A COMPARATIVE STUDY OF BOLUS ADMINISTRATION AND CONTINUOUS INFUSION OF RANITIDINE ON GASTRIC PH WITH INTRAGASTRIC PH-PROBE

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ABSTRACT

The high mortality rate associated with significant bleeding from stress ulceration has promoted efforts to prevent this complication in critically ill patients. Gastric pH is a key factor in the pathogenesis of stress ulceration and maintaining a pH of 4 or greater reduces the risk for development of the gastric ulceration. Our aim was to compare effects of intravenous bolus administration and continuous intravenous infusion of ranitidine on gastric pH in critically ill patients at the intensive care unit (ICU). Twenty patients who met the inclusion criteria were entered this prospective, randomized, cross over study. A total of 1500 gastric pH measurement was obtained for each phase of the study. Continuous infusion of ranitidine maintained a gastric pH greater than 4 over a longer period than that of bolus administration (22.1 hrs vs. 14.2 hrs, respectively; $P<0.001$). The pH-monitoring device which was made locally, was comparable to a standard international device. This study showed that continuous infusion of ranitidine was more effective than administration of an equivalent dose of the drug by bolus in maintaining the appropriate gastric pH required for the prevention of stress ulceration.

Key words: Gastric pH monitoring, pH probe, Ranitidine, Stress related mucosal damage, Intensive care unit, Bolus, Continuous infusion.

INTRODUCTION

Upper gastrointestinal bleeding related to stress ulcer syndrome is estimated to affect as much as 15% of patients in intensive care units (ICUs) and is associated with increased morbidity and mortality (1). Patients admitted to ICU are at risk for stress induced gastric mucosal damages. Endoscopic examination has demonstrated that 80% to 100% of patient admitted to the ICU develop stress-related gastric mucosal damage within 24 hours after admission (2,3,). Although in these patients, bleeding is not common, but when it occurs, mortality rates are reported to be as high as 80%. (4,5) Prevention of stress ulcer may not be necessary for all patients; but, it is appropriate for specific subsets of ICU patients who are considered to be at high risk. While achieving gastric pH greater than 4 appears to be required for efficacy, some investigators have reported that alkaline gastric pH is a risk factor for pneumonia (2,6-8,). The etiology of the pneumonia associated with gastric acid suppression is not agreed universally (6,9-11). Stress ulcer prophylaxis regimens are important in reduction of the numbers of the morbidity resulting from either ineffectiveness or side effects associated with therapy.(12,13) Although the mechanism of acute ulceration is poorly understood, it is believed that intragastric pH of >4 decreases acute stress-related bleeding and gastric perforation (14,15). Some of the risk factors associated with development of stress ulcers are listed in Table 1 (5).

A common clinical approach to prevent stress ulceration is to increase gastric pH and a number of drugs including H_2-receptor blockers are being used for this purpose. Safety and effectiveness of H_2-receptor blockers have made these agents drugs of choice for prevention of stress ulceration (16). H_2-receptor blockers are given traditionally by bolus administration to achieve an acid-neutralizing effect. Continuous infusion of H_2-receptor blockers has received greater interest over the past several years because they require: less labor intensive, less drug, and control gastric pH more consistently than bolus administration (17). This study was designed to compare the relative abilities of

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bolus administration and continuous infusion of ranitidine to raise gastric pH above 4 in Iranian population.

For monitoring the pH, a unique pH-monitoring device with a pH probe (platin and antimony) was developed. After technical approval and in-vitro studies of the device, a clinical trial was conducted to compare this device with the standard pH probe and pH meter (GrapHprobe ST, Zinetics Medical, Salt Lake City, UT) for two methods of ranitidine administration.

METHODS

Study protocol

This prospective, randomized, cross over study was designed to compare the effect of bolus administration versus continuous infusion of ranitidine on gastric pH in ICU patients. Figure 1 shows the flow diagram of the design of the two Phases. Informed consents were obtained from the patients or a member of their families. Twenty patients who met the inclusion criteria (9 male and 11 female, age 24-70 years) entered this study during a 12 - month's period. Endoscopic study was done on each patient before and after the study.

