

STRESS ASSOCIATED GASTRIC BLEEDING IN NEWBORN— ROLE OF RANITIDINE

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ABSTRACT

Stress associated gastric bleeding in sick neonates is an ominous sign and frequently heralds mortality. This study was aimed at evaluating the H₂ receptor antagonist drug—ranitidine in the treatment of this bleeding. Thirty eight neonates with gastric hemorrhage were included in the study. Twenty neonates were given ranitidine while 18 acted as controls. Both groups were well matched with respect to various parameters. Gastric bleeding was controlled earlier in the ranitidine group in contrast to the control group. No untoward side effects were observed with the use of ranitidine. The use of this drug in stress associated gastric bleeding in neonates is recommended.

Key words: Ranitidine, Gastric bleeding.

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Gastric bleeding from stress ulcers in the newborn infants is a known entity(1,2). The factors leading to these stress associated gastric bleeding include birth asphyxia, respiratory distress syndrome, birth injuries, septicemia, prolonged labor, cesarean deliveries and instrumentation. It is believed that after a major physiological disturbance superficial gastroduodenal erosions and ulcers develop, and the bleeding occurs from these sites(3).

It is hypothesized that a high concentration of hydrogen ions in the gastric mucosa or fluid is a major factor in the pathogenesis of stress ulcers. H₂ receptor antagonists have largely been the mainstay of therapy along with the antacids in the management of this condition in the newborns(4,5). The use of cimetidine in these infants has been described(1,2) but it does not entirely bind with H₂ receptors alone and hence has undesirable side effects(6). This problem is circumvented by the use of ranitidine. The experience with this drug in the neonates is very limited. This study was designed to assess the efficacy of ranitidine in treating stress induced gastric bleeding.

Material and Methods

This study was carried out in the Neonatal division of Kalawati Saran Children's Hospital during period January, 1990 to July 1990. Forty eight neonates who had gastric bleeding formed the subjects of this study. All these neonates were born at term and had high risk stress factors, as birth asphyxia (Apgar score <3), respiratory distress, prolonged labor (duration >24 h) and delivery by cesarean section. Vitamin K is routinely administered to all newborns in our nursery.

All neonates who were septicemic, pre-term, had prolonged prothrombin time or

developed disseminated intravascular coagulation were excluded from this study.

Further, the neonates with gastric bleeding were alternatively, divided into two groups, on the basis of odd and even admission numbers.

(i) Group A (Ranitidine group) included 24 neonates forming the study group. They were given injection ranitidine in the loading dose of 0.6 mg/kg followed by 0.15 mg/kg/hour in intravenous infusion. This was continued till there was no bleeding for 24 hours. Along with it, supportive therapy as intravenous fluids, cold saline stomach wash and gastric decompression was provided. Blood transfusion was given if there was excessive bleeding.

(ii) Group B (Non ranitidine group): This was the control group having 24 neonates. In these neonates, only supportive therapy was given to control gastric bleeding. Investigations carried out included complete hemogram including platelet count prothrombin time, blood urea and serum creatinine.

Both the groups were observed for duration of gastric bleeding. The gastric bleeding was checked every 2 hours and assessed by the use of Multistix. Results were tabulated and analysed using unpaired t-test.

Results

At the commencement of the study, 48 neonates were selected with 24 neonates in each of the two groups. During the course of the study 4 neonates in Group A (Ranitidine group) and 6 neonates in Group B (Non-ranitidine group) expired. Out of the deaths, 3 resulted from intracranial hemorrhage, three from hypoxic ischemic encephalopathy and 4 were due to respira-

tory distress syndrome. These neonates were excluded from the analysis so that Group A and Group B had 20 and 18 neonates, respectively.

The stress factors for gastric hemorrhage in the ranitidine group were respiratory distress (50%), birth asphyxia (45%), operative delivery (15%), and prolonged labor (10%). In the non-ranitidine group the incidence of these factors was comparable (Table I).

TABLE I—Factors in Stress Associated Gastric Bleeding

Stress factor	Group A (n=20)	Group B (n=18)
Birth asphyxia	9 (45)	7 (38.9)
Respiratory distress	10 (50)	8 (44.4)
Operative delivery	3 (15)	3 (16.7)
Prolonged labor	2 (10)	2 (11.1)

Three neonates in Group A and 2 neonates in Group B had more than one risk factors. Figures in parentheses indicate percentages.

