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ORIGINAL ARTICLE

Prolonged initial empirical antibiotic treatment and the risk of morbidity and mortality in very low birthweight infants

Tratamiento antibiótico empírico inicial prolongado y riesgo de morbimortalidad en recién nacidos de muy bajo peso al nacer

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Abstract

Introduction: The objective of this study is to evaluate the association between the duration of initial empirical antibiotic treatment and the subsequent development of late-onset sepsis, necrotizing enterocolitis (NEC) and death in very low birth weight (VLBW) infants. **Patients and Methods:** Quantitative, cross-sectional, analytical study of VLBW infants admitted to the neonatal ICU were included over a period of five years. Initial empirical antibiotic therapy was that which started immediately after birth, without knowing the results of blood cultures. It was considered prolonged antibiotic therapy when the treatment duration was ≥ 5 days. Perinatal variables, as well as the incidence of late-onset sepsis, confirmed NEC and mortality were analyzed. **Results:** 266 VLBW infants were studied, with an average gestational age and birth weight of 28.8 ± 2.5 weeks and 1.127 ± 264 g respectively. 213 infants received initial empiric antibiotic therapy (80.0%), which was prolonged in 67.6% of cases. All infants received two different antibiotics. 136 episodes of late-onset sepsis were described. The most common pathogens were *coagulase-negative Staphylococcus* and *Staphylococcus aureus*. Among the newborns with prolonged antibiotic therapy, there were 20 cases of confirmed NEC and 15 of the studied infants died (10.4%). When comparing the use of antibiotic therapy during ≥ 5 days versus treatment less than 5 days duration, a statistically significant association was observed between prolonged antibiotic therapy and late-onset sepsis ($p = 0.03$) and confirmed NEC ($p = 0.03$), but not of mortality ($p = 0.12$). **Conclusion:** The use of empirical antibiotic therapy for five days or more was associated with an increased risk of late-onset sepsis and NEC, but not of mortality in VLBW infants.

Keywords:
Prolonged initial empirical antibiotic; late-onset sepsis; necrotizing enterocolitis; mortality

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Introduction

Antibiotics are among the most commonly used drugs in preterm newborns (NBs) hospitalized in neonatal intensive care units[1-3]. Exposure to antibiotics in very low birth weight (VLBW) neonates can lead to several alterations such as reduction of microbiota biodiversity, delay of normal colonization of the gastrointestinal tract, and/or proliferation of pathogenic organisms that may be resistant to antibiotics[3-6].

The increase in potentially pathogenic organisms, the decrease in the normal intestinal flora, along with the deterioration in the intestinal epithelial barrier produces an abnormal colonization of the gastrointestinal tract; increasing the risk of invasion of the intestinal wall with translocation, and the production of inflammatory cytokines, all of which can trigger nosocomial sepsis, necrotizing enterocolitis (NEC), and secondarily death[3-8].

In recent years, some reports have described in VLBW neonates the association between prolonged initial empirical antibiotic treatment and subsequent adverse events[9-13]. These studies have shown that prolonged initial empirical antibiotic treatment ≥5 days in VLBW neonates without positive cultures increases the risk of developing late sepsis, NEC, and death in this group of patients[9-13].

The hypothesis of this study was that prolonged initial empirical antibiotic therapy in VLBW neonates would be associated with an increase in the incidence of nosocomial sepsis, NEC, and/or death.

Since there is no national information on the effect of the prolonged empirical antibiotic use on VLBW neonates, the objective was to determine the association between the duration of prolonged initial empirical antibiotic treatment and the subsequent development of late sepsis, NEC, and/or death in VLBW neonates whose postnatal cultures were negative.

Patients and Method

Design

Quantitative, analytical cross-sectional study. All VLBW neonates admitted to the Neonatal Intensive Care Unit of the Neonatology Service of the Guillermo Gran Benavente Hospital, Concepcion (HGGB), between January 1, 2009 and December 31, 2013 (five years) were included. A retrospective analysis of the clinical records of VLBW neonates with gestational age less than 32 weeks and/or birth weight less than 1,500 g, who survived more than seven days without developing early sepsis and who received initial empirical antibiotic treatment was performed. Neonates with major congenital anomalies, chromosomal abnormalities, and also those transferred from another hospital and with early proven sepsis (positive blood cultures and/or CSF) were excluded.

Definitions

Initial empirical antibiotic treatment was considered to be that which was initiated since birth, without presenting clinical sepsis, and with negative blood and CSF cultures at 72 hours of life. Prolonged initial empirical antibiotic therapy was established when its duration was five days or more. Clinical sepsis was considered when cultures were negative, but the NB showed three or more of the following signs: increased or decreased axillary temperature (< 36.5°C or > 37.5°C), lethargy, apnea, bradycardia, respiratory distress, abdominal distension, blood in stool; increased oxygen requirements, prolonged capillary filling time, hypotension; associated with alterations in laboratory tests such as: hyperglycemia, thrombocytopenia <150.000/mm^3, leukopenia <5000/mm^3 or leukocytosis >25.000/mm^3, CSF: >10 mg/dl [14-15].

