International Journal of Biological & Pharmaceutical Research

e- ISSN 0976 - 3651
Print ISSN 2229 - 7480

www.ijbpr.com

Research Article

COMPARATIVE STUDY OF PANTAPROZOLE AND SUCRALFATE ON INTRAGASTRIC pH IN PROPHYLAXIS OF ACUTE STRESS RELATED GASTRO INTESTINAL BLEEDING IN CRITICALLY ILL PATIENTS

Dr. Syed Arshaduddin Ahmed & Dr. Bhuvaneshwari *

Assistant Professor, Dept of Pharmacology, Osmania Medical College, Hyderabad, Andhra Pradesh, India.
Assistant Professor, Dept of Pharmacology, Osmania Medical College, Hyderabad, Andhra Pradesh, India.

ABSTRACT

Introduction: Stress-related mucosal damage (SRMD) is a significant cause of morbidity and mortality in critically ill patients due to the gastrointestinal blood loss. Prophylaxis of SRMD with proton pump inhibitors or histamine-2 blockers has gained widespread use in intensive care units. Both demonstrated to be effective in reducing clinically significant bleedings. Aim: The aim of the present study is an evaluation of prophylaxis with sucralfate and pantaprozole and their effects on intragastric pH and acute stress related GI bleeding. Materials and Methods: A total of 48 critically ill patients with risk factors of developing stress ulcer and intragastric pH < 3.0 enrolled to this randomized clinical trial study. Patients were randomly assigned in two treatment groups; Twenty four Patients were randomly assigned to 2 study groups. Group I Received syrup sucralfate 10 ml (1gm) 3 times a day through nasogastric tube. Group 2 Received intravenous bolus pantaprozole 40 mg once a day. Results:The demographic data were comparable without any statistically significance. The duration of study in both sucralfate and pantaprazole was comparable with p value >0.05. In the present study, there was significant differences in the type of risk factors between two groups 83% of patients in sucralfate had respiratory failure whereas the major cause of ICU admission in pantaprozole group was CNS injury (46%). Shock was seen in 43% of sucralfate group and 17% of pantapr0zole group. Medication related side effects i.e diarrhoea was seen in 2 patients of pantaprazole group. Baseline pH In both groups was seen in the same range with mean of 2.56 and 2.64 in the sucralfate and pantaprazole group. 5.7% of the samples on the sucralfate have pH<40 confirming its action of gastric mucosal protective agent without affecting the pH 67% in the pantaprazole group had pH >4.7. No significant overt bleeding was bleeding was found in the study groups. 38% in sucralfate group and 26% in pantaprazole group had occult bleeding. There was no significant difference in overt insignificant bleeding in either of the group (p>0.05).**Conclusion:** Both of them equally effective in the prevention of stress induced GI bleeding. No side effects are associated with pantaprazole and sucralfate.

Key Words: Pantoprozole; Sucralfate, Stress-related mucosal damage prophylaxis; Critically ill patients.

Corresponding Author

Dr.Bhuvaneshwari
Assistant Professor, Dept of Pharmacology, Osmania Medical College, Hyderabad, Andhra Pradesh, India.

Email:- bhuvana2005@gmail.com

INTRODUCTION

Stress-related mucosal disease (SRMD) is known to be a significant cause of morbidity and mortality in critically ill patients in the intensive care unit (ICU). Stress-related mucosal damage causes mucosal erosions and superficial haemorrhages in these patients or in those who are under extreme physiological stress, resulting mild to severe gastrointestinal blood

loss. Upper GI bleeding related to SRMD, estimated to affect 15% of patients in an ICU (1). Morbidity of SRMD and associated stress-related bleeding showed to double the length of stay in the ICU from 4 to 8 days (2). In critically ill patients who develops stress-related mucosal bleeding during the hospitalization, mortality rate varies in the range of 50-77%, which shows as much as 4 times higher than it is in ICU patients without this complication (3).

Stress ulceration occurs due to imbalance of aggressive and defensive mucosal forces. Though disruption of mucosal barrier is the key factor, gastric acid pH appears to play a significant role in the pathogenesis of stress ulceration. Efforts aimed at prophylaxis of stress related bleeding have concentrated on measure that reduces gastric acidity to a certain extent (4,5).

Proton pump inhibitors are the newest and most potent anti secretary agents available for clinical use. Pentapropazole is a proton pump inhibitor that inhibits the gastric H^+-K^+ATpase which is responsible for acid secretion in the parietal cells of stomach (6,7). In the present study this drug is compared with cyto protective agent sucralfate which is considered as preferred drug in the critically ill patients.

