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Research Article

To determine whether duration of antibiotic exposure is an independent risk factor for NEC in NICU

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Abstract

Introduction: Necrotising enterocolitis is one of the major surgical emergencies of neonates admitted to NICU. The widespread use of antibiotics in the neonatal intensive care unit (NICU) population may contribute to gut colonization leading to NEC. This study helps in knowing about antibiotic exposure leading to NEC in the NICU. Thus helps in control of NEC.

Materials and Methods: A case control study of 84 neonates admitted to NICU was done over a period of 12months at Sri Adichuchanagiri Hospital and Research Centre. Out of these, 28 were cases which had received antibiotics. A detailed examination of the neonates was done to see the correlation between receiving antibiotics and NEC.

Results: The incidence of NEC was 5.9% of the neonates admitted to NICU.A significant relation between the use of antibiotics and development of NEC was found. The mean duration of onset of symptoms was 7days.The most common symptom among those affected was abdominal distension.

Conclusion: The rampant use of antibiotics in NICU without any specific protocol or guidelines could indirectly harm the baby.NEC has a significant contribution in neonatal deaths and the use of antibiotics unreasonably could be one of the causative factors in acquiring NEC and thus should be used with caution.

Keywords: NEC, antibiotics

1. Introduction

Necrotizing enterocolitis is the most common life threatening emergency of the gastrointestinal tract in the newborn period. The incidence of NEC is 1-5% of infants in the NICU.[1] It is believed to be a multifactorial disease process with risk factors including prematurity, low birth weight, enteral feeding and alterations in the bacterial colonization of the gut.[2] The mean gestational age of infants with NEC is 30-32weeks, and infants are generally weight appropriate for gestational age. Approximately 10% of infants with NEC are full term. The postnatal age of onset is inversely related to birth weight and gestational age with a mean age at onset of 12days.[3] The gut of a preterm infant cared for in a relatively aseptic neonatal intensive care environment and receiving antibiotics shortly after birth show delayed colonization with a limited number of bacteria species.[4]

The widespread use of antibiotics in the NICU population may contribute to aberrant gut colonization. Antibiotic exposure may reduce the biodiversity of the fetal microbiotia, delay beneficial colonization with normal gastrointestinal flora, and promote proliferation of pathogenic and antibiotic resistant organisms. Thus the increase in potentially pathogenic organisms and decrease in normal gut flora coupled with the impairment in the intestinal epithelial barrier may predispose preterm neonates to NEC.[5] NEC is recognised as the most common intra-abdominal emergency and is the leading cause of short bowel syndrome. With extremely high mortality and morbidity, this enigmatic disease remains a challenge for neonatologists around the world as its definite aetiology has yet to be determined.[6] The present study is designed to determine the association between antibiotic exposure and the risk of developing NEC in newborn intensive care unit.

2. Materials and Methods

The present study was carried out in Sri Adichunchanagiri Hospital and Research Centre, B.G. Nagara, Bellur. A prospective, 2:1 control-case study was performed to investigate the association between the duration of antimicrobial therapy and subsequent diagnosis of NEC among neonates born from December 2011 to December 2012, and admitted to the NICU. The duration of antibiotic exposure included the cumulative number of days a neonate was on any antibiotic. These data were initially collected in hours of exposure which was then converted into days. Data regarding the specific antimicrobial regimen utilized were also collected. Standard empiric antimicrobial therapy in the NICU during the study period included Ampicillin and Gentamicin or Cefotaxim and Amikacin as per the NICU protocol for use of antibiotics. Higher antibiotics like Vancomycin , Meropenem were used in neonates either not responding to the standard therapy or those with culture positive growth or ongoing sepsis. Stool for occult blood, complete hemogram, abdominal Xray's, serum electrolytes were done in order to confirm the diagnosis in neonates receiving antibiotics in NICU. The CRP and blood culture was also done for the neonates to check for any underlying sepsis as the cause for NEC. The CRP levels were repeated 3 days after the last CRP levels were obtained if indicated.

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%)The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc. A P value of $0.05<P<0.10$ was taken as suggestive significance. A P value $0.01<P \leq 0.05$ was moderately significant and a P value ≤ 0.01 was taken as strongly significant.

2.1 Method of collection of data

The case group: included 28 neonates diagnosed with NEC.

Inclusion Criteria: All neonates admitted in the NICU and diagnosed with NEC according to modified Bell's stage.

