /ampoules used

A total of 250 ampoules of PPIs were used which account for a cost of 5000 $

Number of patient	Long of stays (days)	Total ampules	Total cost $
2	1	4	80.00
5	2	20	400.00
10	4	40	800.00
7	6	42	840.00
12	7	84	1680.00
5	12	60	1200.00
41		250	5000.00

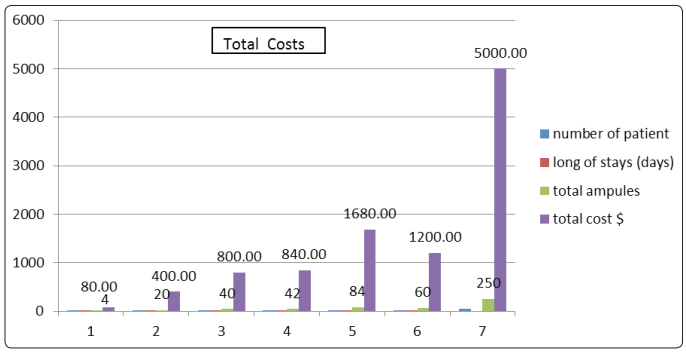

Figure 20: The total PPIs cost /ampoules used

The second audit finding:
Which was done during the last week of June 2016?

Table 21: second audit demographic data, age of the patients:

Age (In years)	Frequency	Percent
41-65	1	50
>65	1	50
Total	2	100

50% of patients were younger than 65 yrs of age the other 50% were older than 65 yrs of age.

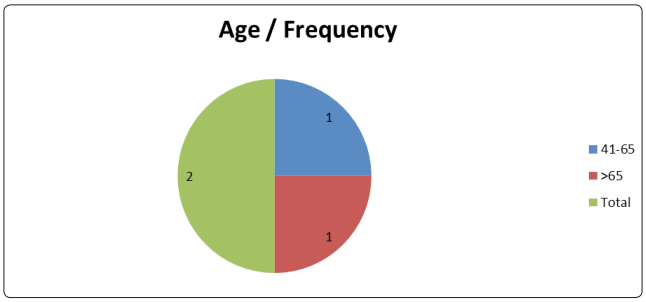

Figure 21: second audit demographic data, age of the patients

Table 22: patient's gender in the second audit

50% of patients were female and the other 50% were male.

Sex	Frequency	Percent
Female	1	50
Male	1	50
Total	2	100

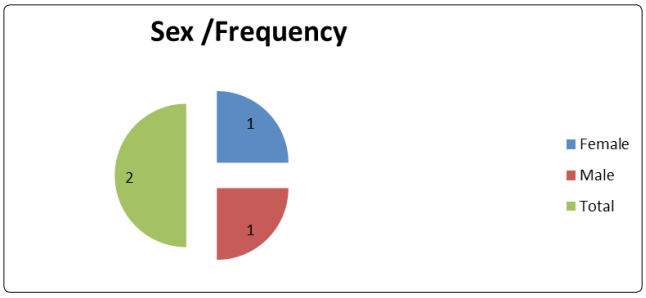

Figure 22: Patient's gender in the second audit

Table 23: In hospital stay data Distribution of patients by Units

In the second audit the in hospital stay data Distribution of patients by Units, were one patient was at medical floor and the other patient as surgical floor.

Unit	Frequency	Percent
MED B	1	50
SURG A	1	50
Total	2	100

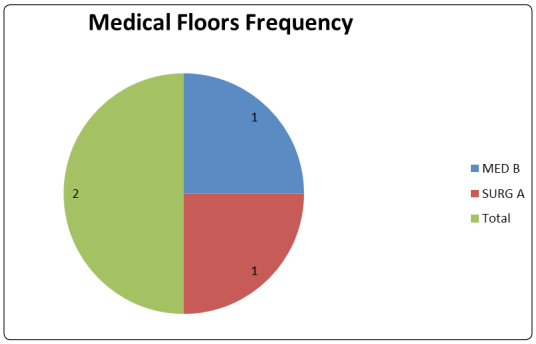

Figure 23: In hospital stay data Distribution of patients by Units

Table 24: Second audit patient's length of stay in the hospital

All patients stayed equal or more than 5 days

Length of Stay	Frequency	Percent
less than or equal 48 hours	0	0
more than 2 and less than 5 days	0	0
equal or more than 5 days	2	100
Total	2	100.0%