Early confirmed sepsis was considered in cases of clinical sepsis with positive blood cultures and/or CSF cultures in the first 72 hours of life, and late sepsis those with clinical sepsis plus positive blood cultures and/or CSF cultures after 72 hours of life.

Only patients with confirmed NEC (stage ≥II according to Bell classification[16] were considered for the study. Neonatal mortality was defined as that which occurred during the first 28 postnatal days.

Statistical analysis

A univariate analysis was performed in which quantitative variables are presented as mean and standard deviations, while qualitative variables are presented in absolute and relative percentage frequency. In order to determine the risk between prolonged duration (≥5 days) and late sepsis, confirmed NEC, and neonatal death, we analyzed through logistic regression. A $p<0.05$ was considered significant using the statistical software SPSS version 19.0.

This study was approved by the Scientific Ethics Committee of the Concepción Health Service.

Results

266 VLBW neonates were analyzed, with a gestational age and mean birth weight ±SD of 28.8 ± 2.5 weeks and 1127 ± 264 g respectively. 131 of them were male (57.7%). Out of the total cases, 80.1% (213/266) received empirical antibiotic therapy and 19.9% (53/266) did not receive initial antibiotics.

Out of the 213 VLBW neonates that received initial antibiotic therapy, it was prolonged in 67.6% of cases

Table 1. Demographic and perinatal characteristics in 213 VLBW infants with prolonged and non-prolonged initial empirical antibiotic treatment

	Prolonged antibiotics (n = 144)	Non-Prolonged antibiotics (n = 69)	p
Gestational Age (Mean ± SD)	27.8 ± 2.0	28.2 ± 2.2	0.52
Birth Weight (Mean ± DS)	1.040 ± 257	1.190 ± 245	0.66
Weight Appropriate to the GA, n (%)	97 (85.1)	53 (76.8)	0.20
Male sex, n (%)	88 (61.1)	32 (46.4)	0.06
Antenatal corticoids, n (%)	123 (85.4)	60 (86.9)	0.83
Cesarean section, n (%)	101 (70.1)	56 (81.1)	0.10
Apgar 5′ ≤ 5, n (%)	13 (9.0)	4 (5.8)	0.59

(144/213). Table 1 shows the demographic characteristics and perinatal history among neonates who received prolonged and not prolonged initial empirical antibiotic therapy. No differences in demographic or perinatal characteristics were observed between the two groups.

In neonates who received initial empirical antibiotics, ampicillin and amikacin were the most commonly used regimen (97%). Out of the 213 NBs with prolonged initial empirical antibiotic therapy, 122 episodes of late sepsis were investigated, of which 80 (65.6%) were bacteriologically proven. 96 pathogenic agents were identified, the most frequent were coagulase-negative Staphylococci, Staphylococcus aureus, Enterobacter cloacae, Acinetobacter baumannii, and Pseudomonas aeruginosa (Table 2).

There were 20 confirmed NEC cases; of them, half required surgical intervention. Out of the 213 VLBW neonates with initial empirical antibiotic therapy, 15 (10.4%) died. There was a statistically significant association between the use of prolonged initial empirical antibiotic therapy and late sepsis (p = 0.03), with an OR of 1.88 ; and with the development of NEC (p = 0.03), with an OR of 9.71; but no evidence of increased mortality (p = 0.12) (Table 3).

Table 2. Pathogens isolated in confirmed late onset sepsis

Pathogens isolated	N	(%)
Staphylococcus coagulasa negativo	37	(38.5)
Staphylococcus epidermidis	12	(12.5)
Stahpylococcus aureus	8	(8.33)
Enterobacter cloacae	7	(7.3)
Acinetobacter baumannii	5	(5.2)
Pseudomonas aeruginosa	5	(5.2)
Enterococcus faecalis	5	(5.2)
Klebsiella pneumoniae	5	(5.2)
Others	12	(12.5)

Table 3. Logistic regression of associated morbidities, according to prolonged treatment of empirical antibiotics

Morbidities	OR	IC 95%	p-value
Late onset sepsis	1.88	1.05 - 3.37	0.03
NEC	9.71	1.27 - 74.35	0.03
Mortality	3.35	0.73 - 15.28	0.12

Discussion

In the Neonatology Service of the HGGB, in the period analyzed approximately 80% of the VLBW neonates received initial empirical antibiotic therapy for an undetermined period of time. Antibiotics are among the most commonly prescribed medications in neonatal intensive care units[1-2]. According to Clark[1] the antibiotics most frequently used in newborns as initial empirical therapy are ampicillin and gentamicin; similar to what was observed in the studied population, with the exception of amikacin to replace gentamicin. The reason why in our center we use amikacin instead of gentamicin is the fact that the most common bacterial isolates are non-fermenting gram-negative bacilli and Pseudomonas aeruginosa, microorganisms that are more sensitive to amikacin than to gentamicin.

