Cost Effectiveness Analysis of Treatment with and Parenteral Oral Proton Pump Inhibitor for Handling Upper GastroIntestinal Bleeding (UGIB) in Adults in Ecuador

Paul Abarca E[3]*, Sofia Ramos[2], Abarca Alejandra[2], Carlonina del Salto[1], Enrique Carrera[1], Jasoom Abarca[1], Isabel Guamán[1], Steven Changoluisa[1], Nestor Basantes[1], Verónica Ayala Ventura[1], Roberto Barreno[1], Wendy Calderon[1] and Gustavo Ayala[1]

[1]*Gastroenterology Specialist, Quito, Ecuador*
[2]*Medical Doctor Specialist, Hospital Nutrition, Ecuador*
[3]*Medical Specialist in Internal Medicine, Gastroenterologist Endoscopist, Health Economist, Pharmacist Economist, Ecuador*

*Corresponding Author: Paul Abarca E, Medical Specialist in Internal Medicine, Gastroenterologist Endoscopist, Health Economist, Pharmacist Economist, Ecuador.

Abstract

The upper gastrointestinal bleeding is a complex and sometimes fatal disease. The prognosis depends largely on the risk of re bleeding. The use of proton-pump inhibitor in continuous, Continuous infusion, high intravenous intermitent dose and oral ingestion are the current options for the clinical management. The purpose of this paper is to analyze the most cost-effective alternative, so an analysis through a decision tree was made and the cost effectiveness of each option was evaluated. The intermittent Intravenous omeprazole is the most cost-effective option compared with alternative solutions for the Ecuadorian public health system.

Keywords: Omeprazole; Gastrointestinal Bleeding, Ecuador

Background

Upper gastrointestinal bleeding (UGIB) in Ecuador is a permanent problem in the second and third level hospitals of the National Public Health System, with a total of 1482 admissions in 2012, 1458 Discharges 24 deaths attributed to This cause, resulting in a case-fatality rate of 1.62 for every 100 earned income [1].

Although management protocols have been validated in several national hospitals in recent years, it is well known in international management guidelines that one of the first lines in the pharmacological approach is proton pump inhibitors (PPIs) to decrease the risk of re bleeding [2-5].

The use of PPIs in the clinical management of Upper gastrointestinal bleeding (UGIB) is broad. The selective inhibition of the proton pump prevents an initial lesion that has bleeding to trigger a new episode due to its direct exposure to acid and alteration of local hemostasis. There are studies that indicate the usefulness of PPIs before or after endoscopic management, indicating that their cost has a low impact compared to the total costs of the patient [6].

Lately several papers have been presented that talk about the adverse effects of PPIs, reason why even its chronic use has been restricted. These adverse effects have been linked more by long-term and indiscriminate use than by use in acute situations such as bleeding. Dementia, nosocomial infections, Clostridium difficile infection, acute myocardial infarction and kidney injury, among others, are the most worrisome but rarely investigated adverse effects [7-9].

PPI therapy is not only used for the management of acute presentation, but also as prophylaxis for bleeding in high risk patients [10].

Cost Effectiveness Analysis of Treatment with and Parenteral Oral Proton Pump Inhibitor for Handling Upper GastroIntestinal Bleeding (UGIB) in Adults in Ecuador

637

Despite knowing its usefulness in the management of upper gastrointestinal bleeding, it should be Clarified that its use should be limited to the management or prevention of bleeding (on the Treitz angle) because when we talk about the midgut it has been shown to be deleterious for the intestinal mucosa and even more so when they are used with NSAIDs, which is why the PPI was started [11].

In Ecuador, several types of PPI are available, including omeprazole, esomeprazole pantoprazole, dexlansoprazole etc. The national health system has established Omeprazol as the only PPI for in-hospital management both enterally and parenterally [12].

Despite this consensus in management, the health system purchases medicines from different laboratories, which fluctuate significantly in prices up to 500% depending on their presentation or distribution [13].

Currently in Ecuador, two types of therapies are used for the management of patients with high acute digestive bleeding. The first involves the infusion of omeprazole at doses of 8 mg/h for 72h followed by oral therapy in high doses, 40 mg every 12h, to complete 30 days, as a cut for prognostic assessment. Another of the therapeutic options used in the country without distinction is the use of omeprazole parenterally, but in intermittent doses, i.e. high doses of 40 mg every 12 hours, without the use of an infusion pump.

Previous meta analyzes have failed to demonstrate the prognostic superiority in administering PPIs in continuous parenteral infusion at high doses (8 mg/h), compared with intermittent doses (40 mg c/12h), noting even that this difference is a determining factor in the use of Hospital resources and their costs [14-16].

