The Use Of Sepsis Calculator In Neonatal For Diagnosis And Management Early Onset Sepsis: a Meta-Analysis

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Abstract

Neonatal sepsis has non-specific and variable clinical manifestations that can worsen rapidly. Thus clinicians will tend to have a low threshold for giving antibiotics. Early diagnosis of sepsis based on clinical and laboratory manifestations is required to initiate antibiotics without waiting for culture results. The sepsis calculator is a validated tool used and researched in various countries to predict the risk of early-onset sepsis. This systematic review and meta-analysis study used secondary data from articles between 2015 to 2020 from the PubMed database, Google Scholar. There were six lead articles that matched the inclusion and exclusion criteria. By analyzing using the Revman Review Manager 5.4. the results showed that the implementation of the sepsis calculator was associated with reduced antibiotic usage (N=172385; OR=0,22;p<0,00001) heterogeneity I^2=99%). From this study, it was found that there was an association between sepsis calculators with antibiotic usage in neonatal with early-onset sepsis.

Keywords: antibiotic usage; early onset sepsis; neonates; sepsis calculator

1. Introduction

Neonatal sepsis is classified into two types based on the age at which it occurs, namely early onset sepsis that occurs within <72 hours and late onset sepsis that occurs after 72 hours of age [1]. Early onset sepsis can cause fatal morbidity in neonates with an incidence of 0.77 cases/1000 live births in 2005-2008. This incidence decreased to 0.5 cases per 1000 in infants more than 37 weeks gestation compared to 3 cases per 1000 live births in infants < 37 weeks gestation with an incidence of 3.71 per 1000 live births. The incidence of neonatal sepsis is one to five per 1000 live births in developed countries, while in developing countries the rate is still higher, namely 10-50 per 1000 live births [2].

The management of early onset sepsis recommended by the American academy of Pediatrics (AAP) is to give antibiotics to newborns with suspected early sepsis regardless of clinical parameters. Antibiotic therapy in the first few weeks of life, including changes in intestinal microbes, increased drug resistance in sepsis and increased fungal infections [3]. The clinician's main challenges are to promptly identify neonates with suspected early onset sepsis and initiate antimicrobial therapy, to differentiate healthy looking infants at high risk or infants with clinical signs of sepsis with available therapies, and to discontinue antimicrobial therapy when there is no evidence of sepsis [4].

The sepsis calculator is a validated tool that has been widely used and researched in various countries to predict the risk of early onset sepsis. The sepsis calculator can be used for newborns over 34 weeks gestation with the probability of early onset sepsis per 1000 live births of specific risk factors for the mother and the condition of the baby [5]. With the sepsis calculator method, not all infants with suspected early onset sepsis will be given antibitics. The use of antibiotics can be reduced by more than 50% by using the sepsis calculator method [6].

Therefore, this systematic review meta-analysis study was initiated to study the consistency of the results of studies that have been carried and to conduct a systematic review of studies reporting outcomes following implementation of sepsis calculator in the management of neonatal EOS.

2. Material and Methods

In this study, the research questions used PICO (Population, Intervention/Issue, Comparison/Context, and Outcome). Research literature was sought through free search or electronic databases. The electronic database in this research literature search used PubMed and Google Scholar to identify relevant research. In this step searching for keywords (search terms) using Boolean Operators (Search Commands) include: AND / OR / NOT. The keywords (search terms) used were “antibiotic usage” OR “infants” OR “sepsis calculator”. The inclusion criteria in this research were journals published between 2015-2020, derived from the PubMed and Medline databases, research subjects are neonates born > 34 weeks of gestation, a prospective cohort study with use of sepsis calculator for management of early onset sepsis vs standard approach (control) as per Centers for Disease Control and Prevention (CDC) guidlines, and used a random effects model assuming wide heterogeneity. Categorical measure of effect size was expressed as odds ratio (OR) (Mantel Haenszel method). The exclusion criteria were case-study articles or case series, major chromosomal and congenital anomalies, literature reviews. The collected data is managed according to the preferred reporting items for systematic review and meta-analysis (PRISMA). All articles collected are identified, screened, eligible, and included to determine which articles were to be analyzed. In assessing the quality of research and journal feasibility, there are several criteria used to evaluate the research results and the journals used. The checklist in Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) was used to evaluate the methodological quality of the study.

In data preparation, the important information is transferred from the selected literature into certain forms/tables to make it easier for researchers to identify the literature. In this study, a modified data collection form from Cochrane (The Cochrane Library) was used. This data collection form from Cochrane contains the identity, characteristics, methods, and results of the research specifically to make it easier for researchers to analyze the literature reviewed and then present it in tabular form to make it easier for researchers to analyze the characteristics of the research being reviewed. The data that has been collected is analyzed using meta-analysis, which is a combination of statistical research results from two or more separate and similar studies, to answer research questions. The Meta-Analysis process includes calculating the treatment effect (using the odds ratio) and the confidence interval in each study, calculating the overall treatment effect as a summary of the results of the analysis. The Meta-Analysis process is carried out using the Revman Review Manager 5.4 software [7]. The results of the meta-analysis are described and explained in the form of forest plots and narratives to facilitate understanding and provide clearer conclusions to readers on the results of the research and synthesis of the articles reviewed, and funnel plots to see any publication bias.

