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Ranitidin and Nosocomial Infection in Very Low Birth Weight Infants

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ABSTRACT

Background: Nosocomial infections increase mortality rate in neonates. Studies have attributed the use of H2 blockers as one of the various factors that increase the risk of nosocomial infections.
Objectives: To define the relationship between nosocomial infection and Ranitidine in very low birth weight (VLBW) infants admitted in the NICU of a tertiary care hospital.
Patients and Methods: All VLBW infants admitted during the study period of 3 years from April 2008 to March 2011 were included. All relevant pre-and peri-natal data including all administered medications was collected from the case notes and documented on a pre-designed questionnaire. Rate of nosocomial infection (NI) had been compared between patients who were administered Ranitidine and those who did not receive this medication.
Results: During the study period, 564 VLBW infants were admitted in the NICU; 157, (27.8%) contracted nosocomial infections, 130 (82.8%) developed pneumonia, 21, (13.4%) had sepsis with positive blood cultures and 6 infants (1.1%) developed necrotizing enterocolitis. Factors remaining independently significant for development of NI after adjustment were as follows: RDS (P = 0.001. OR = 3.29; 95%CI = 1.64–6.6); CLD (P < 0.001. OR = 3.83; 95%CI = 2.06–7.11); anemia (P = 0.005. OR = 1.96; 95% CI = 1.23-3.13); use of Ibuprofen (P = 0.03. OR = 1.99; 95%CI = 1.06-3.74), and treatment with Ranitidine (P = 0.009, OR = 1.92, 95%CI = 1.18-3.12).
Conclusions: Use of Ranitidine was associated with a significantly increased risk of nosocomial infections in VLBW infant.

Keywords: Cross Infection; Infant, Very Low Birth Weight; Ranitidine; Risk Factors; Intensive Care Units, Neonatal

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Implication for health policy/practice/research/medical education:
Nosocomial Infections (Nis) is one of major causes in mortality and morbidity in Very Low Birth Weight (VLBW) infants admitted to NICU. Risk factors of NIs are frequent including BWt, Mechanical Ventilation , CVC, TPN , and Ranitidine which firstly report is at 1994 and frequent studies up to 2012 emphasis on its significance . In the present study we showed that during 3 years, VLBW infants who received Ranitidine comprised five times more likely to get NIs, therefore must consider this potential side effect regarding its administration.

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1. Background

Nosocomial Infections, (NI) are a major cause of mortality in newborns admitted in the neonatal intensive care unit, (NICU) (1-3). It has been estimated that nosocomial infection occurs in approximately 30% of patients in the NICU. Reports from developing countries reveal that nosocomial infections account for 40% of deaths in NICUs (4, 5). Risk factors for NI include prematurity, low birth weight, respiratory distress syndrome (RDS), use of nasal continuous positive pressure (NCPAP), mechanical ventilation, central venous catheters, total parenteral nutrition (TPN), and prolonged hospitalization (1-7).

Histamine H2 blockers including Ranitidine are often used to raise the gastric PH in ill neonates, especially in babies with gastro-intestinal bleeding or gastro-esophageal reflux; these drugs are also prescribed along with indomethacin, steroids and in babies on TPN (8, 9). H2 blockers like Ranitidine normally protect the gastric mucosa against the acidic environment however they may also cause proliferation of bacteria which would normally be inhibited by the strongly acidic milieu present in the stomach (3, 7-12).

2. Objectives

This study was performed to determine the relationship between the rate of nosocomial infection and the use of H2 blockers, especially Ranitidine in very low birth weight (VLBW) neonates admitted in the NICU of a tertiary hospital in Tehran.

3. Patients and Methods

This retrospective study was performed on all VLBW babies admitted in the NICU of Mahdieh Hospital during a period of 3 years from April 2008 to March 2011. Nosocomial infection was defined and categorized in accordance with the NNIS/CDC, Atlanta criteria (13, 14). Diagnosis of confirmed sepsis was made on the basis of clinical manifestations, laboratory results, and a positive blood culture 72 hours after admission. Hospital acquired pneumonia was diagnosed when recent radiographic changes were noticed on the chest x-ray, in addition to the clinical and para-clinical data. Ventilator associated pneumonia (VAP) was diagnosed in accordance with the NNIS/CDC criteria (15). All relevant pre-and peri-natal data was collected from the case notes, and together with all information from the time of birth, admission to the NICU, clinical manifestations, laboratory test results, all medications and hospital course up to the time of discharge from the hospital or death which was documented on a pre-designed questionnaire. Data included specifics regarding the type of delivery, prolonged rupture of membranes, signs of chorioamnionitis, use of prenatal steroids, APGAR score at 1 and 5 minutes, details of resuscitative measures at birth, (including NCPAP/mechanical ventilation), any complications and use of TPN, Ranitidine, Ibuprofen during the hospital admission. The rate of nosocomial infection was determined in patients with and without different perinatal risk factors including, administration of H2 blockers (Ranitidine).