It should be mentioned that orally omeprazole, 40 mg every 12 hours, has much lower costs than parenteral, in addition several studies suggest that it can be used even in cases of digestive bleeding due to peptic ulcer to prevent re-bleeding [17,18]. Although the parenteral route is still indicated, in cases where this is not available, the enteral route at high doses of 40 mg c/12h can be used. Reviews point out that the use of oral PPI is an equally effective alternative to the parenteral route [19]. The use of H2 antagonists to prevent re bleeding has yielded mixed results, which is why they are not taken into account in this analysis [20].

Objectives of the Work

The general objective of the work is the cost effectiveness analysis of the continuous infusion scheme of PPI approved by the of Ministry Public Health (MSP), with intermittent parenteral dose schemes and high oral doses, followed by the enteral administration of PPIs (omeprazole), for the prevention of re digestive bleeding due to peptic ulcer in 30 days [21].

The specific objectives, due to their high variability in cost, are the analysis of intermittent doses with continuous doses, as well as oral doses to prevent re-bleeding in patients admitted due to high-acute digestive bleeding.

In addition, we want to assess the total cost of therapies as the parenteral route at high doses and oral high doses of 40 mg c/12h.

As a hypothesis, it has been suggested that the use of a parenteral intermittent scheme is more cost effective in relation to a continuous high dose schedule and that the use of oral PPI is also cost effective with respect to both parenteral routes.

Material and Method

Patients with a high risk of rebleeding were taken into account in hospitals of second and third level of public attention, either with evidence of active bleeding, visible vessel or adhered clot, since other types of injuries are at low risk and they would not benefit from administration of omeprazole parenterally (Table 1) [14].

Cost Effectiveness Analysis of Treatment with and Parenteral Oral Proton Pump Inhibitor for Handling Upper GastroIntestinal Bleeding (UGIB) in Adults in Ecuador

638

| Stigma of bleeding	Probability of rebleeding
Active bleeding to "squirt" or "drooling"	67 - 95%
Visible vessel not bleeding	22 - 55%
Reddish clot	15 - 30%

Table 1: Risk of bleeding according to endoscopic findings (Forrest scale).

The complications associated with the use of omeprazole have been excluded because those described in the literature are only associated with chronic use.

When referring to the management of an acute pathology, a decision tree model adopting the perspective of the public health funder is used. No discount rates have been applied for the short time horizon of the study.

A simulation was carried out with 1000 patients in each of the branches of the model. The percentages of patients with high risk of re bleeding (> 15%, according to the Forrest scale [22]), the complications associated with the lack of response to treatment, the need for surgery, as well as the percentage of re-bleeding to 30 days were taken from existing international literature.

A search was made of the transition rates between the different proposed states and it was transformed to probabilities. Also, in cases where Odds Ratio (OR) was available, an adjusted OR was used to evaluate the transitions (Figure 1). It should be emphasized that the same odds of rebleeding were used for the intermittent omeprazole and infusion groups since the literature does not indicate clear differences between the two [23-27] but not for the use of oral omeprazole [28], where information is scarcer. In addition, the same literature indicates that the probability of surgical intervention in patients receiving intermittent or infused omeprazole is the same, so the assumed probability for both arms was similar (Figure 1).
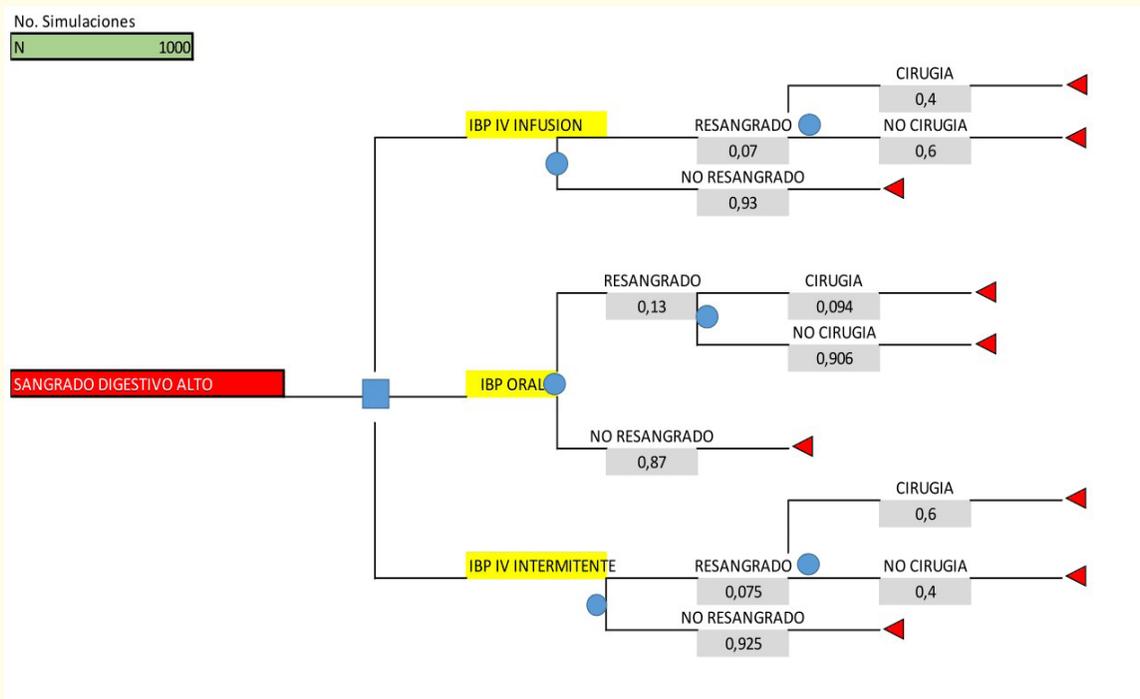
Figure 1: Excel representation of decision tree and probabilities.
The construction of the decision tree can be observed, assessing the probabilities of transition between each of the categories.