The babies were well matched for birth weight and gestation. The mean birth weight in Group A was 2.4 ± 0.6 kg while in Group B it was 2.6 ± 0.8 kg ($p > 0.05$). The gestational age in Group A was 38.3 ± 2.2 weeks while in Group B it was 38.6 ± 2.2 weeks ($p > 0.05$).

The average day of onset of stress associated gastric bleeding in the two groups was similar (Table II).

A highly significant difference was observed in the duration of bleeding in these two groups. In Group A the bleeding lasted for 9.5 ± 10.4 hours after administering ranitidine while in Group B the mean duration was 19.0 ± 19.4 h ($p < 0.0005$).

No side effects of ranitidine administration were observed in Group A neonates.

TABLE II—Comparison of Ranitidine and Non-ranitidine Groups

Parameter	Group A (n=20)	Group B (n=18)
Birth weight (kg)	2.4 ± 0.6	2.6 ± 0.8
Gestation (wks)	38.3 ± 2.2	38.6 ± 2.2
Day of onset of bleeding	2.7 ± 1.6	2.8 ± 1.6
Duration of bleeding* (hours)	9.5 ± 10.4	19.0 ± 19.4

*p<0.005.

Incidentally none of the neonates developed renal dysfunction despite a high incidence of birth asphyxia in the two groups.

Five neonates required blood transfusion due to massive hemorrhage. This included 2 neonates from Group A and 3 from Group B.

Discussion

A significant gastric bleeding from stress ulcers has been reported in 5-20% of critically ill patients(3). Gastric mucosal erosions have been treated by administering H₂ receptor antagonists.

Black and co-workers described drugs which selectively blocked the effects of H₂ receptors mediated histamine but these were not well tolerated(7). Further research led to the safer H₂ blocker cimetidine. This agent, however, was not entirely selective as it was found to bind androgen receptors, the hepatic cytochrome P 450 oxygenase enzyme system and sites in the brain. Further improvement culminated in the development of highly selective H₂ blocker, ranitidine(6).

In our study, the stress factors leading to gastric hemorrhage were comparable in the two groups (Table I). The gastric bleeding which commenced by the 2nd or

the 3rd day was checked significantly faster by the use of ranitidine. The number of deaths in the two groups were comparable.

Rosenthal *et al.*(3) had found the efficacy of ranitidine in stress ulcer bleeding in newborns when given in a dose of 0.2 mg/kg/hrs while Socha *et al.*(9) found its beneficial effect in peptic ulcer related diseases in children 4-18 years of age when a loading dose of 0.5-1 mg/kg was administered.

Brogden *et al.*(10) in their review of ranitidine in treatment of gastric bleeding commented that the studies have been too small to permit any clear conclusions although they found that some studies were definitely encouraging. Nowak *et al.*(11) reported that this drug was certainly helpful and lesser number of patients required blood transfusions. Dawson *et al.* found that the use of ranitidine in adults reduced the risk of rebleeds in ulcer cases(12).

A lot of mechanisms of action are attributed to the H₂ receptor antagonists beneficial role in stress associated gastric bleeding. The various factors include reduction in luminal acid production, neutralization of acidity, increase in secretion of bicarbonate and regeneration of gastric mucosa. The metabolic alkalosis resulting from continuous nasogastric aspiration is also checked(13). Vanden Berg *et al.* also found that the use of H₂ receptor antagonists (ranitidine) helps by increasing the gastric pH(14).

In contrast to the side effects reported from the use of cimetidine in children like cerebral depression, thrombocytopenia, hypotension and AV blocks(15-18) none of these side effects have been reported by any of the workers with the use of ranitidine. Rosenthal *et al.* suggested that the drug could be used in anuric neonates in contrast to cimetidine because of its greater excretion through the liver(8). In

our study too, we didn't encounter any side effects with this drug.

We conclude that ranitidine is a beneficial drug for use in stress associated gastric bleeding. Further since this was a limited trial, more research regarding its use in neonates is necessary.

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