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ORIGINAL ARTICLE

Implementation of a protocol proposed by the Brazilian National Health Surveillance Agency for antibiotic use in very low birth weight infants☆

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Abstract
Objective: To analyze the implementation of a protocol proposed by the Brazilian National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária – ANVISA) to improve sepsis diagnosis in very low birth weight newborns.
Methods: This was a prospective study that evaluated the implementation of a protocol involving clinical and laboratory criteria (hematologic scoring system of Rodwell and C-reactive protein serial measurements), recommended by ANVISA, to improve the diagnosis of neonatal sepsis in very low birth weight newborns. The study included all patients who were born and remained in the neonatal intensive care unit until discharge or death, and excluded those with congenital diseases. The main outcomes measured in newborns before (2006-2007) and after implementation of the protocol (2008) were the rates of early and late-onset sepsis, use of antibiotics, and mortality. Means were compared by Student's *t*-test and categorical variables were compared by the chi-squared test; the significance level for all tests was set at 95%.
Results: The study included 136 newborns with very low birth weight. There was no difference between groups regarding general clinical characteristics in the studied periods. There was, however, a decrease in the number of diagnoses of probable early-onset sepsis ($p < 0.001$), use of antimicrobial regimens ($p < 0.001$), and overall mortality and infection-related mortality ($p = 0.009$ and $p = 0.049$, respectively).
Conclusion: The implementation of the protocol allowed improvement of sepsis diagnosis by reducing the diagnosis of probable early-onset sepsis, thus promoting efficient antimicrobial use in this population.

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PALAVRAS-CHAVE
Sepse neonatal;
Recém-nascido de muito baixo peso;
Diagnóstico

Aplicação de protocolo proposto pela Agência Nacional de Vigilância Sanitária (ANVISA) para uso de antibióticos em recém-nascidos de muito baixo peso

Resumo

Objetivo: Analisar a aplicação de um protocolo proposto pela Agência Nacional de Vigilância Sanitária (ANVISA) para aprimorar o diagnóstico de sepse em recém-nascidos de muito baixo peso.

Métodos: Estudo prospectivo que avaliou a aplicação de protocolo envolvendo critérios clínicos e laboratoriais (escore hematológico de Rodwell e dosagem seriada da proteína C-reativa), recomendado pela ANVISA, para aprimorar o diagnóstico de sepse neonatal em recém-nascidos de muito baixo peso. Participaram do estudo todos os pacientes que nasceram e permaneceram na Unidade Neonatal até a alta ou óbito, e foram excluídos aqueles com doenças congênitas. Os principais desfechos analisados entre os recém-nascidos antes da aplicação do protocolo (2006-2007) e após a aplicação do mesmo (2008) foram as taxas de sepses precoce e tardia, o uso de antimicrobianos e a mortalidade. As médias foram comparadas por meio de teste *t* e as variáveis categóricas pelo teste Qui-quadrado (X^2); o nível de significância para todos eles foi fixado em 95%.

Resultados: Foram incluídos no estudo 136 recém-nascidos de muito baixo peso. Não houve diferença entre os grupos em relação às características clínicas gerais nos períodos estudados. Houve, no entanto, redução na quantidade de diagnóstico de sepse precoce provável ($p < 0,001$), de uso de esquemas antimicrobianos ($p < 0,001$) e da mortalidade geral e associada à sepse ($p = 0,009$ e $p = 0,049$, respectivamente).

Conclusão: A utilização do protocolo permitiu aprimorar o diagnóstico de sepse, reduzindo aquele de sepse precoce provável, promovendo, desta forma, o uso racional de antimicrobianos na população estudada.

Introduction

In spite of advances in obstetric care and intrapartum use of antimicrobial agents for streptococcal infection prophylaxis, neonatal sepsis remains an important cause of morbidity and mortality in newborns (NBs), especially in those who weigh less than 1,500 g.[1–7] The clinical picture of neonatal sepsis and laboratory diagnosis are usually nonspecific.[8,9] Blood cultures, which are considered the gold standard, have widely variable positive results and may be false negative in 20% of cases; moreover, their results are not readily available to define the therapeutic conduct.[10–13] Thus, neonatologists often empirically administer antibiotics to symptomatic NBs or those at high risk of sepsis, while awaiting culture results; even when cultures are negative, they tend to not withdraw the use of antimicrobials.[7]

In 2008, the Brazilian National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária - ANVISA) submitted to public consultation a handbook for the diagnosis of healthcare-related infections (HCRI) in neonatology,[14] which established the diagnosis of primary infection of the bloodstream based on the use of hematological clinical criteria (hematologic scoring system of Rodwell), serial measurements of C-reactive protein (CRP), and partial results of blood cultures collected at the time of sepsis diagnosis.[15,16] The association of normal leukocyte count with serial measurements of negative CRP may help to rule out this diagnosis within one to three days of clinical evolution, increasing the probability of a correct diagnosis.[7,15]

This study aimed to analyze the impact of using a protocol recommended by ANVISA to improve the diagnosis of probable sepsis in NBs with very low weight.

Methods

This prospective study was conducted to analyze the implementation of a protocol for the diagnosis of neonatal sepsis based on clinical and laboratory criteria, in NBs with birth weight of 1,500 g or less from January, 2006 to December, 2008. The period of protocol implementation (January-December 2008) was termed the post-intervention period; the previous period was termed pre-intervention. The study included all patients who were born and remained in the neonatal intensive care unit (NICU) until discharge or death, and excluded those with congenital malformations or diseases, those transferred from other health services, and those who died on the same day as birth.

The study was performed in the NICU of Hospital Universitário Antônio Pedro of the Universidade Federal Fluminense (HUAP/UFF), consisting of 15 beds with a mean of 250 admissions/year. The hospital has a clinical routine that consists of two neonatologists in charge of medical decisions, including the use of antimicrobial agents. Protocol implementation was supervised daily by the clinical routine, and the team's adherence was considered to be very good. During the study period, there were no changes in the health unit staff nor additions of technological features that could differentiate the study periods. There was no obstetric