Cost Effectiveness Analysis of Treatment with and Parenteral Oral Proton Pump Inhibitor for Handling Upper GastroIntestinal Bleeding (UGIB) in Adults in Ecuador

639

In the elaboration of the reference prices, the national basic chart of medicines will be used, as well as the data of the report of the National Council of Pricing of Ecuador of the year 2014. The prices adopted in this model are presented in table 2.

Resource	Cost (USD)*
Cost per Daily cost day of hospitalization - Includes supplies, physicians and hotels (USD)*	117.24
High digestive endoscopy cost	86
Oral omeprazole cost	2.13
Omeprazole parenteral - intravenoso	4.46
Surgical procedure - Operator, surgeon	149.72

***Table 2:** Average cost of resources used by patient.*

*: Average cost Adjusted to the year 2014 in US dollars (USD) Unit price.

The costs of each of the resources used were adjusted for 2014, taking into account the costs that apply to the public sector of the population. For hospitalization costs, an average between the costs of an intermediate care unit and the general ward has been used since the patients are managed indistinctly in both.

In addition, the costs generated by the emergency department to homogenize cases are not included in the costs, as there are several times patients hospitalized directly from the outpatient clinic, avoiding these initial costs.

In the costs for each of the branches, the price per day of hospitalization was included, which includes the average medical supplies in addition to the visit by the specialist and hospital expenses, the initial cost of an upper digestive endoscopy and in the respective branches the price of omeprazole according to its administration scheme, in addition to the costs of a single surgical procedure (artery ligation, vagotomy, pyloroplasty), including fees and operating time with anesthesia. It should be noted that the price system in the country does not differentiate the types of endoscopic procedures performed during bleeding. In each of the branches, the 30-day costs of using oral omeprazole as complement therapy were also included after deciding on ambulatory follow-up. In the cases of re-bleeding costs, a hospital stay was also assumed, which lasted 5 more days, adding a second endoscopic procedure (second look). All the indicated costs were adjusted to the probability of each branch of presenting the simulated event.

In the decision tree the years of life gained (AVG) due to the use of omeprazole were not taken into account since in the literature it does not mention that the use of them decreases the mortality associated with SDA, but if the risk of re bleeding [29-31].

In the calculation of years of life adjusted for quality, as there were no adverse effects associated with short-term medication, the disutility associated with them was not calculated and it is estimated that they have quality of life indexes between 0.68 and 0.75 [32]. These data are assumed to be true since in our environment data on quality of life are not available in patients with digestive bleeding. The model has attributed a quality of life of 0.75 for a first episode of and 0.68 for a clinical-based re-bleeding such as pain, fatigue, asthenia and emotional damage developed with tools such as the EQ-5D HRQoL for a cohort of the 28 days of the bleeding episode. For the calculation of the QALYs, the number of patients that complete each branch was used due to the probability of the event in the decision tree along with the quality of life indexes attributed to them.

In the absence of a uniform agreement in Ecuador on the scheme of omeprazole to be used, it was decided to compare both the scheme in intermittent doses, in doses of infusion for 72h and the use of oral omeprazole.