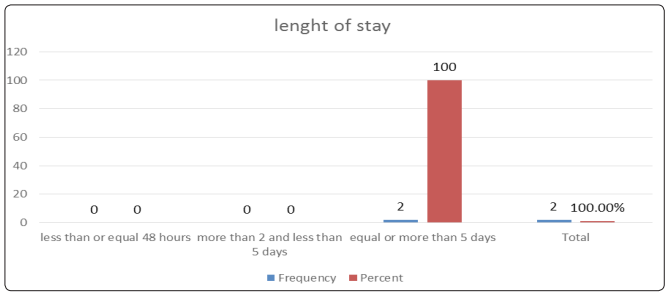

Figure 24: Second audit patient's length of stay in the hospital

Table 25: second audit's PPI Prescription data:

Details on IVPPIs use is described as fellow, Risek and Nexium were equally used in these two cases

Molecule Prescribed	Frequency	Percent
RISEK	1	50
NEXIUM	1	50
Total	2	100

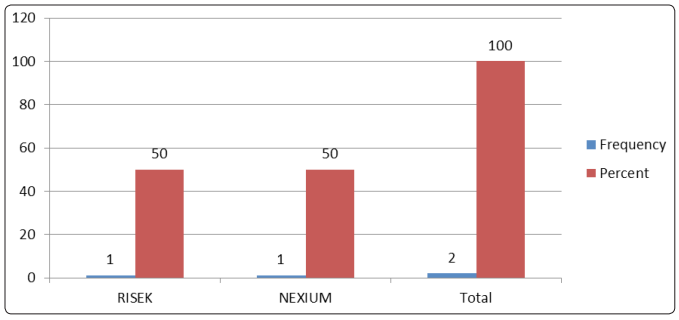

Figure 25: Second audit's PPI Prescription data

Table 26: PPI dosage used in second audit
40mg doses were used in all patients either as Risek or Nexium

Dosage	Frequency	Percent
40 mg	2	100

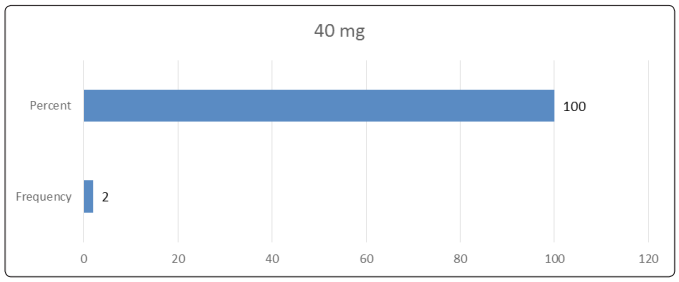

Figure 26: PPI dosage used in second audit

Table 27: Second audit's PPI dosage interval
In 100 % of cases PPI was given once daily (one ampoule per 24 hours)

Interval	Frequency	Percent
24 hours	2	100
12 hours	0	0
Total	2	100

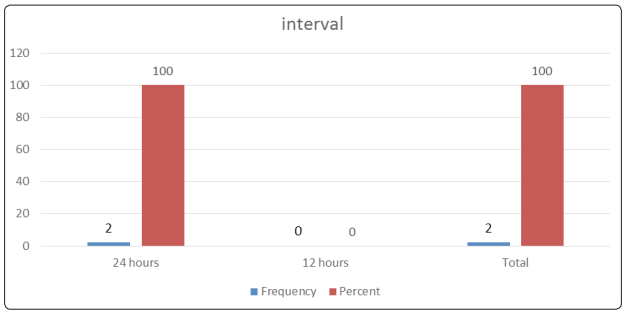

Figure 27: Second audit's PPI dosage interval

Table 28: Second audit's PPI dosage duration
The all patients were given IVPPIS for 5 days duration.

Duration	Frequency	Percent
less than or equal 48 hours	0	0
more than 2 and less than 5 days	0	0
equal or more than 5 days	2	100

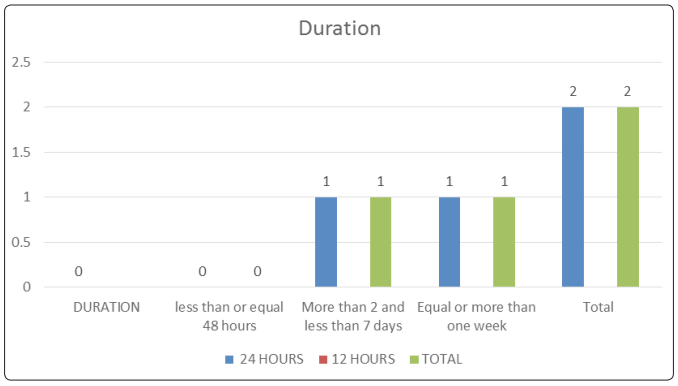

Figure 28: Second audit's PPI dosage duration

Table 29: Second audit's PPI usage indications and compliance
Both patients were 100 % compliant and with proper indication.