In this study, as in other publications[1,3], it is confirmed that a high percentage of preterm NBs who do not have confirmed early sepsis are unnecessarily exposed to prolonged antibiotic use.

The initial and prolonged empirical use of antibiotics in the neonatal population has previously been

described as a possible risk factor in the development of late sepsis, NEC, and death[9-13]. Empirical administration of antibiotics may induce abnormal colonization of the gastrointestinal tract of the neonate by inhibiting or eradicating protective bacteria and favoring the proliferation of potentially pathogenic micro-organisms[4-8]. Different studies have determined that the overgrowth of pathogenic species is higher after three days of exposure to antimicrobials [9,11].

Cotten et al[9] reported that exposure to prolonged initial empirical antibiotic therapy longer than or equal to five days with negative blood cultures was associated with an increased likelihood of the combined outcome of NEC and/or death (OR 1.50 (95% CI: 1.22 - 1.83]); only NEC (OR:1.34 [95% CI: 1.04 - 1.73]), and death (OR:1.86 [95% CI:1.45 - 2.39]) in extremely low birth weight neonates (<1000 g). On the other hand, Kuppala et al[11] showed that the duration of initial antibiotic therapy longer than or equal to five days in preterm NBs less than 32 weeks of gestation, with negative blood cultures in the first week of life, was subsequently associated with an increase in late sepsis, NEC and death[11]. Another case-control study[10] evaluated if exposure to antibiotic therapy immediately after birth was an independent risk factor for NEC and reported that the longer duration of antibiotic therapy was associated with a higher risk of bacteriologically proven late sepsis, and NEC[10], consistent with the results of this study.

Ting et al[17] also analyzed the rate of antibiotic use (antibiotic days/days of hospitalization) and reported a 10% increase in risk of adverse outcomes. They considered as adverse outcomes stage 3 or higher retinopathy of prematurity, mortality, and the compound outcome (mortality and/or significant morbidities, such as periventricular leukomalacia, bronchopulmonary dysplasia, or retinopathy). Cantey et al[18] also evaluated the impact of antibiotic exposure on VLBW neonates, finding that each additional day of antibiotics, after reaching clinical improvement, increased the risk of developing bronchopulmonary dysplasia, which was also more severe[18]. Similar studies in Egypt[12], Australia[13], and Mexico[19] have also reported results consistent with the above publications, confirming the risk of prolonged exposure to antibiotics in VLBW neonates. The results of these publications[9-13,17-19] are similar to the findings of this study, in which it was observed that prolonged exposure (≥5 days) to empirical antibiotics after birth increased the risk of late sepsis and NEC, OR=1,88, and OR=9,71 respectively. It should be noted that in all these reports[9-13,17-19], the studied population has similar characteristics (very low or extreme low weight NBs). On the other hand, there is a high rate of positive blood cultures (65.6%) among the cases of late clinical sepsis in this study, where the most frequently isolated microorganism is the coagulase-negative Staphylococcus, which is consistent with what has been reported in other studies[9,11,13].

Despite the solid evidence reported in the above studies[9-13,17-19], the excessive and inadequate use of empirical antibiotics is a reality in many health centers. A clinical analysis with a cohort of 742 extremely low birth weight neonates with negative blood cultures reported that 60% of the NBs received empirical antibiotics for more than three days[20], concluding that the duration of initial empirical antibiotic therapy was an institutional decision and not based on obvious clinical signs and symptoms of infection [20].

In addition to the consequences that the prolonged exposure to antibiotics can have for NBs, this clinical practice implies an important cost for hospitals, both in terms of supplies and length of stay[1,3,21-22]. Based on international information and that obtained in the current study, it would not be reasonable or ethical to conduct a randomized controlled prospective study, but it would be possible to conduct a prospective, but not randomized, case-control study to determine if the use of empirical antibiotics prolonged for five days or more is associated with different morbidities and mortality. Therefore, the proper and justified use of antibiotics, especially in VLBW neonates, is a clinical as well as an institutional necessity.

In recent years there has been greater awareness regarding the responsible use of antibiotics, especially in VLBW neonates[23]. As a consequence, different strategies have been developed in order to reduce the indication and duration of these treatments. One of them is the re-evaluation and adaptation of clinical guidelines for diagnosis and treatment of sepsis[24] or the development of predictive mathematical models[22] that have succeeded in reducing the use and abuse of antibiotics.

Recently, strategies have also been implemented in Chile in order to adapt the use of antimicrobials in Neonatology units[25], which has resulted in a reduction both in cases of late sepsis and in the associated costs[25].

In conclusion, the use of initial empirical antibiotic therapy ≥ 5 days was associated with an increased risk of late sepsis and NEC, no association was found with mortality. It is necessary to constantly evaluate and monitor the prudent use of initial empirical antibiotics in VLBW neonates and to timely discontinue the therapy if blood cultures are negative and the clinical condition of the neonate allows it.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

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Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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