In order to carry out the modeling, intermittent omeprazole therapy has been used as a comparator since it is one of the standardized procedures in the country. Then the decision tree was elaborated to compare the other two schemes. Subsequently, the costs for each of the branches have been calculated, including the cases of rebleeding, as well as the QALYs resulting from them, and both oral omeprazole and omeprazole have been compared in infusion to relate the most cost effective alternative.

Cost Effectiveness Analysis of Treatment with and Parenteral Oral Proton Pump Inhibitor for Handling Upper GastroIntestinal Bleeding (UGIB) in Adults in Ecuador

640

We also present the structure of the decision tree model to perform the simulation, as well as all the rates and ORs found in the literature transformed into transition probabilities for each branch. All the attachments have been processed in Excel 2016.

Results

The simulation of 1000 patients was performed for a period of 30 days of evolution of the disease. All those who presented a Forrest scale of up to IIb, or a risk of high bleeding re (> 15%) were included.

The hospital costs, in any circumstance, after an episode of digestive bleeding surpass $ 75,000 US dollars in Ecuador, for an estimated 1000 cases admitted to a public hospital. More than 30% of the costs derived from this pathology are represented exclusively by the hospital stay. At the same time, the cost of a patient that requires surgical intervention rises by 40% only due to costs derived from it.

In each of the branches of the study it was possible to demonstrate the different proportions of patients who reached them. Table 3 summarizes the costs and QALYs for each of the branches proposed in the model.

		Costs (usd)	AVACs
Omeprazole in continuous infusion			
Surgery percentages	2,80%	44004.24	19,0
Percentage of rebleeding without surgery	4,20%	59718.12	28.6
Percentage Without rebleeding	93,00%	697183.8	678.9
Intermittent Omeprazole (40mg every 12h)			
Percentage of surgeries	4.5%	68914,8	30.6
Percentage of re bleeding without surgery	35%	41451,6	20.4
Percentage Without re bleeding	92.5%	656306	675.3
Omeprazol Oral (40mg cada 12h)			
Percentage of surgeries	1.22%	18543,3612	8.3
Percentage of re bleeding without surgery	11.78%	161092,417	80.1
Percentage Without re bleeding	87%	605119,8	635.1

**Table 3:** *Percentage of patients of each therapeutic option, associated costs and QALYs earned.*

In addition, a comparison was made between each of the options to check the most effective cost of the 3 alternatives.

The results were reviewed with the intermittent omeprazole as buyer for the other alternatives, calculating the difference between each of them in both costs and QALYs gained estimating the Incremental Cost Effectiveness Ratio (ICER). These results are shown in table 4.

Therapeutic Option	Total costs (USD)	AVACs totals		Difference of HVACs	Difference of Costs	RCEI
Omeprazole intermittent	766672,4	726,25	Comparator			
Omeprazole and infusion	800906,16	726,5		0,25	34233,76	136935,04
Omeprazole Oral	784755,58	723,5		-2,75	18083,18	6575,7

Table 4: *Comparison of therapeutic alternatives, cost difference, difference in QALYs and ICER for 1,000 patients.*

Cost Effectiveness Analysis of Treatment with and Parenteral Oral Proton Pump Inhibitor for Handling Upper GastroIntestinal Bleeding (UGIB) in Adults in Ecuador