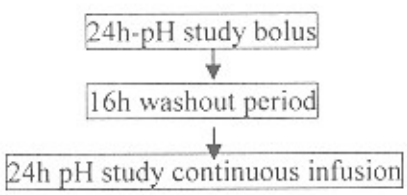

Figure 1. Flow diagram of the design of two Phases:

Patients who were admitted to the ICU and met the inclusion criteria were eligible for the study. Inclusion criteria were as follows: age greater than 18 years, a clinical need for a nasogastric tube and stress ulcer prophylaxis, have not eaten by mouth for 72 hours, and baseline gastric pH<4 within 24 hours of the initiation of monitoring. Exclusion criteria included: pregnancy, treatment with a H_2-receptor antagonist within the 8 hours before entering the study, treatment with antacids within 4 hours prior to entering the study, a hypersensitivity to H_2-receptor blockers, a history of esophageal varices, previous gastric ulcer, surgery, Zollinger-Ellison Syndrome, renal failure (a serum creatinine concentration >3mg/dL), increase in the liver enzymes (increase in aspartate aminotransferase or alanine aminotransferase concentration greater than three times of the upper limit of normal), receiving investigational drugs within 30 days, being fed by enteral nutrition, or receiving non-steroidal anti-inflammatory agents

Study medications

Ranitidine hydrochloride (Chemi Daru Inc., Tehran) were administered either by bolus or continuous intravenous infusion. For the continuous infusion, 150mg of the drug (50mg/2mL solution) was premixed with 5% dextrose solution (94mL) and was administered by a syringe pump (IVAC, Model P-1000, USA) at the rate of 6.2mg/hr. For the bolus administration, 50mg of the drug were administered three times a day after 16 hours completion of the washout period. Patients were then crossed over to the second phase of the study. Baseline chemistries, complete blood count, and other relevant data were obtained. Laboratory determinations were repeated at 24 and 48 hours. Continuous vital support measurements were also recorded on the hourly basis.

Intragastric pH measurements and monitoring

Upon admission to the study, combined nasogastric tube with pH probe (Iran Biomedical Engineering co., Tehran, Iran) with platin-antimony probe and a separate skin reference electrode were placed in patients and its position was confirmed with chest radiography. Hourly recording were started at 8:00 AM and lasted for 72 hours. Calibration was accomplished using control pH solutions of 1 and 4 (Merck, Germany) before placement.

Statistical analysis

A paired-samples t-test statistics was used to compare the means of bolus and continuous infusion of ranitidine in these patients. A p-value <0.05 was considered statistically significant. The Statistical package for social sciences (SPSS 6.0) in a Windows environment was used for all calculation.

RESULTS AND DISCUSSION

Twenty patients (9 male, 11 female: mean age ± SD 48.00 ± 16.24 years) were enrolled in this study. Their demographic information are described in Table 1.

Figure 2 shows the result of intragastric pH (mean ± SE) of patients receiving intravenous infusion of ranitidine (6.2mg/hr) and bolus administration (50mg three times a day) obtained by intragastric pH probe (Iran Biomedical

Engineering co). The time in which intragastric pH were above 4 is shown in Table 3.

Table 1. Risk Factors associated with the development of stress ulcers (5)

Major trauma
Burns covering 25% or more of total body surface area
Sepsis
Respiratory failure requiring mechanical ventilation
Thrombocytopenia
Hepatic failure
Multiple risk factors (two or more of the above. factors)
Sever head injury
Major surgical procedures
Hypotension
Coagulopathy
Elevated PT/PTT