Cyto protective agents like sucralfate prevent or reduce mucosal injury via mechanism other than the reduction in gastric acidity. Sucralfate has been shown to be effective in the treatment of peptic ulcer and may prevent disruption of gastric mucosa in response to noxious agents (8).

The aim of the present study is an evaluation of prophylaxis with sucralfate and pantaprozole and their effects on intragastricph and acute stress related GI bleeding. It is an attempt to put forth a comparative assessment of the above two drugs and to highlight the relative merits and demerits of each in prophylaxis.

Materials and Methods

Place of the study

This study was a randomized clinical trial and was done at Osmania Medical College, Hyderabad from January 2009 to December 2009. The study was conducted in patients admitted to acute medical care respiratory and burn intensive care units of Osmania General Hospital to evaluate the effect of pantaprozole and sucralfate on

1. Intragastric pH
2. Stress related Gastrointestinal Haemorrhage

Patient selection

Informed consent was taken from all patients. 48 patients were selected randomly to receive prophylaxis by either sucralfate or IV pantaprazole.

Twenty four Patients were randomly assigned to 2 study groups according to a computer-generated table of random numbers.

Group –I: Received syrup sucralfate 10 ml (1gm) 3 times a day through nasogastric tube.

Group -2: Received intravenous bolus pantaprozole 40 mg once a day.

Inclusion criteria were as follows

Non per oral (NPO) patients, with the need of mechanical ventilation, the presence of a nasogastric tube with a gastric position confirmed on the abdominal radiography and the baseline gastric juice with pH equal to or lower than 3.0 and the presence of at least one risk factor other than ventilation for a gastro duodenal stress ulcer that would commonly indicate the SRMD prophylaxis (i.e. shock, severe sepsis, burns, head trauma, coagulopathy, major surgery).

Exclusion criteria

- If they had documented oesophageal, gastric or duodenal mucosal diseases, esophageal vericeal bleeding or gastric surgery within 6 months prior to consideration
- The patients did not receive any H_2-blocker, proton pump inhibitor, or antacids for the last two days and the entered feeding was not allowed during the study period.
- Patients younger than 18 years
- Patients with renal or hepatic failure were excluded from the study.
- If they had evidence of bleeding prior to study admission in the nasogastric aspirates.

The use of treatment placebo group was prohibited on the basis of published efficacy of antacid on the prevention of stress related gastrointestinal bleeding in critically ill patients,

Naso gastric aspirates were collected 8 ^{ho}urly through Ryles tube placed in the stomach.

The position was confirmed by every time a sample was taken and when the pH fluctuated abruptly. The samples were tested for pH and bleeding (both occult and overt) pH was tested by pH sensitive litmus paper. Occult blood was tested as follows. Benzedrine reagent (3ml) was added to 3 ml of gastric juice. To this few drops of fresh hydrogen peroxide was added. Bluish green discoloration was observed if blood pigments were present.

In all patients with significant bleeding, the protocol called for endoscopy. In the present study, 48 patients were selected. Out of these, 5 patients had insignificant overt bleeding and none had significant overt bleeding.

Monitoring

All the patients under went daily physical examination and minimum laboratory analysis that

includes complete blood picture, serum creatinine, Urea, Complete urine examination.

Statistical analysis

Characteristics of patients are represented as mean ± SD.\

Results

The above table shows the number of risk factors in either group of patients, the values are number of patients with percentage in brackets. Patients with 3 risk factors in sucralfate group were significantly more than patients in pantaprozole group ($p<0.05$).

In the present study, there was significant differences in the type of risk factors between two groups 83% of patients in sucralfate had respiratory failure whereas the major cause of ICU admission in pantaprazole group was CNS injury (46%). Shock was seen in 43% of sucralfate group and 17% of pantaprozole group.

The patients were assigned to each group randomly and there was no intentional exclusion or inclusion in any of the risk category in any of the two groups.

There were very few medications missed in either group, through fewer were missed in the sucralfate group compared to the pantaprazole group. Medication related side effects i.e diarrhoea was seen in 2 patients of pantaprozole group.

Table 7 shows that effect on the prophylaxis on intra gastric pH

Baseline pH In both groups was seen in the same range with mean of 2.56 and 2.64 in the sucralfate and pantaprazole group. 5.7% of the samples on the sucralfate have pH<40 confirming its action of gastric mucosal protective agent without affecting the pH 67% in the pantaprozole group had pH>4.7(p value <0.05).