641

In the comparison of the alternatives with respect to the intermittent omeprazole, administration in infusion is more expensive and more effective, whereas the use of omeprazole orally is a more expensive alternative, but at the same time less effective than the original comparator, being dominated by this, so RCEI would not be relevant. In addition, its relationship with the efficiency threshold that is summarized in figure 2 has been estimated.
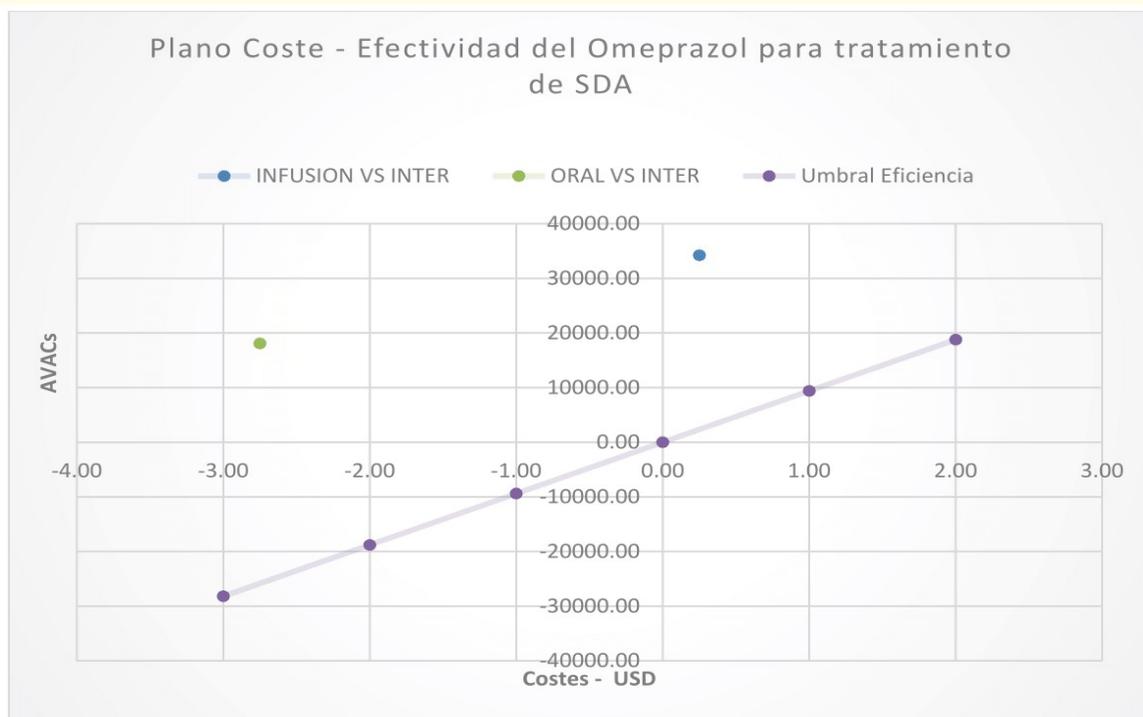
Figure 2: Cost Plan - effectiveness of the use of omeprazole in SDA.
It is observed how the alternative infusion is located in the first quadrant of the cost effectiveness plane, being more costly, but at the same time more effective than the intermittent (comparator). The gray coordinate represents the oral omeprazole in quadrant IV, which indicates that it is a less effective alternative but more expensive, therefore, dominated by the comparator. In addition, you can see how the efficiency threshold is placed on the graph (yellow line) with an approximate ratio of 9300 usd per QALY gained.

Post-discharge costs are based exclusively on outpatient management with oral omeprazole in the next 30 days to the event being $ 128 US dollars.

The QALYs earned were calculated for each of the branches of the model. These were greater in all the branches each time the patients did not present re bleeding. In the cases of re-bleeding, the QALYs gained are greater as long as the patient has not undergone surgery, a fact that is more influential in the case of oral omeprazole, where these decrease dramatically when being operated on by surgery.

Discussion

This work is carried out to explore the use and costs associated with three different schemes of treatment with omeprazole, for people presenting with SDA in public hospitals of the Ecuadorian national health system, from admission to hospitalization up to 30 days after the event In addition, the quality of life of the patients expressed in quality-adjusted life years (QALYs) is evaluated to perform a cost-effectiveness analysis of each of these, using a decision tree model.

Cost Effectiveness Analysis of Treatment with and Parenteral Oral Proton Pump Inhibitor for Handling Upper GastroIntestinal Bleeding (UGIB) in Adults in Ecuador

642

For the simulation, a number of 1,000 patients was used, the average recommended for this type of analysis [33].

The cost related to an episode of high digestive bleeding in Ecuador exceeds $ 75,000 in a period of 30 days for a simulation of 1000 patients. These, however, are costs related to the public health system that are far below the cost associated with the private health system in the country, so they cannot be generalized for the entire medical practice.

It should be noted that 30% of the costs are associated with the hospital stay represented by medical visits, supplies and hospitality. While the most important overall difference is based on the frequency and amount of medication use it is important to note that, in addition, the costs associated with the procedures resulted in an additional $ 86,000 for endoscopic procedures without re bleeding.

The time in which the endoscopy is performed (< 12h or > 12h) has been shown to influence the final costs due to the fact that the length of hospital stay decreases by an average of 1.7 days for early interventions [34]. However, in our environment, we must consider adding the costs derived from resources in order to perform an early EDA. In addition, there are works that indicate even longer hospital stay for an episode of SDA than modeling [35].

For all patients who had re bleeding episodes, the hospital stay was prolonged by an average of 5 days. Within the simulation model, the decrease in hospital stay, being a more variable data, did not change the projection of the final results. Assuming that the stay lasted for only two days, it was observed that oral omeprazole presented final costs slightly lower than the comparator (intermittent) by an average of $ 1200 for 1000 simulated patients, something that has been considered of little importance taking into account the lower effectiveness of it compared to the alternatives.