The results of this study showed that controlling the intragastric pH plays an important role in prevention of stress ulceration. H_2-receptor blockers are currently used for stress ulcer prevention in critically ill patients. However, recommended dosing regimens may not consistently maintain an appropriate gastric pH necessary for prevention of stress ulceration (3,4,17). There are other mechanism such as mucosal ischemia due to a decrease in mucosal blood flow, and gastric epithelium autodigestion that may play roles in stress ulceration. Hypersecretion of acid is a prerequisite for stress mucosal injury (18). Continuous infusion of these agents is an alternative way of administration of H_2-receptor antagonist. By this route the administration is easy, less labor intensive and may be more effective than bolus administration. Studies comparing intravenous bolus with constant infusion of cimetidine have demonstrated that the later method has improved control of intragastric pH and reduces formation of stress ulcers (19,20). Continuous infusion of ranitidine has shown to be potentially more effective in controlling gastric pH than bolus administration (21).

Our study presents effectiveness of a continuous infusion of ranitidine in comparison with intermittent bolus administration in neurosurgical and general ICU patients.

A study by Schuster et al. (1984) for evaluation of the risk of upper gastrointestinal bleeding after admission to medical ICU has shown that continuous infusion of famotidine compared with intermittent bolus administration of the drug every 12-hr, maintained appropriate gastric pH necessary for prevention of stress ulceration (10).

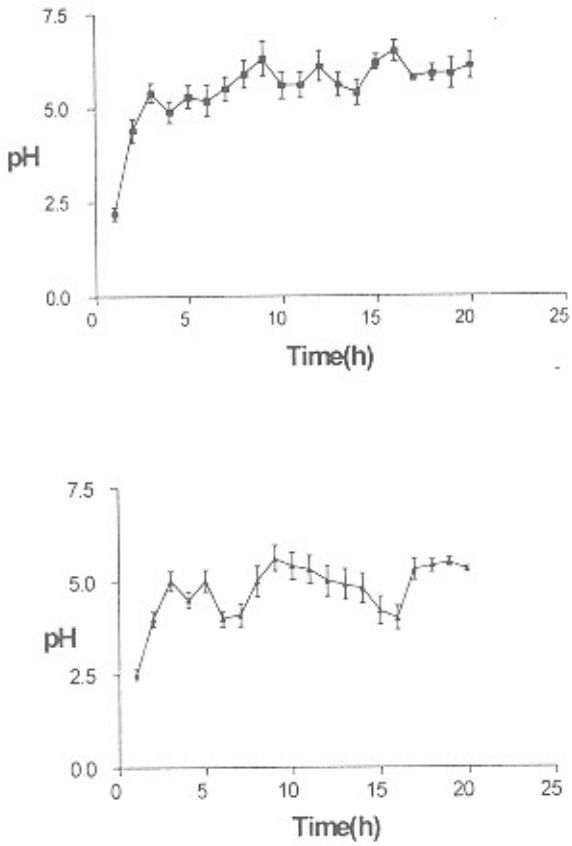

Figure 2. Intragastric pH (mean ± SE) of patients receiving intravenous infusion (■) of ranitidine (6.2mg/hr) and bolus (▲)administration (50mg three times a day).

A potential explanation for the superiority of continuous infusion of ranitidine over bolus administration can be seen from the pH vs. time plots. Gastric pH decreased in eighteen of twenty patients during the last 3 hours of the bolus-dosing interval. Intermittent bolus administration of ranitidine was successful in maintaining a pH greater than 4 for 5 hrs in this population of patients. These data suggest that more frequent dosing may be required for effective bolus administration of ranitidine in the ICU patients. A number of explanations for this effect are possible, one of which might be the increase in clearance of ranitidine in critically ill patients. Higher plasma concentration may be required for a therapeutic effect in

Table 2. Demographic data of study patients.