3.1. Statistical Methods

Categorical data were reported as frequency and percentage and continuous variables as mean ± standard deviation (SD). The relationship between nosocomial infection and suspected risk factors were evaluated by simple and multiple logistic regression analysis. P-values less than 0.05 considered as statistically significant.

4. Results

During the study period, 564 VLBW infants were admitted in the NICU; 157 (27.8%) contracted nosocomial infections, 130 (82.8%) developed pneumonia, 21 (13.4%) had sepsis with positive blood cultures, and 6 infants (1.1%) got necrotizing enterocolitis, (NEC).

Ranitidine was prescribed with a dose of 3mg/kg/day for 167 VLBW neonates (29.6%) whereas indications for prescription were as follows: GI bleeding, 149 infants; GER, 14 newborns and in 4 babies Ranitidine was administered along with TPN or postnatal steroid therapy. Simple regression analysis revealed the following risk FACTOR as significant for development of nosocomial infections: gestational age less than 28 weeks ($P < 0.001$), APGAR score less than 6 at 1 and 5 minutes ($P < 0.05$), bag and mask resuscitation at birth ($P = 0.01$), TPN ($P < 0.001$), respiratory distress syndrome ($P < 0.001$), chronic lung disease ($P < 0.001$), patent ductus arteriosus ($P < 0.001$), anemia ($P < 0.001$), leukopenia ($P < 0.001$), chest tube ($P = 0.001$), use of Ibuprofen ($P < 0.001$), treatment with Ranitidine ($P < 0.001$), increased duration of oxygen therapy ($P < 0.001$), and non-invasive ventilation ($P < 0.001$) (*Table 1)*.

Eighty-eight of the 167 neonates (52.7%), who were prescribed Ranitidine developed NI in comparison to 17.4% of the infants who did not receive this medication (OR = 5.30, P-value < 0.001). Variables with a P-value ≤ 0.15 and no sparse data were selected for multiple logistic regressions. Factors remaining independently significant for development of NI following adjustment were as follows: RDS ($P = 0.001$ OR = 3.29; 95% CI = 1.64–6.6), CLD ($P < 0.001$. OR = 3.83; 95%CI = 2.06–7.11), anemia ($P = 0.005$ OR = 1.96; 95%CI = 1.23-3.13), use of Ibuprofen ($P = 0.03$. OR = 1.99; 95%CI = 1.06-3.74), and treatment with Ranitidine ($P = 0.009$. OR = 1.92; 95%, CI = 1.18-3.12) (*Table 2)*.

Table 1. Demographic and Characteristic of Cases

Characteristic	With NIs (n = 157)	Without NIs (n = 407)	OR	95%CI	P-Value
Gender					
Male	87 (30.0%)	203 (70.0%)	1.25	0.86-1.81	0.24
Female	70 (25.5%)	204 (74.5%)	1		
Birth weight (gr)	1155 ± 257	1189 ± 258			0.16
≤ 750	12 (28.6%)	30 (71.4%)	1.22	0.59-2.53	0.44
751-1000	32 (30.5%)	73 (69.5%)	1.34	0.81-2.22	
1001-1250	48 (31.4%)	105 (68.6%)	1.4	0.9-2.18	
1251-1500	65 (24.6%)	199 (75.4%)	1		
Gestational age (Wk)	28.8 ± 2.0	30.0 ± 2.7			< 0.001
≤ 28	78 (39.8%)	118 (60.2%)	2.42	1.66-3.53	< 0.001
> 28	79 (21.5%)	289 (78.5%)	1		
Type of delivery					
Cesarean	114 (27.4%)	302 (72.6%)	0.92	0.61-1.40	0.70
NVD	43 (29.1%)	105 (70.9%)	1		
Antenatal steroid					
Administered	156 (27.8%)	406 (72.2%)	0.38	0.02-6.18	0.48
Not administered	1 (50.0%)	1 (50.0%)	1		
Chorioamnionitis					
Yes	3 (27.3%)	8 (72.7%)	0.97	0.25-3.71	1.00
No	154 (27.8%)	399 (72.2%)	1		
PROM					
Yes	14 (28.6%)	35 (71.4%)	1.04	0.54-1.99	0.90
No	143 (27.8%)	372 (72.2%)	1		
Apgar score at one minute	6.0 ± 2.0	6.5 ± 2.1			0.009
≥ 6	287 (74%)	101 (26%)	1		0.16
< 6	120 (68.2%)	56 (31.8%)	0.75	0.51-1.11	
Apgar score at five minute	7.6 ± 1.6	8.0 ± 1.7			0.02
Resuscitation at birth (bag ventilation)					
Yes	82 (33.3%)	164 (66.7%)	1.62	1.12-2.35	0.01
No	75 (23.6%)	243 (76.4%)	1		
Intubation at delivery room					
Yes	24 (34.8%)	45 (65.2%)	1.45	0.85-2.48	0.17
No	133 (26.9%)	362 (73.1%)	1		
RDS					
Yes	146 (36%)	259 (64%)	7.58	3.98-14.46	< 0.001
No	11 (6.9%)	148 (93.1%)	1		
PDA					
Yes	82 (44.8%)	101 (55.2%)	3.31	2.25-4.87	< 0.001
No	75 (19.7%)	306 (80.3%)	1		
IVH ≥ 3					
Yes	11 (44%)	14 (56%)	1		0.07
No	146 (27.1%)	393 (72.9%)	0.47	0.21-1.07	
CLD					