No significant overt bleeding was bleeding was found in the study groups. 38% in sucralfate group and 26% in pantaprozole group had occult bleeding ($p>0.05$). There was no significant difference in overt insignificant bleeding in either of the group ($p>0.05$).

Reason for discharge in the study groups from the study were found predominantly to be

1. Starting of tube feedings>100 ml/hr was the end point for 34% in sucralfate and 46% in pantaprozole.

Completion of 72 hours was the end point for 50% in sucralfate and 38% in panatprozole.

Table 1. Demographic data of two groups (Age & Sex)

Group	Age (Yrs)	Mean±SD	Sex ratio	
			Male	Female
Sucralfate	18-58	31.87±10.91	16	08
Pantaprozole	18-65	35.01±12.18	17	07

The demographic data were comparable without any statistically significance ($p>0.05$).

Table 2. Duration from admission to inclusion into study

Group	Hours from Admn, To conclusion (range)	Mean
Sucralfate	6-15 hrs	9.7 hrs
Pantaprozole	6-18 hrs	11.2 hrs

There was no spastically significance and the above data was comparable in both groups ($p>0.05$) by t-test

Table 3. Showing the Duration of the study

Group	Hrs in study	Mean
Sucralfate	48-72 hrs	65.66
Pantaprozole	48-72 hrs	63.58

The duration of study in both sucralfate and pantaprazole was comparable with p value >0.05 by t-test.

Table 4. Risk factors in the two groups

Groups	Number of risk factors		
	1	2	3
Suralfate	15 (62%)	7(29%)	2(9%)
Pantaprozole	15(62%)	8(34%)	1(4%)

Table 5. Risk factors for stress related bleeding on admission to the study

Risk factors	Sucralfate		Pantaprozole	
	No	%	No	%
Respiratory failure	20	83	4	17
CNS injury	2	8	11	46
Renal failure	1	4	4	17
Shock	8	43	4	17
Burns>15%	0	0	7	29
Sepsis	4	16	0	0
CHF	2	8	2	8
Steroids	1	4	2	8

Table 6. Number of medications missed and reported side effects

Group	% of missed Medications	Side effects
Sucralfate	4.5(9/197)	0
Pantaprozole	5.8(4/69)	2

Table 7.Effect on intra gastric PH

Intra gstric PH	Sucralfate	Pantaprozole
Baseline (Mean)	**2.56%**	**2.64%**
% of Samples ≤2.5	**8%**	**0.6%**
2.6-40	**49%**	**32%**
>4.0	**43%**	**67.4%**

Table 8. Effect on stress related bleeding

GI Bleeding	Sucralfate	Pantaprozole
Insignificant		
Occult	9(38%)	6(25%)
Overt	2(9%)	3(12.15%)
Significant	0	0

Table 9. Reason for discharge

Reason	Sucralfate	Pantaprozole
72 hrs completed	12(50%)	9(38%)
Discharge	3(12%)	4(4%)
Death	1(4%)	0(0%)
Tube feeding	8(43%)	11(46%)

Table 10. Total duration of hospital stay including completion of study

Group	Mean±SD	Range
Sucralfate	9.00±2.91	5-14
Panatprozole	9.54±3.87	4-22

There was no difference in the total days hospitalized between the two groups ($p<0.05$)

Table 11. Total duration in hospital after completion

Group	Mean±SD	Range
Sucralfate	6.12±2.49	2-12
Panatprozole	7.00±4.80	1-20

There was no difference in the total days hospitalized or in days hospitalized after completion of the study between the two groups on follow up ($p>0.05$).

Table 12. Discharge status

Group	Alive	Dead
Sucralfate	21(87.5%)	3(12.5%)
Panatprozole	19(79%)	5(21%)

DISCUSSION

Numerous studies have demonstrated a high incidence of gastric mucosal erosions and related bleeding in high risk patients. The incidence of bleeding is related to the severity of illness and several studies have demonstrated a decrease in bleeding when patients receive prophylaxis with antacids and in some cases H_2 receptors antagonists (9-11).

The reported incidence of upper GI bleeding in intensive care units not receiving prophylaxis varies depending on the bleeding criteria used. But it is usually between 8-25% reported the occurrence of either overt or occult GI bleeding in 14% of non prophylactically treated patients with 6% incidence of overt significant bleeding. This problem takes on immense proportions when one consider that a history suggesting stress related bleeding can occur in 5% of patients in whom endoscopy is requested for upper GI bleeding (11-13).

