


Introducing multi-modal enteral medication reduced morbidity and mortality associated with necrotising enterocolitis

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Abstract

Aim: Necrotising enterocolitis (NEC) is still a disease with high morbidity and mortality. The aim of the study was to analyse retrospectively whether the introduction of a multi-modal three-component enteral medication regimen resulted in a change in morbidity and mortality in neonates with NEC.

Methods: When diagnosis of NEC was established, the following multi-modal three-component enteral medication regimen was administered enterally (via nasogastric tube): an antibiotic, an antifungal agent and a probiotic. The primary outcome parameters were intestinal perforation, surgical interventions and mortality during the observational periods.

Results: In the study period, 2212 patients were admitted to the NICU, out of which 200 (9%) developed NEC. Significantly fewer infants died in the Intervention Group (13 of 104 infants, 13%) compared to the Control Group (38 of 96 infants, 40%) ($P = .0001$). No infant in the Intervention Group (0%) presented with an intestinal perforation, as compared to 15 infants (16%) within the Control Group ($P = .0001$). In the Control Group, 21 infants (22%) needed surgical intervention, whereas 0 (0%) infants needed this in the Intervention Group.

Conclusion: The introduction of an enteral multi-modal three-component medication regimen resulted in a significant reduction of mortality and of need for surgical intervention in infants suffering from NEC.

KEYWORDS

enteral therapeutic approach, morbidity, mortality, necrotising enterocolitis, preterm infants, term infants

Abbreviations: BW, body weight; CMV, conventional mechanical ventilation; HFNC, high flow nasal cannula; IUGR, intrauterine growth restriction; NCPAP, nasal continuous positive airway pressure; NEC, necrotising enterocolitis; NICU, neonatal intensive care unit.

Arman Harutyunyan and Berndt Urlesberger both authors contributed equally to this study.

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1 | INTRODUCTION

Neonatal necrotising enterocolitis (NEC) is still the most frequent lethal disease of the gastrointestinal tract in preterm neonates.^{1,2} The usual onset of this disease is between the 7th and 14th day of life, although the later onset of NEC was documented in the literature.^{3,4} The clinical presentation of NEC includes variable signs, which are often non-specific for gastrointestinal dysfunction. According to Bell, NEC is classified into three stages.⁵ Stages 3A and 3B, in particular, are advanced stages of disease and are associated with a high mortality since they lead to intestinal perforation with peritonitis, septic shock and the need for surgical interventions.

Necrotising enterocolitis is still a disease with a high mortality rate. A systematic review article presented contemporary outcome numbers for infants with NEC. The overall mortality was 23.5% in all neonates with confirmed NEC (Bell stage 2+), 34.5% for neonates that underwent surgery for NEC, 40.5% for extremely low birth weight infants (<1000 g) and 50.9% for extremely low birth weight infants with surgical NEC.⁶ Necrotising enterocolitis is not only a disease of preterm infants: in a retrospective chart analysis of 170 infants, NEC was found in 28 (17%) term infants.⁷ A 5-year analysis before the start of the present study in a third level University Neonatal Intensive Care Unit (NICU) at the Muratsan Clinical Complex in Yerevan, Armenia, showed that out of 3028 admitted newborn infants, 213 (7%) presented with a diagnosis of NEC.⁸ Of these 213 patients, 11 (5%) were term-born infants, and 77 (36%) died, thus showing a high NEC-associated mortality rate in Armenia.⁸ It is well known that preterm infants with NEC not only have a high mortality but also a high morbidity, with significantly longer hospitalisation times and significantly higher treatment costs compared to infants without NEC.^{9,10} Several studies have identified interventions that resulted in reductions of the incidence of NEC, such as breast milk feeding, use of probiotics, progression of enteral feeds and enteral antibiotic prophylaxis.¹¹⁻¹³