Yes	77 (74.8%)	26 (25.2%)	14.1	8.51-23.39	< 0.001
No	80 (17.4%)	381 (82.6%)	1		
Anemia					
Yes	108 (42.4%)	147 (57.6%)	3.9	2.63-5.78	< 0.001
No	49 (15.9%)	260 (84.1%)	1		
Leukopenia					
Yes	24 (48%)	26 (52%)	2.64	1.47-4.76	0.001
No	133 (25.9%)	381 (74.1%)	1		
Brufen					
Yes	51 (65.4%)	27 (34.6%)	6.77	4.05-11.32	< 0.001
No	106 (21.8%)	380 (78.2%)	1		
Ranitidine					
Yes	88 (52.7%)	79 (47.3%)	5.3	3.55-7.9	< 0.001
No	69 (17.4%)	328 (82.6%)	1		
Amino acid days	21.5 ± 17.8	10 ± 10.8			< 0.001
Interalipid days	8 ± 13.8	3 ± 7.5			< 0.001
Chest tube					
Yes	21 (48.8%)	22 (51.2%)	2.7	1.44-5.07	0.001
No	136 (26.1%)	385 (73.9%)	1		
Duration of O2 therapy	11.3 ± 12.2	4.3 ± 7.4			< 0.001
Duration of NIV	7.8 ± 11.1	1.4 ± 3.6			< 0.001
Duration of mechanical ventilation	12.3 ± 19	5.7 ± 7.3			0.14

Abbreviations: CLD, chronic lung disease; IVH, intra ventricular hemorrhage; PROM, premature rupture of membranes; RDS, respiratory distress syndrome

Table 2. Independent Risk Factors for NICU Nosocomial Infection

Characteristic	Adjusted OR	95%CI	P-Value
RDS	3.29	1.64-6.6	0.001
CLD	3.83	2.06-7.11	< 0.001
Anemia	1.96	1.23-3.13	0.005
Ibuprofen administration	1.99	1.06-3.74	0.03
Ranitidine administration	1.92	1.18-3.12	0.009

Abbreviations: CLD, chronic lung disease; RDS, respiratory distress syndrome

5. Discussion

Neonatal mortality rate is an indicator of the quality of health care and is regarded as an index of overall development of societies (16). TPN, using central venous catheters, (CVC), mechanical ventilation, administration of dexamethasone, indomethacin, Ibuprofen and Ranitidine have all been identified as risk factors for nosocomial infections in the NICU which in turn are the major cause of mortality in VLBW infants (17-21). NI occurred in approximately 28% of our VLBW infants; NI rates vary between 22-50% in reports from different parts of the world reflecting different levels of care and also the complexities of making a definite diagnosis, (4-6, 22). Similar to some other studies (5, 16, 23) pneumonia was the most frequent form of NI in our patients; some studies report sepsis as the most common presentation of NI (1, 3, 6). High prevalence of RDS and CLD in our patients necessitated the use of prolonged mechanical ventilation which may have been the major risk factor resulting in the high rate of pneumonia in our neonates. On the other hand, a lower rate of sepsis could be accounted by the fact that definite diagnosis of sepsis was only made in the presence of positive blood cultures which are vulnerable to various errors at multiple stages starting from sample collection till final isolation of the microorganism in the laboratory.