The frequent administration of antacids with adequate titration of the gastric pH is demonstratably effective for the prophylaxis f stress related bleeding, but requires significant nursing time and is associated with side effects such as severe diarrhoea, alkalosis, hyper magnesium H_2 receptor antagonists may be less effective for the prophylaxis in critically ill patients and may interest with variety of medications these patients are given (14, 15).

Sucralfate forms a protective barrier on eroded mucosal surfaces. Its uses have been associated with minimal side effects or drug interactions and the suspension is easily administered through nasogastric tube. It has been considered ideal for prophylaxis in stress related GI bleeding (16).

Pantaprozole is the newest and most potent anti secretary drug belonging o the proton pump inhibitor group. It decreases the gastric and pH by inhibiting the H^+-K^+ATPase. In the parietal cells its efficacy in the prophylaxis stress related GI bleeding awaits further research. In the present study, it is compared to sucralfate which has been the gold standard in the prophylaxis of SRMD.

In the current study, patients who were selected were matched in both group og age, sex, hours of admission to ICU to inclusion into the study and total duration of study. Each patient had at least on e risk factor associated with stress related bleeding.

29% of patients in sucralfate group and 34% of patients in pantaprozole group had more than one risk factors. The majority of patients(83%) in sucralfate group needed mechanical ventilation for respiratory failure, a potent risk for stress GI bleeding. 46% of patients in pantaprazole group had CNS injury which predisposes to stress ulcers. 33% of sucralfate and 17% of pantaprozole were hypotensive. Sepsis was also major contributing factor.

Few doses of medications of missed in either group, although significantly fewer doses were missed in sucralfate group. No medication related side effects were noted in the sucralfate. Constipation, a potent effect was not noted in the study. Serum albumin levels were not measured in the sucralfate group. Such levels have been demonstrated not to be significantly increased in patients with gastric or duodenal ulcers receiving therapeutic doses of sucralfate on long term basis.

Two patients from pantaprozole complained of diarrhoea. Other complaints of nausea, flatulence, and headache were not noticed. No drug interactions could be found in patients receiving the drug. Further, the single dose per day made administration of drug easy and simple.

The baseline pH in both the groups before the start of prophylaxis was almost similar i.e., 2.56 and 2.64. The pH in the sucralfate group was less than 4 in 57% of patients in keeping with the classification of sucralfate as a cytoprotective agent with week antacid properties. The pH in the pantaprozole group was predominantly less acidic with 67% of pH values more than 4.0. It was documented earlier that the incidence of GI bleeding is substantially decreased when acid neutralization occurred to maintain pH around 4.0.

GI bleeding was comparable in both the groups. Occult bleeding occurred in 38% of sucralfate patients and 25% of pantaprazole. Insignificant overt bleeding occurred in 2 patients of sucralfate and 3 patients of pantaprozole.

The prophylaxis was considered to have failed when significant overt bleeding occurred. The incidence of significant bleeding was nil in the study. This is similar to the previous studies, though the incidence of overt bleeding insignificant and overt bleeding was somewhat higher (17, 18).

No Patients in either group had significant overt bleeding. There was no fall in haemoglobin levels within 24 hours and 3 out of 5 patients tested negative for occult blood in stools.

The end points of majority of patients in either group were completion of 72 hours and tube feeding greater than 100 ml/hr. 50% in sucralfate and 38% in panatprozole completed 72 hours of study. 34% of sucralfate and 46% of patients had tube feedings> 100ml/hrs as their endpoints. One person in the sucralfate died while the study was in progress.

The duration of hospital stay was 9.00±2.91 days in sucralfate group and 9.54±3.87 in pantaprozole. The patients were followed up for a mean of 6 days and 7 days in sucralfate group and pantaprozole respectively. None of the study of either group developed significant GI bleeding after completion of the study. 12.5% of patients sucralfate group and 21% in panatprozole group died. This highlights the severity of the medical illness for which they had admission.

CONCLUSION

Both pantaprozole and sucralfate are comparable in prevention of acute stress related GI bleeding. Pantaprozole by it's of action raised the intra gastric pH more than 4 sucralfate on the other hand. Being cyto protective agents with weak antacid properties did not change the pH significantly. Both of them equally effective in the prevention of stress induced GI bleeding. No side effects are associated with pantaprozole and sucralfate.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgement

The authors are thankful to Dept of Pharmacology and Osmania Medical college& General Hospital, Hyderabad for providing facilities to carry out this work.