Patient	Age (yr.)	Sex	Basal Gastric pH	BUN/Scr i	BUN/Scr f	PTi/PTTi	PTf/PTTf	Risk Factors
1	24	F	3.2	21/0.5	13/0.2	15/30	16/41	Head Trauma
2	27	M	3.4	27/0.5	39/0.6	16/30	15/50	Head Trauma
3	30	F	3.0	28/0.9	30/0.9	17/31	16/40	Respiratory Failure
4	24	F	2.5	6/0.8	10/0.5	18/32	17/30	Status epilepticus
5	54	F	1.8	13/1.0	10.1.2	15/30	16/39	Coma
6	43	F	1.4	9/0.6	7/0.8	17/35	16/32	Multiple Trauma
7	69	M	3.2	22/1.3	18/11	15/30	16/31	CVA
8	70	M	2.0	40/1.4	30/1.2	19/35	18/32	MI
9	63	M	2.4	80/1.7	60/1.5	16/33	17/34	Myasthenia Gravis
10	64	M	1.24	17/1.5	19/1.6	16/30	15/30	Respiratory failure
11	58	F	0.99	26/2.0	27/2.2	17/32	16/30	CVA
12	28	M	1.22	14/1.3	18/1.6	16/31	15/30	Multiple Trauma
13	26	F	1.06	16/1.7	19/1.8	15/33	16/31	Sepsis
14	56	M	2.09	23/2.1	28/2.4	16/34	16/30	Respiratory Failure
15	47	F	1.54	20/1.7	24/1.9	15/31	15/32	Sepsis
16	42	F	2.4	17/1.2	7/0.8	17/35	16/32	Multiple Trauma
17	65	M	2.8	23/1.5	18/11	15/30	16/31	CVA
18	57	F	2.9	34/1.2	30/1.2	19/35	18/32	MI
19	60	M	2.7	65/1.4	60/1.5	16/33	17/34	Myasthenia Gravis
20	53	F	2.2	24/1.7	19/1.6	16/30	15/30	Respiratory failure

Table 3: The time for which intragastric pH>4

Time	Bolus	Infusion	P Value
Number of hrs Gastric pH≥4	14.2 ± 5.4	22.1 ± 3.6	P<0.001
Percent of time Gastric pH≥4	59.20 ± 4.5	92.08 ± 5.0	P<0.001

this population. Further studies are required to show the mechanism for this reduced duration of action.

Acute gastrointestinal lesions are well known in critically ill patients. Such lesions, which vary from mucosal damage to ulcers, have been reported in up to 100% of cases in some series studies (21). Evaluation of the pH vs. Time plots also showed that the continuous infusion of ranitidine maintained gastric pH at >4 for most of the dosing interval. This observation implies that lower doses may be appropriate for sub-population of these patients, and as a result costs and potentially adverse reactions of the drug may decreases. Pharmacogenetic differences may play a role in this finding.

Continuous infusion of ranitidine is superior to every 8-hr intermittent administration of the drug in main-taining appropriate gastric pH required for prevention of stress ulceration. These results are similar to the published reports (13,15) for comparison of continuous infusion vs. inter-mittent administration of ranitidine in critically ill patients.

In conclusion bolus dose of ranitidine does not provide adequate pH control for the full dosing interval. Reduced doses of ranitidine given as continuous infusion may be effective for prevention of stress related mucosal damage and might reduces cost of the drug. Employing intragastric pH probe for monitoring the gastric pH is a convenient way of monitoring the gastric pH and a good tool for rational use of H_2-receptor antagonists in critically ill patients.