Although on simple regression analysis, various variables were shown to increase the rate of NI (*Table 1*), similar to some studies (5, 7, 17, 20) RDS, CLD, anemia and

administration of Ibuprofen and Ranitidine were the factors that remained significant following multiple regressions analysis (*Table 2*). Our results were in accordance with other reports (6, 7, 12, 20).

Use of Ranitidine was associated with increased risk of NI in our patients; this observation has been made in various other reports as well (3, 7-12, 21, 24, 25). Increased NI rates with H2 blocker usage have been attributed to the decline in the proteolytic activity of gastric secretions at pH ≥ 4 and colonization of the stomach by gram negative rods; aspiration of contaminated gastric contents may result in pneumonia and gram negative sepsis (25). Ranitidine is used empirically for prevention of stress ulcers, when blood is detected in the nasogastric tube and also with a presumptive diagnosis of GER in irritable infants or in babies with feeding difficulties (26). Although Ranitidine has not been approved for use in infants less than 1 year of old by the FDA, nevertheless according to different studies, use of Ranitidine increased 7 fold during the period of 1999-2004 and 4 fold during 2000-2003 (27). In 1994, Beck-Sague reported a 4 fold increase in the risk of NI following the use of H2 blockers, (21) subsequent studies have confirmed this observation (3, 7-12, 24). H2 blockers have been cited as being predisposing factors for nosocomial infections in neonatal textbooks, as well (28-30). Additionally, these drugs have not proved to be effective in decreasing the rate of lung damage, or clinical manifestations attributed to GER; also, no positive effect has been noticed on the growth and development of neonates (11, 30, 31). Usage of H2 blockers in neonate is associated with an increase in harmful side effects and an absence of any proven benefit. If indicated, then researchers cited the recommended dose as 0.5 mg/kg/twice daily, which should be given for less than 7 days, consider birth weight and gestational age regarding NEC, and discontinued if the infant is unresponsive (12, 21).

In our study, more than 50% of the 167 neonates who received Ranitidine (for an average duration of 11 days) developed NI, a figure which is significantly higher than those who were not given any H2 blocker whease other studies have reported related findings (3, 7-12, 21, 24, 25).

Our findings reveal that Ranitidine usage is associated with a significantly increased risk for nosocomial infections in VLBW infant. This drug should not be used empirically for prophylaxis of GI bleeding or presumed GER; if indicated for treatment then the least effective dose should be administered for the shortest possible duration. Moreover, risk benefit ratio of using H2 blockers should always be considered prior to starting treatment with these agents.

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Authors' Contribution

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References

1. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. *Pediatrics*. 2002;**110**(2 Pt 1):285-91.
2. Gaynes RP, Edwards JR, Jarvis WR, Culver DH, Tolson JS, Martone WJ. Nosocomial infections among neonates in high-risk nurseries in the United States. National Nosocomial Infections Surveillance System. *Pediatrics*. 1996;**98**(3 Pt 1):357-61.
3. Rojas MA, Efird MM, Lozano JM, Bose CL, Rojas MX, Rondon MA, et al. Risk factors for nosocomial infections in selected neonatal intensive care units in Colombia, South America. *J Perinatol*. 2005;**25**(8):537-41.
4. Pessoa-Silva CL, Richtmann R, Calil R, Santos RM, Costa ML, Frota AC, et al. Healthcare-associated infections among neonates in Brazil. *Infect Control Hosp Epidemiol*. 2004;**25**(9):772-7.
5. Kawagoe JY, Segre CA, Pereira CR, Cardoso MF, Silva CV, Fukushima JT. Risk factors for nosocomial infections in critically ill newborns: a 5-year prospective cohort study. *Am J Infect Control*. 2001;**29**(2):109-14.
6. Tavora AC, Castro AB, Militao MA, Girao JE, Ribeiro Kde C, Tavora LG. Risk factors for nosocomial infection in a Brazilian neonatal intensive care unit. *Braz J Infect Dis*. 2008;**12**(1):75-9.
7. Graham PL, 3rd, Begg MD, Larson E, Della-Latta P, Allen A, Saiman L. Risk factors for late onset gram-negative sepsis in low birth weight infants hospitalized in the neonatal intensive care unit. *Pediatr Infect Dis J*. 2006;**25**(2):113-7.
8. Guillet R, Stoll BJ, Cotten CM, Gantz M, McDonald S, Poole WK, et al. Association of H2-blocker therapy and higher incidence of necrotizing enterocolitis in very low birth weight infants. *Pediatrics*. 2006;**117**(2).
9. Kuusela AL, Ruuska T, Karikoski R, Laippala P, Ikonen RS, Janas M, 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**(2):346-51.
10. Bianconi S, Gudavalli M, Sutija VG, Lopez AL, Barillas-Arias L, Ron N. Ranitidine and late-onset sepsis in the neonatal intensive care unit. *J Perinat Med*. 2007;**35**(2):147-50.
11. Orenstein SR, Hassall E, Furmaga-Jablonska W, Atkinson S, Raanan M. Multicenter, double-blind, randomized, placebo-controlled trial assessing the efficacy and safety of proton pump inhibitor lansoprazole in infants with symptoms of gastroesophageal reflux disease. *J Pediatr*. 2009;**154**(4):514-20 e4.
12. Terrin G, Passariello A, De Curtis M, Manguso F, Salvia G, Lega L, et al. Ranitidine is associated with infections, necrotizing enterocolitis, and fatal outcome in newborns. *Pediatrics*. 2012;**129**(1):e40-5.
13. Emori TG, Culver DH, Horan TC, Jarvis WR, White JW, Olson DR, et al. National nosocomial infections surveillance system (NNIS): description of surveillance methods. *Am J Infect Control*. 1991;**19**(1):19-35.
14. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. *America J Infect Control*. 1988;**16**(3):128-40.