Due to the high incidence of NEC and high NEC-associated mortality in Armenia, some doctors from Armenia spent an observer ship period at the Medical University of Graz, Austria, at the Department of Pediatric Surgery and the Division of Neonatology. In these two units in Austria, they saw the use of a NEC prevention protocol, which had been used over the last 20 years, and which resulted in a very low incidence of NEC of 1% in preterm neonates less than 1500 g.¹⁴ The Graz protocol is a multi-modal three-component regimen for NEC prevention and consists of enteral application of a probiotic in combination with enteral application of an antibiotic and an antifungal substance. Based on the data of the Medical University of Graz, the same regimen was introduced at the NICU of Muratsan Clinical Complex at Yerevan State Medical University, Armenia. The Muratsan Clinical Complex is the main level III referral hospital for neonates in Armenia. As no neonates are born in the clinical complex, the multi-modal three-component enteral medication regimen was initially introduced in neonates who had been transferred to the hospital, and in which the diagnosis of NEC (of any stage according to Bell's criteria) was already established. Thus, the regimen was not

Key notes

- Necrotising enterocolitis is still associated with high mortality and morbidity.
- The present study analyses retrospectively how the introduction of a multi-modal three-component enteral medication regimen as a new therapeutic approach reduced necrotising enterocolitis associated mortality and morbidity.
- The results of this retrospective analysis need prospective studies to prove efficacy of such a new approach.

used as preventive medication, as published by Schmolzer et al,¹⁴ but as a therapeutic approach. Only in a second step was a preventive approach for NEC in all preterm infants of Muratsan Clinical Complex planned for the future.

The aim of the present single-centre, retrospective, case-control study was to analyse the impact of the introduction of the multi-modal three-component enteral medication regimen on morbidity and mortality of neonates with NEC by comparing the periods 12 months before versus 24 months after regime-introduction. It was hypothesised that the multi-modal three-component enteral medication regimen possibly causes a reduction of morbidity and mortality in neonates with NEC.

2 | METHODS

2.1 | Study design and patients

The single-centre, retrospective, case-control study was conducted at the NICU of Muratsan Clinical Complex of Yerevan State Medical University. The Graz protocol of multi-modal three-component regimen for NEC prevention was introduced, but the present analysis does not include any patients of Graz.

The Graz protocol of multi-modal three-component regimen for NEC prevention consists originally of enteral application of a probiotic, *Lactobacillus rhamnosus*, in combination with enteral application of an antibiotic, gentamicin and an antifungal substance, nystatin.¹⁴ For the implementation at the Muratsan Clinical Complex in Armenia, the Austrian protocol was revised as the same probiotic was not available in Armenia. It was therefore replaced with the synbiotic LactoG, which was locally available. This synbiotic consists of a prebiotic, fructooligosaccharide, in a 37.5 mg/capsule and probiotics containing the following strains: *Bifidobacterium longum* [1×10^9 CFU/capsule], *Bifidobacterium bifidum* [1×10^9 CFU/capsule], *Bifidobacterium infantis* [1×10^9 CFU/capsule] and *Lactobacillus acidophilus* [2×10^9 CFU/capsule]. Thus, in Yerevan the following medication was administered enterally via a nasogastric tube: an enteral antibiotic gentamicin sulphate [7.5 mg/kg BW-12 hourly], an antifungal agent nystatin [2.500 IU/

kg BW–6 hourly] and a synbiotic [LactoG: BW < 2000 g–¼ capsule pulveris 12 hourly; BW > 2000 g–½ capsule pulveris 12 hourly].

In the present analysis, only neonates with an already established diagnosis of NEC in all stages were included. During the Intervention period A (1 December 2016 to 30 November 2017), patients with NEC received the multi-modal three-component enteral medication regimen described above. During this period, parents had to give informed written consent to the use of the multi-modal three-component enteral medication regimen. Ethical approval was received for implementation of this protocol from the Internal Committee of YSMU Muratsan Clinical Complex (reference number 0/29-1061/1 30 November 2016). After Intervention period A, a local interim analysis was done, and the hospital decided that the multi-modal three-component scheme was included as standard in the local NEC treatment protocol. Therefore, during Intervention period B (1 December 2017 to 30 November 2018) no parental consent was needed anymore. As there were parents, that refused consent during Intervention period A, the infants without parental consent did not receive the multi-modal

three-component enteral medication regimen during that period. These infants were enclosed into Control Group. Furthermore, we enclosed into Control Group infants from a historical Comparison period (1 December 2015 to 30 November 2016), during which no enteral medication was given. Intervention Group consisted of infants from Intervention periods A, who had received the multi-modal three-component medication regimen, and all infants of Intervention period B (see Figure 1).

