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Original Article

Prophylactic Ranitidine in Prevention of GI Bleeding in Neonatal Intensive Care Units

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Abstract

Background: Upper gastrointestinal (GI) bleeding remains a problem in critically ill-newborns. The use of H_2 blockers, by maintaining gastric pH ≥ 4, reduces the risk of stress-ulceration and gastric hemorrhage. This study therefore, has evaluated the effects of short-term prophylactic ranitidine in controlling gastric pH and prevention of GI bleeding in neonates.

Methods: This randomized controlled study was carried out on 80 neonates admitted to Neonatal Intensive Care Unit ward of Nemazee Hospital, Shiraz, Iran. They were randomly divided into case and control groups and their gastric pH, stool occult blood and macroscopic bleeding were determined. Intravenous ranitidine was administrated (5 mg/kg/day) for four days in case group. Their gastric pH was measured before, one hrs, and two or three days after injection and successful prophylactic treatment was considered if gastric pH was ≥ 4.

Results: Upper GI bleeding was observed in 41% of all patients. After ranitidine, there was a significant increase in gastric pH which accompanied with the reduction of the frequency of upper GI bleeding. Furthermore, no significant changes were noted in gastric pH of control group.

Conclusion: Prophylaxis with ranitidine seems to reduce the frequency of upper GI bleeding by significantly increasing gastric pH.
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Keywords ● H_2 blockers ● prophylaxis ● NICU ● GI bleeding

Introduction

Stress-related mucosal damage of the upper gastrointestinal (GI) tract is a common finding in patients treated in intensive care units (ICUs).[1] The reported incidences varies from 6% to 100% depending on how aggressively the bleeding sites are examined.[1] In recent years, clinical and investigative attentions have directed at the findings of both pathogenesis and prevention of stress-ulceration.[1] The results of experimental studies have revealed that the presence of acid fluid in the gastro-duodenal lumen is an essential precondition for the development of stress-erosion or ulceration.[1] Gastric and esophageal lesions are frequently seen in preterm infants under stress.[2] Stress increases gastric acid secretion and is shown to play a key role in stress-ulceration in older children and adults.[2] However, the role of acid in induction of gastric lesions is uncertain in neonates.[2]

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Infants under stresses, specially those require mechanical ventilation, nasogastric tubing, or drug therapy may be predisposed to ulceration.[1,3] Maintenance of gastric pH ≥ 4 has shown to reduce the risk of stress-ulceration and gastric hemorrhage.[4] Therefore, this randomized prospective trial is designed to assess the effects of short-term prophylactic ranitidine treatment on gastric pH and stress-ulcer in newborn infants.

Patients and Methods

This study was approved by Ethics committee of Shiraz University of Medical Sciences, Shiraz, Iran. The procedure was described to the patients of the admitted neonates, if agreed about the test a written consent was obtained.

This is a randomized, prospective study carried out on 80 neonates (58% male and 42% female) admitted to the Neonatal intensive care unit (NICU) ward of Nemazee Hospital, Shiraz University of Medical Sciences, Shiraz Iran, evaluated immediately after admission to NICU, irrespective of their gestational age. The clinical characteristics included: age, sex, birth weight, gestational age, Apgar score at one and five min, underlying disease, and clinical complications such as the amount of GI bleeding, the number of blood transfusions and surfactant therapy. Exclusion criteria consisted of those patients that had renal failure (serum Cr>1.5 mg/dl), nasal or pharyngeal bleeding or bleeding tendency, abnormal PT, PTT, platelet count, abnormal liver function test, or received oral feeding. They were randomly divided into two equal numbers of case and control groups. A nasogastric tube was inserted for taking one ml of gastric fluid, as required, for the evaluation of gastric pH. Neonates in the case group got three daily doses of prophylactic intravenous (iv) ranitidine (5 mg/kg/day) for four days irrespective of gastric pH and control group only received no prophylactic treatment.

Gastric pH was measured on admission, one hr, two or three days after iv ranitidine and at concurrent times in control group. Measurement of pH consisted of the mid-point between the preceding and succeeding doses of ranitidine as well as after stool examination for occult blood by guaiac test. Prophylaxis was considered unsuccessful, if the values of gastric pH did not reach to four in any of the last two measurements.

Statistical analysis

Data are presented as Mean+SD and Student's t test was used to evaluate their differences and at $p<0.05$ the differences were considered as statistically significant.

Results

There was no significant differences between the results of case and control groups in terms of sex, age, birth weight, gestational age as well as Apgar scores at one and five minutes. None of the patients showed any evidence of adverse reaction to ranitidine. The mean weight, gestational age, and neonatal age of on admission were 2090±1290 g, 33.74±6.26 wks and 4.3±1.4 days, respectively. The mean of Apgar scores at one and five min were 7.4±1.38 and 9.09±0.91.

Diagnoses of the underlying diseases of both groups are listed in (Table1). The most common underlying disease was respiratory distress syndrome (RDS) with concurrent prematurity in both groups.