15. Afjeh SA, Sabzehei MK, Karimi A, Shiva F, Shamshiri AR. Surveillance of ventilator-associated pneumonia in a neonatal intensive care unit: characteristics, risk factors, and outcome. *Arch Iran Med*. 2012;**15**(9):567-71.
16. *Reduced Child Mortality: The Millennium Development Goals Report*. 2008 Available from: http://www.un.org/millenniumgoals/pdf/The%20Millennium%20Development%20Goals%20Report%202008.pdf.
17. Bizzarro MJ, Raskind C, Baltimore RS, Gallagher PG. Seventy-five years of neonatal sepsis at Yale: 1928-2003. *Pediatrics*. 2005;**116**(3):595-602.
18. Stoll BJ, Temprosa M, Tyson JE, Papile LA, Wright LL, Bauer CR, et al. Dexamethasone therapy increases infection in very low birth weight infants. *Pediatrics*. 1999;**104**(5):e63-e.
19. Herson VC, Krause PJ, Eisenfeld LI, Pontius L, Maderazo EG. Indomethacin-associated sepsis in very-low-birth-weight infants. *Am J Dis Child*. 1988;**142**(5):555-8.
20. Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants. *Cochrane Database Syst Rev*. 2010;**4**:CD003481.
21. Beck-Sague CM, Azimi P, Fonseca SN, Baltimore RS, Powell DA, Bland LA, et al. Bloodstream infections in neonatal intensive care unit patients: results of a multicenter study. *Pediatr Infect Dis J*. 1994;**13**(12):1110-6.
22. Nagata E, Brito AS, Matsuo T. Nosocomial infections in a neonatal intensive care unit: incidence and risk factors. *Am J Infect Control*. 2002;**30**(1):26-31.
23. Xu Y, Zhang LJ, Ge HY, Wang DH. [Clinical analysis of nosocomial infection in neonatal intensive care units]. *Zhonghua Er Ke Za Zhi*. 2007;**45**(6):437-41.
24. Garvey BM, McCambley JA, Tuxen DV. Effects of gastric alkalization on bacterial colonization in critically ill patients. *Crit Care Med*. 1989;**17**(3):211-6.
25. Jeong IS, Jeong JS, Choi EO. Nosocomial infection in a newborn intensive care unit (NICU), South Korea. *BMC Infect Dis*. 2006;**6**:103.
26. Khoshoo V, Edell D, Thompson A, Rubin M. Are we overprescribing antireflux medications for infants with regurgitation? *Pediatrics*. 2007;**120**(5):946-9.
27. Barron JJ, Tan H, Spalding J, Bakst AW, Singer J. Proton pump inhibitor utilization patterns in infants. *J Pediatr Gastroenterol Nutr*. 2007;**45**(4):421-7.
28. Fanaroff AA, Martin RJ. *Neonatal-perinatal medicine: diseases of the fetus and infant*. 1987.
29. Remington JS, Klein JO, Alpert JJ. Infectious diseases of the fetus and newborn infant. *Saunders*. 1995.
30. Frakaloss G, Burke G, Sanders MR. Impact of gastroesophageal reflux on growth and hospital stay in premature infants. *J Pediatr Gastroenterol Nutr*. 1998;**26**(2):146-50.
31. Malcolm WF, Gantz M, Martin RJ, Goldstein RF, Goldberg RN, Cotten CM. Use of medications for gastroesophageal reflux at discharge among extremely low birth weight infants. *Pediatrics*. 2008;**121**(1):22-7.