Every simulated patient after a surgical intervention had a total cost increase in an average of 40% associated with the intervention and a clear reduction in the simulated quality of life according to data from the literature [32]. The deterioration of the quality of life of patients with re-bleeding is attributed in greater proportion to abdominal pain, problems with daily activities, discomfort, anxiety and depression.

The probabilities of transition between the different states vary according to the therapeutic option chosen for the model, being the probability of re bleeding the highest in the oral omeprazole group, however, it is striking that in this same group the risk the need for a surgical intervention is lower compared to the other groups, causing in turn that the QALYs gained in this option are greater than the comparators or alternatives.

The probability of re bleeding in patients receiving omeprazole parenterally in any of the groups is similar, however, those who are in the group of need for surgical intervention is less with intermittent PPI therapy, which would explain why This therapy becomes dominant when we talk about costs and effectiveness gained by it.

Since the need for surgical intervention is different among the alternatives, analyzing the adverse effects of it would be a priority in an extension of the present work.

When reviewing the most cost effective option, oral omeprazole was ruled out because it was dominated by the original comparator (intermittent omeprazole), so it's ICER is not presented, a finding discussed with revised economic drug literature [36-39].

The strategy with omeprazole IV in infusion for 72h is a more expensive and at the same time more effective strategy, however, the increase in effectiveness is modest (0.25 QALYs) compared to the cost of this approximate to $ 34,230 which represents a total cost of $ 136,920 for earn a QALY on this model.

The costs after hospital discharge are very variable, although patients may have been managed on an outpatient basis exclusively with omeprazole orally in the following 30 days, it can also be assumed that re bleeding occurs during this period of time, raising even more the costs of re bleeding due to the inclusion of emergency care. In the current construction model it is assumed that the bleeding episode occurred only during hospitalization, so the variability of costs after discharge is almost nil among all therapeutic options.

Cost Effectiveness Analysis of Treatment with and Parenteral Oral Proton Pump Inhibitor for Handling Upper GastroIntestinal Bleeding (UGIB) in Adults in Ecuador

643

It is important to note that although omeprazole in infusion has a slightly lower probability of bleeding than intermittent bleeding, the costs avoided by Re adimittance, including emergency costs, have not been considered in this analysis.

As health decision-makers, it is necessary to consider that the efficiency threshold and the cost of QALYs proposed for the country were related between the Gross Domestic Product (GDP) and the population density, resulting in that for our environment the willingness to pay can range from $ 9,390/QALY gained up to $ 27,960/QALY. Where in neither case would it exceed the threshold to gain 1 QALY by the use of omeprazole in infusion.

Since these cost effectiveness ratios use the effects only 30 days after bleeding, the data presented is expressed in this period. A work that estimates long-term effectiveness and evaluates its consequences will show long-term results in each of the alternatives.

By crossing the variables in the cost effectiveness plane (Figure 2) we can see how the option of omeprazole in infusion, despite being more expensive and more effective, exceeds the efficiency threshold that we as health decision-makers would be willing to cover, resulting in It is the most cost - effective alternative for our environment. In turn, oral omeprazole is dominated by the comparator.

Sensitivity analysis has not been carried out because the data have been taken as true since there is no other information that yields alternative values of them.

The work presents some limitations that must be considered before being generalized. First, the perspective of the health financier has been taken, for this reason the social context and the costs incurred by the patient were not considered. Second, the cost data has been taken from Ecuadorian public information, so its external validity is compromised even for private areas in the same environment.

Although most economic analyzes take into account the costs to reduce a rebleeding episode, it has been decided to measure the QALYs as another measure of independent effectiveness.

Based on the foregoing, we believe that the intermittent omeprazole alternative is underestimated within hospital management, taking into account the high costs involved in maintaining an episode of SDA with continuous infusion therapy in our setting.

To validate the data presented, studies of quality of life in our environment are mandatory as they could influence the model and the interpretation of these results.

Conclusions

- This is the first work that quantifies the costs related to health in the UGIB in Ecuador.
- Intermittent omeprazole is the most cost effective alternative for managing UGIB in the public health system in Ecuador.
- The alternative chosen for the acute management of this pathology is the key to define the related costs. Costs beyond the health sector are important and should be considered in future research lines.
- These data can assist health decision-makers in developing protocols that include the least expensive option without significant loss of effectiveness and may help future research to assess the impact of new therapies for managing SDA.

The data have been taken as certain. there is not enough information about alternative values of variables that could be uncertain. That's why we have not performed an sensitivity analysis.