The impact of the multi-modal three-component enteral medication regimen was analysed by comparing Intervention versus Control Group using the following primary outcome parameters: intestinal perforation, surgical interventions and mortality during the observational periods. A secondary outcome parameter included the stage of NEC according to Bell at establishment of diagnosis and the maximum stage reached. Diagnosis of NEC was carried out according to accepted international standards using the Bell stages.⁷ Additionally to the enteral medication, all infants received a standard iv Antibiotics regimen, which consisted of penicillin G (100 mg/kg BW 12 hourly), and gentamicin (4 mg/kg BW 24 hourly).

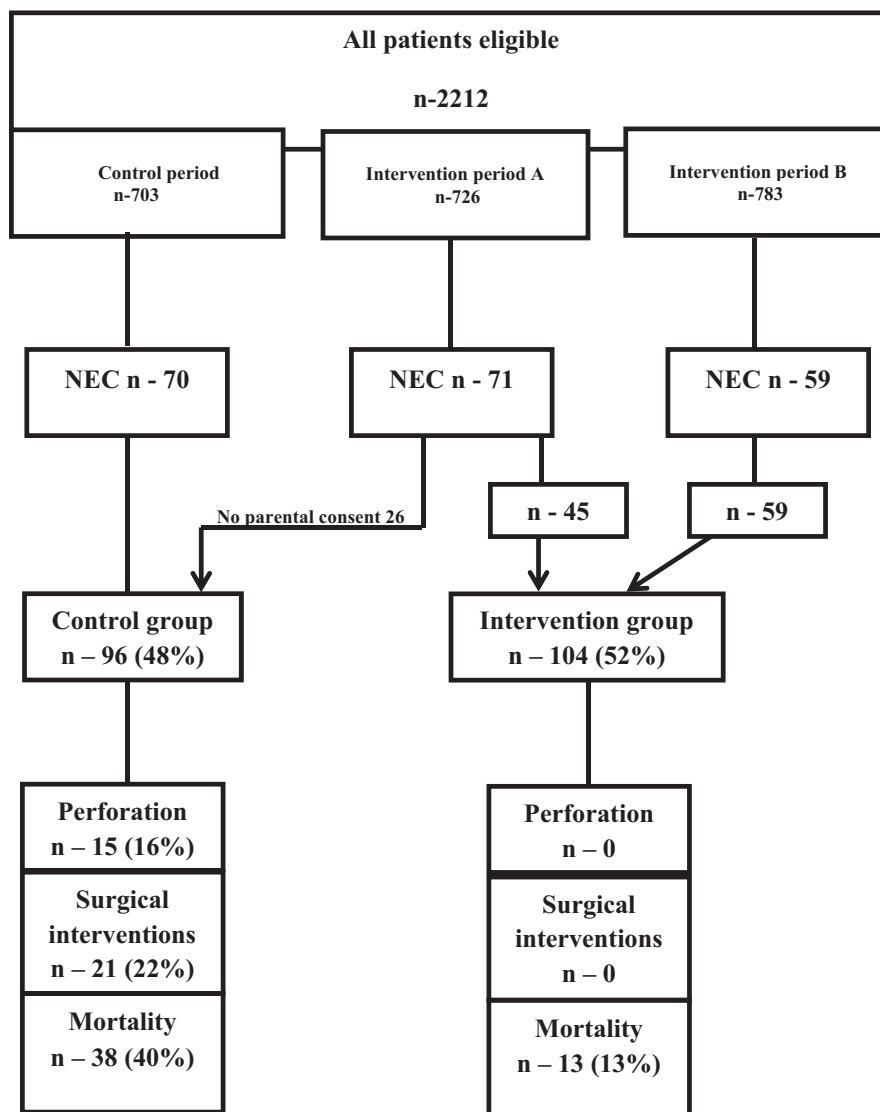


FIGURE 1 Flow-chart displaying the enrolment, group assignment and results. During Control period (1 December 2015–30 November 2016) no enteral medication was done. During the Intervention period A (1 December 2016–30 November 2017) and Intervention period B (1 December 2017–30 November 2018) patients with NEC received the multi-modal three-component enteral medication regimen