REFERENCES

1. Zuckerman GR and Shuman R. Therapeutic goals and treatment options for prevention of stress ulcer syndrome. *Am. J. Med.* (1987) 83: 29-35.
2. Schuster DP, Rowley H, Feinstein S, McGue MK and Zuckerman GR. Prospective evaluation of the risk of upper gastrointestinal bleeding after admission to a medical intensive care unit. *Am. J. Med*. (1984) 76: 623-30.
3. Sesler JM. Stress-related mucosal disease in the intensive care unit: an update on prophylaxis. *AACN adv. Crit. Care* (2007) 18: 119.
4. Martindale RG. Contemporary strategies for the prevention of stress-related mucosal bleeding. *Am. J. Health-System Pharm.* (2005) 62: S11.
5. Mutlu GM, Mutlu EA and Factor P. GI Complications in patients receiving mechanical ventilation. *Chest* (2001) 119: 1222.
6. Meyer TA, Wang J, Tiao GM, Ogle CK, Fischer JE and Hasselgren PO. Sepsis and endotoxemia stimulate intestinal interleukin-6 production. *Surgery* (1995) 118: 336-42.
7. Mester M, Tompkins RG, Gelfand JA, Dinarello CA, Burke JF and Clark BD. Intestinal production of interleukin-1 [alpha] during endotoxemia in the mouse. *J. Surg. Res.* (1993) 54: 584-91.
8. Roumen RMH, Redl H, Schlag G, Zilow G, Sandtner W, Koller W, Hendriks T and Goris RJA. Inflammatory mediators in relation to the development of multiple organ failure in patients after severe blunt trauma. *Crit. Care Med*. (1995) 23: 474.
9. Tamion F, Richard V, Sauger F, Menard JF, Girault C, Richard JC, Thuillez C, Leroy J and Bonmarchand G. Gastric mucosal acidosis and cytokine release in patients with septic shock. *Crit. Care Med.* (2003) 31: 2137.
10. Pharmacology: Fifth edition. H.P Rang and M.M. Dale, 2008.
11. Donati A, Battisti D, Conti G, Caporelli S, Adrario E, Pelaia P, Recchioni A, Paoletti P and Pietropaoli P. Predictive value of interleukin 6 (IL-6), interleukin 8 (IL-8) and gastric intramucosal pH (pH-i) in major abdominal surgery. *Intens. Care Med.* (1998) 24: 329-35.
12. Mojtahedzadeh M, Rastegarpanah M, Malekzadeh R, Khalili H, Ganji MR and Gholami K. A comparative study of bolus administration and continuous infusion of ranitidine on gastric pH with intragastric pH-probe. *DARU J. Pharm. Sci*. (2002) 10: 153-157.
13. Azevedo JR, Soares MG, Silva G and Palacio G. Prevention of sress ulcer bleeding in high risk patients. Comparison of three drugs. *Critical Care Med.* (1999) 27: A145.
14. Namazi MR and Jowkar F. A succinct review of the general and immunological pharmacologic effects of proton pump inhibitors. *J. Clin. Pharm. Ther*. (2008) 33: 215-7.
15. Kedika RR, Souza RF and Spechler SJ. Potential anti-inflammatory effects of proton pump inhibitors: a review and discussion of the clinical implications. *Dig. Dis. Sci.* (2009) 54: 2312-7.
16. Burgess P, Larson GM, Davidson P, Brown J, Metz CA (1995) Effect of ranitidine on intragastric pH and stress-related upper gastrointestinal bleeding in patients with severe head injury. Dig Dis Sci 40:645–650
17. Cannon LA, Heiselman D, Gardner W, Jones J (1987) Prophylaxis of upper gastrointestinal tract bleeding in mechanically ventilated patients. A randomized study comparing the efficacy of sucralfate, cimetidine, and antacids. Arch Intern Med 147:2101–2106
18. Conrad SA, Gabrielli A, Margolis B, Quartin A, Hata JS, Frank WO, Bagin RG, Rock JA, Hepburn B, Laine L (2005) Randomized, double-blind comparison of immediate-release omeprazole oral suspension versus intravenous cimetidine for the prevention of upper gastrointestinal bleeding in critically ill patients. Crit Care Med 33:760–765.