The data of quality of life have been taken from the literature, since no quality of life indexes are available in our field. It is therefore supposed, therefore, given. A natural extension of the work would be obtaining own data of quality of life related to health.

Note on the AVAC: The selected period for effects is only 30 days. The calculated rcei refer to that period. An extension of the work could estimate the results throughout the time, estimate, in its case, the mortality and the evolution in the time of the problems in each alternative.

Cost Effectiveness Analysis of Treatment with and Parenteral Oral Proton Pump Inhibitor for Handling Upper GastroIntestinal Bleeding (UGIB) in Adults in Ecuador

644

Costs: The adverse effects of surgery should be analyzed, since the probability of surgery is very different between alternatives.

Declaration

I declare that the present work is original and has been prepared by me in its entirety. In addition, I declare no conflicts of interest in this subject or in some of the parts of the work development.

Note: This article has won Roemmers Price for best original investigation at the national Gastroenterology Congress

Bibliography

1. Clavijo. "Anuario de Estadísticas Hospitalarias Camas y Egresos". Quito: MSP, DIRECCIÓN DE ESTADÍSTICAS SOCIODEMOGRÁFICAS (2012).

2. Barkun A. "Consensus recommendations for managing patients with nonvariceal upper gastrointestinal bleeding". *Annals of Internal Medicine* 139.10 (2003): 843-857.

3. Barkun AN., *et al*. "International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding". *Annals of Internal Medicine* 152.2 (2010): 101-113.

4. Gralnek IM "Diagnosis and management of nonvariceal upper gastrointestinal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) Guideline". *Endoscopy* 47.10 (2015): 1-46.

5. Rosenstock SJ., *et al*. "Improving quality of care in peptic ulcer bleeding: nationwide cohort study of 13,498 consecutive patients in the Danish Clinical Register of Emergency Surgery". *The American Journal of Gastroenterology* 108.9 (2013): 1449-1457.

6. Lu Y., *et al*. "Timing and Dosing of IV Proton Pump Inhibitors in acute GI bleeding has low impact on costs". *The American Journal of* Gastroenterology 111.10 (2016): 1389-1398.

7. SH W., *et al*. "High Morbidity and mortality of clostridium difficile infection and its associations". *Journal of Infection* 73.2 (2016): 115-122.

8. A A., *et al*. "Proton Pump Inhibitors use and change in bone mineral density". *International Journal of Rheumatic Diseases* 19.9 (2016): 864-868.

9. JA., *et al*. "Adverse Event Reporting for Proton Pump Inhibitors Teraphy: An overview of Systematic reviews". *Otolaryngology–Head and Neck Surgery* 155.4 (2016): 547-554.

10. F A., *et al*. "Efficacy ans Safety of proton pomp inhibitors for stress ulcers prophylaxis in critical ill patients". *Crtical Care* 20.1 (2016): 120.

11. E W., *et al*. "Proton Pump Inhibitors increase incidence od NSAIDS drug- Induced small bowel Injury". *Clinical Gastroenterology and Hepatology* 14.6 (2016): 809-815.

12. Salud CNd. "Cuadro Nacional de medicamentos básicos". Quito: MSP, Comisión Nacional de Medicamentos e Insumos (2013).

13. HUMANO. "Secretaría técnica de fijación y revisión de precios de medicamentos de uso humano". QUITO: MSP, SECRETARIA TÉCNICA (2013).

14. John R Saltzman MF. "Overview of the treatment of bleeding peptic ulcers". UpToDate (2015).

15. Laine LJD., *et al*. "Management of patients with ulcer bleeding". *The American Journal of Gastroenterology* 107 (2012): 345-360.

Cost Effectiveness Analysis of Treatment with and Parenteral Oral Proton Pump Inhibitor for Handling Upper GastroIntestinal Bleeding (UGIB) in Adults in Ecuador

645

16. Sachar H., *et al*. "Intermittent vs continuous proton pump inhibitor therapy for high-risk bleeding ulcers: a systematic review and meta-analysis". *JAMA Internal Medicine* 174.11 (2014): 1755-1762.

17. Spiegel B., *et al*. "The cost-effectiveness and budget impact of intravenous versus oral proton pump inhibitors in peptic ulcer hemorrhage". *Clinical Gastroenterology and Hepatology* 4.8 (2006): 988-997.

18. Soi J., *et al*. "Meta-analysis: comparison of oral vs. intravenous proton pump inhibitors in patients with peptic ulcer bleeding". *Alimentary Pharmacology and Therapeutics* 38.7 (2013): 721-728.