Exclusion Criteria: Neonates with Congenital malformations or infections, sepsis, neonates on H_2 blockers and those with history of maternal infection and prolonged PROM were excluded from the study

The Control Group: Each identified case was matched to two controls. It included 56 neonates who were not on any antibiotics. The control population included neonates without NEC with matching performed on age (number of hospital days prior to NEC in matched cases), gestational age (± 1 week), birth weight (± 200 grams) and Sex.

All neonates in the study had the following done:

- Stool for occult blood
- Complete hemogram
- Abdominal X-ray's
- Serum electrolytes
- The CRP and blood culture was also done for the neonates to check for any underlying sepsis as the cause for NEC

Sample Collection: The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1 , Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc**.**

3. Results and Observations

A total 474 newborns were admitted to the NICU. There were 28 cases of NEC accounting for 5.9% of total NICU admission. In our study, it was interestingly found that 67.9% babies were term.

This study showed that 32.1% of babies affected with NEC were born through normal vaginal route.67.9% of neonates was born through LSCS. In the present study the mean age for development of NEC was found to be 7 days. Duration of antibiotics was found to be significant in relation to NEC. Neonates receiving antibiotics for more than a period of 5 days was found to have more incidence of NEC.

Table 1: Duration of antibiotics

Duration of antibiotics	Cases	Controls	Total
Nil	0(0%)	56(100%)	56(66.7%)
<3	4(14.3%)	0(0%)	4(4.8%)
3-5	7(25%)	0(0%)	7(8.3%)
5-7	10(35.7%)	0(0%)	10(11.9%)
>7	7(25%)	0(0%)	7(8.3%)
Total	28(100%)	56(100%)	84(100%)

Duration of antibiotics is significantly associated with cases with P<0.001**

When the symptoms that the neonates exhibited were taken into account, it was found that 60.7% of the cases had abdominal distension. 39.3% of neonates in our study showed gross appearance of blood in stools, which was statistically significant. Among the cases, 75% had nasogastric aspirate before feeding and 50% had vomiting.

Table 2: Comparison of complications in two groups studied

Complications	Cases	Controls	Total	P value
Nasogastric aspirate	21(75%)	0(0%)	21(25%)	<0.001**
Vomiting	14(50%)	0(0%)	14(16.7%)	<0.001**
Iileus and distension	6(21.4%)	1(1.8%)	7(8.3%)	0.005**
Interloop thickening	3(10.7%)	0(0%)	3(3.6%)	0.034*
Pneumatosis intestinalis	2(7.1%)	0(0%)	2(2.4%)	0.108
Portal venous gas	0(0%)	0(0%)	0(0%)	-
Pneumoperitoneum	0(0%)	0(0%)	0(0%)	-

The antibiotics used in the neonates comprised of either a combination of ampicillin and gentamycin, cefotaxim and amikacin or other higher antibiotics like piperacillin with tazobactom or meropenem. This study showed that among the cases, 60.7% had received cefotaxim with amikacin and 25% had received ampicillin with gentamycin.

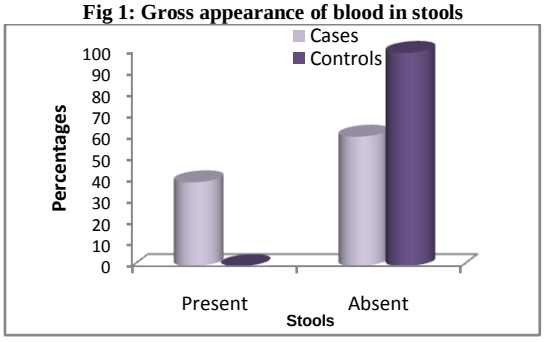
The group which did not receive any antibiotic comprised of 7.1% and 2 neonates had received higher antibiotic which was piptaz and meropenem. These two babies were switched over to higher antibiotic because they were clinically deteriorating. Surgical intervention was not required in any of the babies because most of the babies were categorized into stage I and II as per Bells Staging criteria.

It was seen that in this study, the sodium levels were significantly affected in the neonates with NEC.64.3% of the cases had hyponatremia. In the control group, 89.3% had normal sodium levels, whereas 3.6% showed hyponatremia.

The potassium levels did not show any statistical significance. The potassium levels were not altered with the development of NEC.

Out of the 28 cases, except for 1 case, all the other neonates had a positive stool for occult blood. This could probably suggest that stool for occult blood would invariably be positive in NEC.