TABLE 1 Demographic data of included infants

	Intervention group (n = 104)	Control group (n = 96)	P value
Birth weight, g Median (Interquartile range)	1785 (932.5)	1605 (1205)	.61
Male Gender (%)	46%	56%	–
Gestational age, wk Median (Interquartile range)	33 (5)	32 (6)	.29
IUGR, N (%)	15 (16%)	25 (24%)	.06
Term newborns, N (%)	16 (15%)	18 (19%)	.92
Preterm infants (≥ 1500 g), N (%)	53 (51%)	35 (36%)	.70
Preterm infants (<1500 g), N (%)	35 (34%)	43 (45%)	.86
Apgar 1 min Median (Interquartile range)	6 (2)	6 (3)	.07
Apgar 5 min Median (Interquartile range)	7 (1.25)	7 (2)	.09

Abbreviation: IUGR, intrauterine growth restriction.

An indication for surgical laparotomy was the presence of intestinal perforation diagnosed using abdominal x-ray.

Analysed hospital records included information regarding demographics, prescribed medications, procedures and diagnoses of infants. Demographic data included sex, birth weight (BW), gestational age (GA) and Apgar score. Whether mortality was due to NEC or other causes was defined according to the results of autopsy and histological examination.

2.2 | Statistical analysis

Mean values and standard deviation (SD) were used for descriptive analysis; if there was no normal distribution, median and interquartile range (IQR) were used. Fisher's exact test was performed to analyse the group differences and threshold probability; value of $P < .05$ was used to indicate statistical significance. The t test was performed to compare group differences. Microsoft Excel (Microsoft Cooperation) and Epi Info tools (Centers for Disease Control and Prevention) were used for statistical analysis.

3 | RESULTS

In the study period, 2212 patients were admitted to the NICU. During the historical Control period, 703 patients were admitted, 70 (10%) of which presented with NEC. During Intervention period, A 726 patients were admitted, 71 (10%) of which presented with NEC. During Intervention period, B 783 patients were admitted, 59 (8%) of which presented with NEC. Out of the 71 NEC patients of Intervention period A, who met the inclusion criteria, 45 (63%) infants were exposed to the multi-modal three-component enteral medication regimen and 26 (37%) did not receive the medication

TABLE 2 Clinical data of the included infants

	Intervention group (n = 104)	Control group (n = 96)
CMV	41 (39%)	37 (38%)
NCPAP	46 (45%)	43 (45%)
HFNC	17 (16%)	16 (17%)
NEC diagnosis, d after birth (Mean \pm SD)	6.8 (± 5.7)	6.9 (± 4.9)
NEC diagnosis, d after admittance (Mean \pm SD)	3.4 (± 3.6)	4.2 (± 3.7)
Intestinal perforation with subsequent surgery, d after admittance (Mean \pm SD)	No perforation No surgery	10.8 (± 6.5) (N = 15)

Abbreviations: CMV, conventional mechanical ventilation; d, days; HFNC, high flow nasal cannula; NCPAP, nasal continuous positive airway pressure; NEC, necrotising enterocolitis.

regimen, because parents did not give consent. They were merged with the infants of the historical Control period, forming the Control Group (Figure 1). Thus, all infants of Intervention period A, who received the medication, plus all infants of Intervention period B were summed up to form the Intervention Group. The Intervention Group included 104 patients, whereas the Control Group included 96 patients (Figure 1). Table 1 shows the demographic data of both groups. There were no significant differences between the two groups in regard to demographic data. The nutritional protocol consisted of minimal enteral feeding starting on day one. Of all admitted infants, 89 (93%) in the Control Group and 98 (94%) in the Intervention Group received formula feeding. As there is no human milk banking system in Armenia, the number of infants receiving breast milk was small, only 7 (7%) in the Control