COMPLIANCE (N=2)	Frequency	Percent
Indications	2	10.0
Duration	2	10.0
Interval	2	10.0
Overall	2	10.0

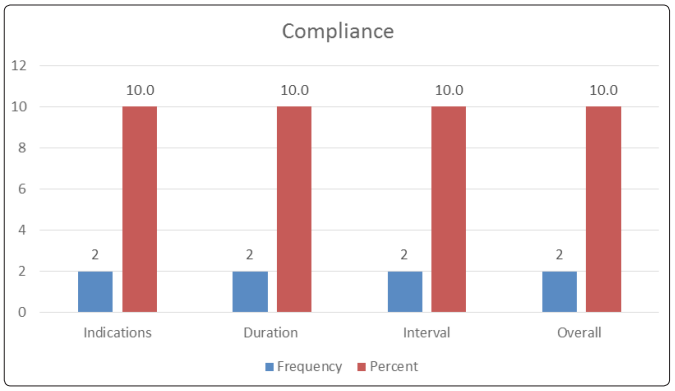

Figure 29: Second audit's PPI usage indications and compliance

Results of second audit:

Data analysis showed that in all 100 % of cases (2/2) Intravenous Proton-pump inhibitors (PPIs) were indicated,

Table 30: The first and second audit's PPI usage indications, duration, and interval

COMPLIANCE (%)	1st audit (N=41)	2nd audit (N=50)
Indications	7.3	10.0
Duration	4.9	10.0
Interval	4.9	10.0
Overall	4.9	10.0

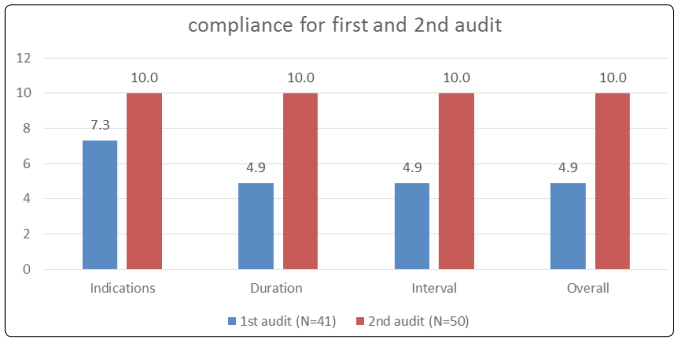

Figure 30: The first and second audit's PPI usage indications, duration, and interval

Table 31: IV PPIs daily cost in the second audit
A total of 2 ampoules of PPI were used per day and the daily cost were 40 $.

Number of patient	Ampule /day	Daily cost /$
1	1	20
1	1	20
total 2	2	40

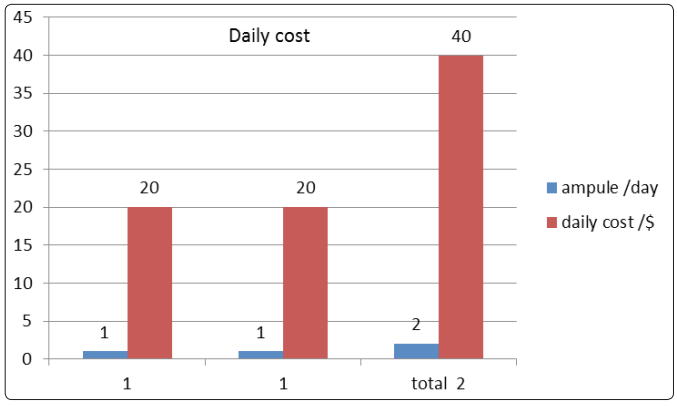

Figure 31: IV PPIs daily cost in the second audit

Table 32: IV PPIs total cost in the second audit
A total of 10 ampoules of PPIs were used in the post restriction period, which account for a total cost of 200 $ only.

number of patient	long of stays (days)	total ampules	total cost $
1	5	5	100.00
1	5	5	100.00
total		10	200.00

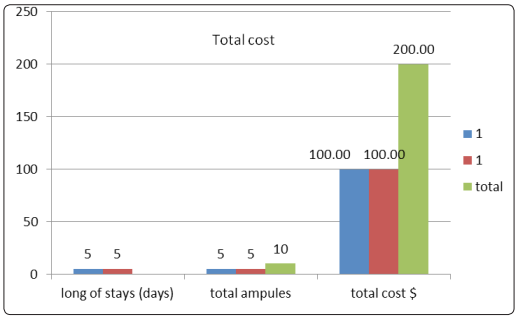

Figure 32: IV PPIs total cost in the second audit

Table 33: The first and second audit's IVPPIs cost difference.
There were statistically cost difference in the daily consumption of IVPPIs were 48 vials (960$) in the pre-restriction period as compared to only 2 vials (40$) in the post restriction period, therefore the associated daily cost was reduced from 960$ to 40$ and the total cost also reduced from 5000$ to 200$.