Fig 1: Gross appearance of blood in stools



Thrombocytopenia was seen in all the cases with NEC.39.3% showed mild thrombocytopenia, whereas 28.6% and 14.3% showed moderate and severe thrombocytopenia respectively.

This study showed a majority of cases with normal leukocyte count, 71.4%. When compared to the controls, 98.2% in the control group had normal leukocyte count.

The CRP levels were measured to check if there is any underlying sepsis, as it is a marker of infection. It did not show any significance. But it was seen that 13.1% of the study group had a positive CRP.

4. Discussion

Stoll et al stated that the incidence of NEC is most often as 1% to 7% of all neonatal intensive care unit (NICU) admissions, or 1 to 3 per 1,000 live births[7] which was similar to our study. Population studies from India on this condition are not widely publicised and to do this it requires a definition criteria, as many cases of NEC might get coded as 'sepsis'. More of term babies showed symptoms of NEC in this study. This could be because the etiology of NEC in the full-term population seems to differ from the etiology for the preterm group in its intestinal location and in the timing of its onset as stated by Maayan-Metzger et al in his study.[8]

Caesarean section deliveries may be associated with increased necrotizing enterocolitis. This association is more pronounced in newborn infants >1500 g compared to those <1500 g. Further studies are needed to explore underlying mechanisms.

Grosfeld et al[9] reported on a 25-year cohort of infants with surgical NEC and identified average age at diagnosis of 13 days for infants with BW.1000 g and 21days for infants with BW ,1000 g. The authors of previous epidemiologic studies have described early- and late-onset NEC with early-onset NEC presenting in the first week of life in term infants.

In the present study the mean age for development of NEC was found to be 7 days. When the symptoms that the neonates exhibited were taken into account, it was found that majority of the cases had abdominal distension. The antibiotics used in the neonates comprised of either a combination of ampicillin and gentamycin, cefotaxim and amikacin or other higher antibiotics like piperacillin with tazobactom or meropenem. This study showed that among the cases, 60.7% had received cefotaxim with amikacin and 25% had received ampicillin with gentamycin.

There are not many studies with regards to NEC and antibiotics. However, Vanaja et al[2] in his study reported that the type of antibiotic exposure differed only with respect to a significantly higher proportion of clindamycin use in the case population as compared with controls. C.Michael Cotton *et al* conducted a retrospective cohort analysis from 1998-2001, conducted on 5693 extremely low birth weight neonates concluded that prolonged initial empirical antibiotic therapy may be associated with increased risk of necrotizing enterocolitis or death and should be used with caution.[10]

It was seen that in this study, the sodium levels were significantly affected in the neonates with NEC.64.3% of the cases had hyponatremia. The potassium levels did not show any statistical significance. The potassium levels were not altered with the development of NEC..This study is supporting the study done by Badowics[11], who in his study showed that neonates with NEC had significantly lower sodium level and he stated that hyponatremia may constitute an easily available laboratory finding serving as an indicator for surgical intervention in NEC.

All neonates had a positive stool for occult blood, excluding one. This could probably suggest that stool for occult blood would invariably be positive in NEC.

Our study showed that thrombocytopenia was an important lab parameter in diagnosing NEC. Mitul parikh found that Platelet counts were found to decrease significantly with the progression of disease in NEC.[12]The leucocyte count did not differ significantly among the case and control group. The CRP levels were measured to check if there is any underlying sepsis, as it is a marker of infection. It did not show any significance.

5. Conclusion

Necrotising enterocolitis is a major problem accounting for a significant number of NICU admissions. Although it was thought to be that preterms are more affected with NEC due to immaturity of gut ,it is seen that there are other factors which can cause NEC in term neonates as well .In this study ,it was seen that antibiotics do have an important role in development of NEC in term as well as preterm neonates. As sepsis is a co morbid condition arising with NEC, a clear cut line of separation between NEC and sepsis could not be done.

This study is an attempt to decrease the widespread use of antibiotics in NICU and thus in turn helps in preventing NEC. Although there are many factors which can be attributed to the development of NEC, the use of antibiotics could be regarded as one of the preventable factors in development of NEC.

This study further emphasizes on the need of clinical and laboratory evidence before starting antibiotics for the neonates. This helps in controlling the rampant use of antibiotics in the NICU until its proven to be a boon or bain.

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