19. Sung JJ., *et al*. "Effects of intravenous and oral esomeprazole in the prevention of recurrent bleeding from peptic ulcers after endoscopic therapy". *The American Journal of Gastroenterology* 109.7 (2014): 1005-1010.

20. van Rensburg C., *et al*. "Clinical trial: intravenous pantoprazole vs. ranitidine for the prevention of peptic ulcer rebleeding: a multicentre, multinational, randomized trial". *Alimentary Pharmacology and Therapeutics* 29.5 (2009): 497-507.

21. Cheng HC Wea., *et al*. "Double oral esomeprazole after a 3-day intravenous esomeprazole infusion reduces recurrent peptic ulcer bleeding in high-risk patients: a randomised controlled study". *Gut* 63.12 (2014): 1864-1872.

22. Forrest JA FNSD., *et al*. "Endoscopy in gastrointestinal bleeding". *Lancet* 17 (1974): 394-397.

23. Bai Y., *et al*. "Intravenous Esomeprazole for Prevention of Peptic Ulcer Rebleeding: A Randomized Trial in Chinese Patients". *Advances in Therapy* 32.11 (2015): 1160-1176.

24. Sung JJ., *et al*. "Intravenous esomeprazole for prevention of recurrent peptic ulcer bleeding: a randomized trial". *Annals of Internal Medicine* 150.7 (2009): 455-464.

25. Kim K., *et al*. "Can proton pump inhibitors reduce rebleeding following Histoacryl sclerotherapy for gastric variceal hemorrhage?". *The Korean Journal of Internal Medicine* 30.5 (2015): 593-601.

26. El Ouali S., *et al*. "Timing of rebleeding in high-risk peptic ulcer bleeding after successful hemostasis: a systematic review". *Canadian Journal of Gastroenterology and Hepatology* 28.10 (2014): 543-548.

27. Neumann., *et al*. "Comparison of different regimens of proton pump inhibitors for acute peptic ulcer bleeding". *The Cochrane Database of Systematic Reviews* 6 (2013).

28. GI Leontiadis., *et al*. "Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding". *Health Technology Assessment* 11.51 (2007): 1-164.

29. Alshamsi F., *et al*. "Efficacy and safety of proton pump inhibitors for stress ulcer prophylaxis in critically ill patients: a systematic review and meta-analysis of randomized trials". *Critical Care* 20.1 (2016): 120.

30. Health ODaTi., *et al*. "Continuous versus Intermittent Intravenous Pantoprazole for Acute Gastrointestinal Bleeding: A Review of the Clinical Effectiveness and Guidelines". *Rapid Response Reports* (2015).

31. Zhang Y., *et al* ".Proton pump inhibitors therapy vs H2 receptor antagonists therapy for upper gastrointestinal bleeding after endoscopy: A meta-analysis". *World Journal of Gastroenterology* 21.20 (2015): 6341-6351.

32. H E Campbell., *et al* . "Costs and quality of life associated with acute upper gastrointestinal bleeding in the UK". *British Medical Journal* 5.4 (2015).

33. Crespo C SDRJ., *et al* . "Técnicas de modelización en evaluación económica de medicamentos y tecnologpias sanitarias" (2016).

34. JairathV KB., *et al* . "Outcome following acute nonvariceal upper gastrointestinal bleeding in relation to time to endoscopy". *Health Tech* 1 (2007): 164.

Cost Effectiveness Analysis of Treatment with and Parenteral Oral Proton Pump Inhibitor for Handling Upper GastroIntestinal Bleeding (UGIB) in Adults in Ecuador

646

35. Adam V., *et al* . "Estimates of costs of hospital stay for variceal and nonvariceal upper gastrointestinal bleeding in the United States". *Value Health* 11.1 (2008): 1-3.

36. Alan N., *et al*. "Barkun Cost Effectiveness of High-Dose Intravenous Esomeprazole for Peptic Ulcer Bleeding". *Pharmacoeconomics* 28.3 (2010): 217-230.

37. Barkun AVea., *et al*. "The cost-effectiveness of high-dose oral proton pump inhibition after endoscopy in the acute treatment of peptic ulcer bleeding". *Alimentary Pharmacology and Therapeutics* 20.2 (2004): 195-202.

38. BL E., *et al*. "Cost-effectiveness of proton pump inhibitor therapy for acute peptic ulcer-related bleeding". *Critical Care* 32.6 (2004): 1277-1283.

39. Spiegel Bea., *et al* . "Minimizing recurrent peptic ulcer hemorrhage after endoscopic hemostasis: the cost-effectiveness of competing strategies". *The American Journal of Gastroenterology* 98.1(2003): 86-97.