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REFERENCES

1. Zuckerman, G.R., Cort, D., Shuman, R. (1988) Stress ulcer syndrome. Intensive Care Med. 3:21-25.
2. Skillman, J.J., Bushnell L.S., Goldman H., Silen W., (1969) Respiratory Failure, Hypotension, Sepsis And Jaundice: A Clinical Syndrome Associated With The Lethal Hemorrhage From Acute Stress Ulceration Of Stomach. Am. J. Surg. 117: 523-530.
3. Basso, N., Bagarani M., Materia M., Fiorani S., Lunardi P., Speranza V. (1981) Cimetidine and antacid prophylaxis of acute upper gastrointestinal bleeding in high-risk patients. Am. J. Surg. 141:33-41.
4. Priebe, H.J., Skillman, I. (1981) Methods Of Prophylaxis In Stress Ulcer Disease. World Surg. 5: 223-33.
5. Wilcox C.M., Spenney J.G. (1988) Stress Ulcer prophylaxis in Medical Patients: Who, What and how much? Am. J.Gastroenterol. 83: 1199-1211.
6. Thompson J.C., Walker J.P. (1984) Indications for the use of parenteral H2- receptor ntagonists. Am. J. Med. 19: 111-115.
7. Schuster, D.P., Roughly, H. (1984) Prospective Evaluation Of The Risk Of Upper Gastrointestinal Bleeding After Admission To Medical ICU. Am. J. Med. 76:623-30.
8. Levine R.L., Fromm R.E. Mojtahedzadeh M., Baghaie A.A., Opekun A.R., (1994) The equivalence of litmus paper and intragastric pH probes for intragastric pH monitoring in the ICU. Crit. Care Med. 22: 945-948.
9. Mojtahedzadeh, M., Robert, F., Baghaie A. (1994) Intermittent versus continuous infusion of famotidine on gastric pH in critically ill. Crit. Care Med. 21: 163-5.
10. Schuster D.P., Rawley H., Feinstien S., McGue M.K., Zuckerman G.R. (1984) Prospective evaluation of the risk of upper gastrointestinal bleeding after admission to medical ICU. Am. J. Med. 76: 623-30.
11. Baradaran M., Mojtahedzadeh M., Roshanzamir F. (2000) Gastric pH, concentrations of ranitidine in gastric juice and plasma, and the pharmacokinetics of infused ranitidine in critically ill patients. Pharm. Pharmacol. Commun. 6:135-140
12. Moore J.G., Clemer T.P., Taylor S., Bishop A.L., Maggio S., (1992) Twenty-four-Hour Intragastric pH Patterns in ICU patients on Ranitidine. Dig. Dis. Sci. 37: 1802-1809
13. Morris D.L., MarkhamS.J., Beechey A., Hicks F., Summers K., Lewis P., Stannard V., Hutchinson A., Byrne A.J. (1988) Ranitidine-Bolus or infusion prophylaxis for stress ulcer. Crit. Car. Med. 16: 229-232.
14. Peura, D.A. (1987) Stress-related mucosal damage: an overview. Am. J. Med. 83(Suppl 6 A): 3-7
15. Critchlow J.F. (1987) Comparative efficacy of parenteral histamine H2-Antagonists in acid suppression for the prevention of stress ulceration. Am. J. Med. 83(6A): 25-28.
16. Zuckerman G.R., Shuman R. (1987) Therapeutic goals and treatment options for prevention of stress ulcer syndrome. Am. J. Med. 83 (6 A): 29-35
17. Shuman R.B., Schuster D.P., Zuckerman G.R. (1987) Prophylactic therapy for stress ulcer bleeding. Ann. Intern. Med. 106: 562-567
18. Peura D.A., Johnson L.F. (1985) Cimetidine for prevention and treatment of gastroduodenal mucosal lesions in patients in an ICU. Ann. Intern. Med. 103:173-177.
19. Ballesteros M.A., Hogan D.L., Koss M.A., Isenberg J.L., (1990) Bolus or intravenous infusion of ranitidine: Effect on gastric pH and acid secretion. Ann. Intern. Med. 112:334-339
20. Lamothe P.H., Rao F., Serra A.J., Castellano J., Woronik C.L., McNicholas K.W. (1991) Comparative efficacy of cimetidine, famotidine, ranitidine, and Mylanta In Postoperative stress ulcers. Gastroenterology. 100: 1515-1520
21. Santucci L., Fiorucci S., Pelli M.A., Calderazzo A., Biasini B., Calderazo P.L. (1991) Control of gastric pH with ranitidine in critically ill patients. Digestive Diseases and Sciences. 36: 583-587.