Table1: Major diagnosis of underlying diseases in patients of the case (C) and control (CNT) groups.

Type of the disease	C n(%)	CN n(%)
RDS	1 (2)	2 (5)
Sepsis	4 (10)	5 (12)
Prematurely	3 (7)	4 (10)
congenital pneumonia	6 (15)	4 (10)
congenital pneumothorax	2 (5)	0 (0)
Hypoxic ischemic encephalopathy	2 (5)	2 (5)
RDS + Prematurely	14 (35)	22 (55)
Surgery*	2 (5)	1 (2)
Others**	6 (15)	0 (0)
Total	40 (100)	40 (100)

RDS=respiratory distress syndrome
*Surgery included bowel obstruction, bladder extrophy, imperforated anus and fistula of scrotom.
**Others included necrotizing entrocolitis, RDS + sepsis, sepsis + Hypoxic ischemic encephalopathy, RDS + congenital pneumonia.

The results of controlling (successful) or not being able to control (unsuccessful) gastric pH of case group are presented in Table 2. The initial mean values of gastric pH were bellow 4.0 in 82% patients of case group before iv ranitidine, and 75% in control group. In case group iv ranitidine increased gastric pH to ≥4.0 which was significantly higher than pH of both pre-treated of case group and simultaneous pH of control group (Table 2; $p<0.005$). Significant differences were also found between gastric pH before, and one hr, the mid-point and two or three days after administration of ranitidine ($P<0.05$). In overall iv ranitidine successfully controlled gastric pH in 26 (65%) patients of case group, whereas, no significant differences were found between sequential gastric pH measurements of control group (Table 2).

A significant difference was found between the frequency of upper GI bleeding before (59.5%) and after (20%) administration of raniti-

dine in case group. In three patients who had surgery, ranitidine could control GI bleeding efficiently without affecting their gastric pH. Whereas, the values of positive guaiac tests of both case and control groups were not significantly different.

Table2: The relationship between increased gastric pH and reducing (successful) or not reducing (unsuccessful) GI bleeding in case group before (BA), one hr (AA) and two or three days (Mid) after administration of ranitidine.

	Successful		Unsuccessful	
	pH	N (%)	pH	N (%)
BA	4.8 ± 0.8	7 (17)	2.6±1.4	33 (82)
AA	4.6 ± 1.7	26 (65)	3.1±1.2	14 (35)
Mid	5.2 ± 1.2	26 (65)	2.5±1.4	14 (35)

Discussion

Most infants admitted to NICU wards were severely ill and required long term mechanical ventilation. These infants frequently had problems such as septic shock, RDS and hypotension that lead to ischemia of GI mucosa.[1] Therefore, it is not surprising to find the same frequency of gastric mucosal lesions in both infants and adults under stress treated in the ICU.[5] The use of prophylactic treatment for the stress-induced gastric lesions in pediatric ICU is still controversial, and limited studies are done in the field of neonatology.[5,6]

H_2 blockers such as ranitidine, cimetidine, etc. are used in reducing the secretion of gastric acid. Ranitidine is a more potent drug with a longer duration of action than cimetidine and thus requires less frequent administration.[7] It seems to be safe and more effective in children with acid peptic disease and should be considered as a first-line of treatment for children with peptic lesions and for prophylaxis of stress-ulceration.[7,8]

The present study showed that prophylactic treatment with ranitidine increased controlled gastric pH to ≥4.0 and successfully reduced the frequency of upper GI bleeding during stress. The initial samples obtained from the infants who did not receive prophylactic treatment showed only 25% of them had gastric pH≥4 and in the remaining gastric pH well bellow 4.0. This is demonstrating that the majority of critically ill infants had an increased acid secretion during the illness. It was also shown that 35% of patients treated with ranitidine had poorly controlled gastric pH. Therefore, the reason for unsuccessful outcomes in these patients might be due to inadequate doses of ranitidine, intense stress, surgery or severe underlying diseases.

The incidence of upper GI bleeding in our patients was high (41.3%) at the time of admission. Our results demonstrated that critically ill neonates, who do not received prophylaxis, had a higher rate of upper GI bleeding than those who received such a treatment (47% vs. 20%; $p<0.05$). The frequency of upper GI bleeding was estimated to be around 38%,[9] whereas in untreated neonates this frequency was 47% and in adults it was 20%.[1] The reason for seeing a higher rate of upper GI bleeding in neonates, as compared with that of adults could be due to more frequent drug therapy,[2] mechanical ventilation for long periods.[10] Underlying diseases such as RDS or coagulopathies,[10] sepsis, acidosis, as well as hypotension and shock that leading to ischemia of gastric mucosa are the main cause of stress-ulceration.[11] Our findings showed in case group the frequency of upper GI bleeding before iv ranitidine was 59.5%. Ranitidine decreased this value to 20% which was significantly lower ($p<0.05$). This suggested that a routine prophylactic treatment for GI bleeding that arises from stress-ulceration may be necessary in critically ill neonates.