	daily ampoule used	total ampoule used	daily cost $	total cost $
1st audit (N=41)	48	250	960	5000
2nd audit (N=2)	2	10	40	200

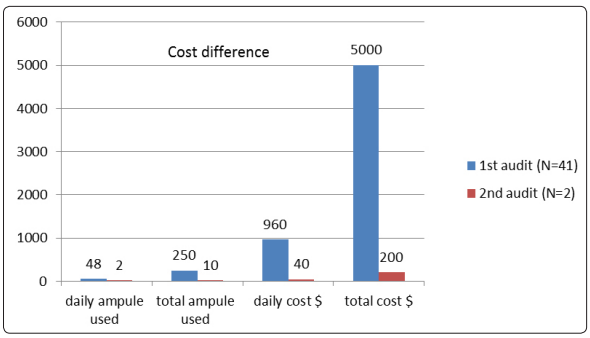

Figure 33: The first and second audit's IVPPIs cost difference

Conclusion and Recommendations

Proton-pump inhibitors (PPIs) remain the leading evidence-based therapy for upper gastrointestinal disorders, including gastro esophageal reflux disease (GERD), dyspepsia, and peptic ulcer disease [72]. The effectiveness of PPIs has led to overutilization in multiple treatment arenas, exposing patients to an increasing number of potential risks. Our data showed a high frequency of unnecessary use of Intravenous proton Pump inhibitors in hospitalized non-critically ill patients and highlight the high cost expenditure during the first period of the study. Potential consequences of prolonged PPI therapy include hypergastrinemia, enterochromaffin-like cell hyperplasia, and parietal cell hypertrophy, leading to rebound acid hyper secretion. PPIs have been linked to increased risk of enteric infections including Clostridium difficile-associated diarrhea, community-acquired pneumonia, bone fracture, [73, 74].nutritional deficiencies, and interference with metabolism of antiplatelet agents. Reducing inappropriate prescribing of IV PPIs can minimize potential for adverse events, and foster controllable cost expenditure. Improving prescribing awareness through educational interventions to promote evidence-based practice during residency training education and a more active involvement of clinical pharmacist Frequent review of therapy and improved communications between physicians, residents and clinical pharmacist were vital to rationalize and effectively reduced the inappropriate use of IVPPIs and reduced expenditure as seen in the data of second period of our study. The results of our audit highlight the effectiveness of interventions, including dispensing authorization restriction form application, implementation of institutional protocols and prescriber education. And when PPIs were used for the appropriate indications and by correct route of administration as seen in the second period of the study at least 920$ could have been saved daily, the results of this study are comparable with several trials made in Europe, UK, USA, Canada and Asia, that discussed the inappropriate use of IVPPIs in several institutions [75, 76].

Recommendations

With regard to the limitations of this study, the study was observational and conducted in a single academic medical center in Lebanon; in addition, there are no applied current established guidelines for the appropriate use of IVPPIs in AL-Zahraa university hospital (ZUH) at the time of the study, to evaluate their actual use.

This study highlights the over utilization of PPIs via the intravenous (IV) route of administration and for claimed indications which results in increased cost to the patients, institution and third party payers.

Improving the prescribing patterns requires the hospital pharmacy and therapeutics committee to establish guidelines with input from gastroenterologists on the proper indications for IVPPIs.

Criteria for switching dosing and duration of therapy, implementation of these guidelines require multidisciplinary involvement and education of health care professional (doctors, nurses) concerning the proper and appropriate use of this class of medication in order to reduce the side effects of this route of administration and ultimately decrease the improper high cost.

Other approaches include creating and applying an IV order template, clinical pharmacists reviewing orders before dispensing to patients and automatic switching to oral form when possible based on the hospital guidelines.

Plan & Corrective Actions

The following action plan was initiated to minimize these deficiencies:

Action	Responsibility	Expected date
Conference about indications of IV PPI	Project leader Dr Mahmoud Hallal	The last Monday of March 2016
First audit on the indications of IV PPI	Project team	The last week of March 2016
Revision of the guidelines in order to simplify instructions.	Project team	March 2016
Prepare dispensing authorization restriction form for IVPPIs in non-critically ill patients.	Project leader Dr Mahmoud Hallal	March 2016
Distribute simplified guidelines to GI staff and Heads of Medical and surgical divisions.	Project leader Dr Mahmoud Hallal	The last week of March 2016
Diffusion of the checklist and dispensing authorization restriction forms to the medical and surgical floors (should be filled by physicians or residents)	Nursing staff	Starting April 1st 2016
Apply the dispensing authorization restriction forms for IVPPIs	Clinical Pharmacist	Starting April1st 2016
Second audit on the indications of IV PPI	Project team	Last week in June 2016

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