Group and 6 (6%) in the Intervention Group. As the NICU is a tertiary referral centre, all 200 infants were transferred due to serious illness, and all of them needed respiratory support (Table 2). In the Control Group 31 (32%) infants were admitted with a diagnosis of NEC, and 49 (47%) infants in the Intervention Group. Details of the day of diagnosis of NEC and days until surgery are shown in Table 2. The multi-modal three-component enteral medication regimen was given for 23.4 (± 16.4) (mean/ \pm SD) days in the Intervention group.

Out of 200 infants with NEC, 51 (26%) died. Significantly fewer infants died in the Intervention Group (13 infants, 13%) compared to the Control Group (38 infants, 40%) ($P = .0001$, OR: 0.2, CI – 0.1–0.4). According to the autopsy reports, mortality was directly linked to NEC in 15 infants (16%) in the Control Group, but in none (0%) in the Intervention Group ($P = .0001$). Furthermore, the number of deaths not associated with complications due to NEC (pneumothorax, intracranial haemorrhage and septicaemia) was 13 (13%) in the Intervention Group, compared to 28 infants (30%) in the Control Group ($P = .003$, OR: 0.34, CI – 0.16–0.7). Hence, both overall mortality and NEC-related mortality were reduced significantly in the Intervention Group compared to the Control Group (Figure 1).

No infant in the Intervention Group (0%) presented with an intestinal perforation, as compared to 15 infants (16%) in the Control Group ($P = .0001$). All 15 infants with intestinal perforation from the Control Group were treated surgically, three received abdominal drainage and 12 underwent laparotomy.

4 | DISCUSSION

Necrotising enterocolitis continues to be one of the most devastating diseases affecting preterm infants in particular, with persistent high mortality and morbidity.⁶ Injury in NEC usually begins with a breach of the intestinal mucosal barrier leading to bacterial translocation across the epithelium and exacerbation of the inflammatory cascade, resulting in the clinical signs of NEC. The most common NEC-associated morbidity includes intestinal perforation and sepsis, intestinal stricture, short-bowel syndrome and parenteral nutrition-induced cholestasis.¹⁵

The introduction of a multi-modal three-component enteral medication regimen in infants with NEC was associated with a significant reduction in NEC-associated morbidity and mortality. Compared to the Control Group in the Intervention Group, there was a significant reduction in the need for surgical interventions, and most importantly, a significant reduction in mortality. Not only was there no longer any NEC-associated mortality in patients in the Intervention Group, there was also reduced mortality from causes not primarily associated with NEC. To our knowledge, there is no study in the literature using an enteral medication regimen approach in preterm infants already suffering from NEC. Until now, all the literature analysed involves attempting to reduce NEC incidence by various prevention strategies. The present study adds a

new perspective which describes the possible therapeutic power of such an approach in the management of NEC by showing a reduction in NEC-associated morbidity and mortality. Such an approach may be potentially important especially in countries where there is still a high NEC-associated mortality and morbidity. Following international protocols, all infants with NEC did not receive any type of enteral feeding, but only the multi-modal three-component enteral medication regimen.

The use of probiotics to prevent NEC has been investigated by many trials. The authors' of a Cochrane Review mentioned in their conclusion, that enteral supplementation of probiotics prevents severe NEC and all-cause mortality in preterm infants.¹¹ However, the authors advocated that further studies are needed to assess the most effective preparation, timing and length of therapy to be used.¹¹ The present study used a synbiotic LactoG, which is both a probiotic and prebiotic, as this preparation was available in Armenia. In 2017, a publication showed that the prophylactic use of an oral synbiotic was associated with a significant reduction in the primary outcome, a combination of death and sepsis in India.¹⁶ In 2017, a systematic review of the literature showed that the use of preventive probiotics has significant potential to reduce mortality and morbidity in preterm neonates in low-income and middle-income countries, too. Taking the results of the present study into consideration, we speculate that probiotics may not only be helpful in prevention of NEC, but they may play even a therapeutic role in the reduction of NEC-associated morbidity and mortality, too.