It appears that the routine investigation of microscopic hemorrhage (guaiac test) is not useful in the critically ill neonates, because we did not find significant differences in positive guaiac test in case group before and after administration of ranitidine. In addition, the guaiac testing is nonspecific and might yield false-positive results during administration of cimetidine or trauma of nasogastric tubing as reported.[13]

However, in our study the limitation was that we assessed gastric pH intermittently and its acidity might have fluctuated throughout the day. Therefore, the most accurate results are obtained by continuous monitoring of gastric pH.[6] It was possible that some patients that did not successfully respond to the treatment might have experienced isolated episodes of reduced gastric pH which may have precluded at the time of pH measurements.

Many critically ill newborns are at risk for bacterial sepsis. The acid environment of the stomach serves as an important defense mechanism against intestinal colonization of potentially pathogenic bacteria.[14] Previous studies have showed that short-term ranitidine treatment did lead to significant increase in gastric pH with subsequent rise in the rate of bacterial colonization, without any increase in the frequency of infection.[12] Whereas, Kuusela et al. and others showed that short-term prophylactic ranitidine therapy did not increase the risk of suspected or proven bacteremias in their studies.[5,12] Therefore, this suggested that a routine prophylactic treatment for GI bleeding, not increased in frequency of infection was found in ranitidine–treated infants.[12] Our study, however, is falling short in revealing the cause of improved

GI bleeding in response to increased gastric pH in prophylactic ranitidine treated neonates.

Finally, the incidence and severity of upper GI tract hemorrhage in the neonates admitted in NICU decreased during the past ten years.[2] This may in part, be due to the improved critical care, early diagnosis and treatment of this entity. Therefore, we believe the aggressive use of H_2 blockers may significantly reduce the frequency of GI bleeding.

Conclusion

Short-term prophylactic ranitidine treatment significantly reduced the frequency of upper GI bleeding in neonates admitted in NICU. However, results of the present investigation, due to the small sample size and the short duration of treatment, did not allow us to evaluate the long-term benefits of prophylactic ranitidine.

References

1 Zinner MJ, Zuidema GD, Smith PL, Mignosa M. The prevention of upper gastrointestinal tract bleeding in patients in an intensive care unit. *Surg Gyn Obstet* 1981; 153: 214-20.

2 Maki M, Russka T, Kussela AL. High prevalence of asymptomatic esopHageal and gastric lesions in preterm infants in intensive care. *Crit care Med* 1993; 21: 1863-8.

3 Darlong V, Jayalakhsmi TS, Kaul HL, Tandon R. Stress ulcer prophylaxis in patients on ventilator. *Trop Gastroenterol* 2003; 24: 124-8.

4 Harrison M, Lugo RA, Vernon DD. Gastric pH control in critically ill children receiving intravenous ranitidine. *Crit Care Med* 1998; 26: 1433-6.

5 Kuusela AL, Ruuska T, Karikoski R, et al. A randomized controlled study of prophylactic ranitidine in preventing stress induced gastric mucosal lesions in neonatal intensive care unit patients. *Crit Care Med* 1997; 25: 346-51.

6 Sanchez LC, Lester GD, Merritt AM. Intragastric pH in critically ill neonatal foals and the effect of ranitidine. *J Am Vet Med Assoc* 2001; 218: 907-11.

7 Kelly DA. Do H_2 receptor antagonists have a therapeutic role in childhood? *J Pediatr Gastroentrol Nutr* 1994; 19: 270-6.

8 Anapreung P, Vanprapar N, Susiva C, et al. A randomized clinical trial comparing the efficacy of ranitidine and famotidine on intragastric acidity in critically ill pediatric patients. *J Med Assoc Thai* 1998; 81: 185-9.

9 Lopez-Herce J, Dorao P, Ruza F, et al. Frequency and prophylaxis of upper gastrointestinal hemorrhage in critically ill children: a prospective study comparing the efficacy of almagate, ranitidine and sucralfate. *Crit Care Med* 1992; 20: 1082-9.

10 Navab F, Steingrub J. Stress ulcer: is routine prophylaxis necessary? *Am J Gastroentrology* 1995; 90: 708-12.

11 Priebe HJ, Skillman JJ. Methods of prophylaxis in stress ulcer disease. *World J Surg* 1981; 5: 223-33.

12 Cothran DS, Borowitz SM, SutpHen JL, et al. Alteration of normal gastric flora in neonate receiving ranitidine. *J Perinatol* 1997; 17: 383-8.

13 Cook DJ, Cook RJ, Witt LG, et al. Stress ulcer prophylaxis in the critically ill: a meta-analysis. *Am j med* 1991; 91: 519-27.

14 Dinsmore JE, Jackson RJ. The protective role of gastric acidity in neonatal bacterial translocation. *J Ped Surg* 1997; 32: 1014-6.