In 2000, a Cochrane analysis suggested that the use of enteral antibiotics is effective in prevention of NEC.¹⁸ However, this strategy has never been widely adopted due to concerns about emergence of resistant bacteria and absorption of antibiotics from the gut. These concerns about emergence of resistant bacteria are important for a preventive approach, but may have less importance in a restricted use in patients with already diagnosed NEC. With all precautions necessary, the present study indicates a possible role of oral Gentamycin in treatment of NEC. Oral gentamicin is not absorbed during its passage within the gastrointestinal tract and does not affect calculation and prescription of parenteral antibiotics.^{18–20} In 2020, it was shown that the use of an oral antibiotic for prevention of NEC was found not to be associated with a reduced diversity or reduced abundance of microbiome signatures within the first 2 weeks of life.²¹ There is always a need for iv antibiotic regimens in the treatment of NEC. Until now different iv antibiotic regimens were used for treatment of NEC, but several randomised and quasi-randomised controlled trials provided insufficient evidence to recommend a particular antibiotic regimen for the treatment of NEC.²² In the present study, patients received antibiotics intravenously as routine management in both groups without any changes in administration policy during the observation period.

Regarding the use of antifungal substances, experience of using such agents among preterm infants in the prevention of systemic *Candida* infections has been good using both application modalities, oral administration and IV administration.^{23,24}

Incidence of NEC varies all over the world. Whereas in some countries the focus of efforts is on prevention of NEC, in other countries the focus of efforts is on reduction of mortality rates. Nevertheless, what is indisputable is that this disease still has high mortality rates all over the world. Until now, therapeutic approach of the disease focused on parenteral antibiotics, management of septicaemia and strictly parenteral nutrition. Adding a further treatment option, namely the use of an enteral medication regimen might be interesting for all countries. We are aware that further prospective randomised studies will be necessary to enable such a therapeutic approach, but we see this report as being very important in moving such endeavours on.

Limitations of this analysis have to be acknowledged. As this was a retrospective observational analysis, the multi-modal three-component enteral medication regimen was applied not at the same day of life for all infants since the infants were admitted to the hospital at different days of life. We cannot differentiate whether one component or all three components of the regimen were responsible for the results. Further studies are needed to analyse these aspects in future. For the moment, however, we have to consider all three to be potentially important.

As it is a retrospective analysis possible bias cannot be ruled out. There was no blinding of the doctors to the multi-modal three-component enteral medication regimen. Nevertheless, indication for surgery was diagnosis of bowel perforation, which seems quite objective. No obvious changes in structure of staff were reported. Nevertheless, a retrospective analysis cannot completely rule out changes in the structure of staff of a NICU. As no newborn infants are actually born at Muratsan Clinical Complex, the preterm and term infants being transferred may vary in their medical history. The authors tried to compensate for this by including infants in that analysis only after diagnosis of NEC. It cannot be ruled out that there was some absorption of gentamycin via the gastro-intestinal tract, as there were no blood level measurements of gentamycin. The authors are unable to report in detail on possible kidney toxicity in infants included in the study. All included infants underwent otoacoustic testing before discharge – there were no reports of pathological findings. This was a retrospective observational case-control analysis. As such, it is only hypothesis generating. Larger prospective and randomised trials will have to prove the described observation.

5 | CONCLUSION

A multi-modal three-component enteral medication regimen was introduced as a new therapeutic approach in neonates with NEC. Introduction of this regimen resulted in significantly reduced NEC-associated morbidity and mortality in the Intervention Group. To our knowledge this is the first study to report the use of an enteral medication regimen to reduce NEC-associated morbidity and mortality. The results of the present study potentially have great impact on treatment of NEC in the future, especially in countries with a high NEC incidence. Nevertheless, as the present data are only

observational data, they are only hypothesis generating. Further prospective and randomised studies with larger cohorts are needed to verify the effects described in the present study.

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CONFLICT OF INTEREST

The authors have no conflict of interests to declare.

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