3. Results

There were 6 studies selected from the screening of titles related to the sepsis calculator of antibiotic usage for neonatal early onset sepsis [8] [9] [10] [11] [12] [13]. The determination of the selected research criteria is based on the availability of data and the validity of the measurement method. The following is the PRISMA flow diagram in Figure 1.

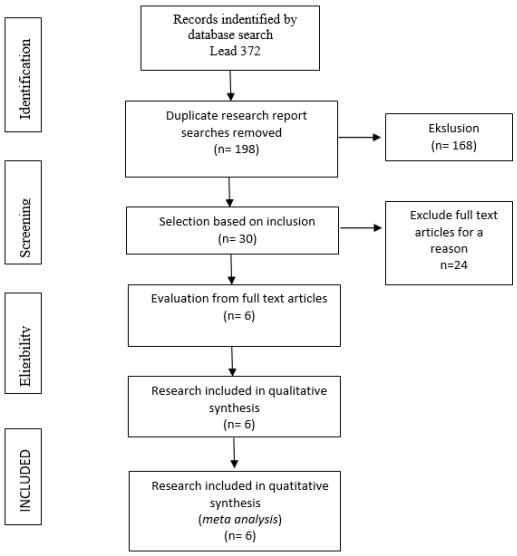

Fig. 1. PRISMA flow chart

Of the 372 articles originally identified in the literature search, 6 studies qualify for inclusion criteria and all studies evaluated antibiotic usage. All studies included in the review were of high methodological quality based on the checklist on Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) shown in Table 1.

Table 1. Assessment of article's quality

Title	Study design	Setting	Participants	Variables	Data Sources/Measurement	Bias	Study Size	Quantitative Variables	Statistical Method	Score
Kuzniewicz et al, 2017	+	+	+	+	+	+	+	+	+	9
Achten et al, 2018	+	+	+	+	+	+	+	+	+	9
Strunk et al, 2017	+	+	+	+	+	+	+	+	+	9
Dhudasia et al, 2018	+	+	+	+	+	+	+	+	+	9
Gievers et al, 2018	+	+	+	+	+	+	+	+	+	9
Beavers et al, 2018	+	+	+	+	+	+	+	+	+	9

Data extraction was carried out using a modified data collection from Shaikh. The data that the researcher collected from the articles included: author, article title, research location, research sample, study design, purpose, and results shown in Table 2.

Table 2. Lead journal characteristics

No.	Study Country	Gest weeks/Sample size (N)	Desain	Main outcome	Results
1	Kuzniewicz 2017 USA	>35 N=151604 SC=56261 C=95343	Prospective cohort	1. Antibiotics administration in first 24 hours 2. Use of blood culture 3. Antibiotics administration between 24 and 72 hours	1. Reduction in antibiotic use from 5 to 2,6% 2. Reduction in blood culture use from 14,5% to 4,9% 3. No difference in antibiotic use between 24 and 72 hours
2	Achten 2018 Netherlands	>35 N=3953 SC=1877 C=2076	Prospective cohort	1. Antibiotics usage for EOS 2. Adherence to sepsis calculator 3. Time to start antibiotics therapy	1. Reduction in antibiotics use 2,7 vs 4,8% (p<0,001) 2. Sepsis calculator adherence was 91% 3. No difference in start or duration of antibitics
3	Strunk 2017 Australia	>35 N=4234 SC=2502 C=1732	Prospective cohort	1. Antibiotics usage for EOS	1. Reduction for antibiotics usage from 12% to 7,6% (p<0,001)
4	Dhudasia 2018 USA	>36 N=11782 SC=6090 C=5692	Prospective cohort	1. Antibiotics usage for EOS 2. Use of any laboratory test for evaluation of EOS	1. Reduction in antibiotics use 6,3% to 3,7% (p<0,001) 2. Reduction in use of any laboratory test for EOS from 26,9% to 4,9%
5	Gievers 2018 USA	>35 N=356 SC=143 C=213	Prospective cohort	1. Antibiotics usage for EOS 2. Use of laboratory test for evaluation EOS	1. Reduction in antibiotics from 95% to 9% (p<0,01) 2. Reduction in use of laboratory test for EOS from 96% to 22% (p<0,01)
6	Beavers 2018 USA	>34 N=256 SC=76 C=180	Prospective cohort	1. Use of antibiotics	1. Reduction in antibiotics use from 94% to 37% (p<0,001)

EOS:Early onset sepsis; SC:sepsis calculator; C:control; N:sample/size

In this systematic review, analysis was done by meta-analysis method using Review Manager 5.4 software. At the meta-analysis stage, it was carried out by summarizing and comparing the odds ratio and the confidence interval from the sepsis calculator with the results of using antibiotics for neonatal early onset sepsis. Here are the forest results plot in Figure 2.

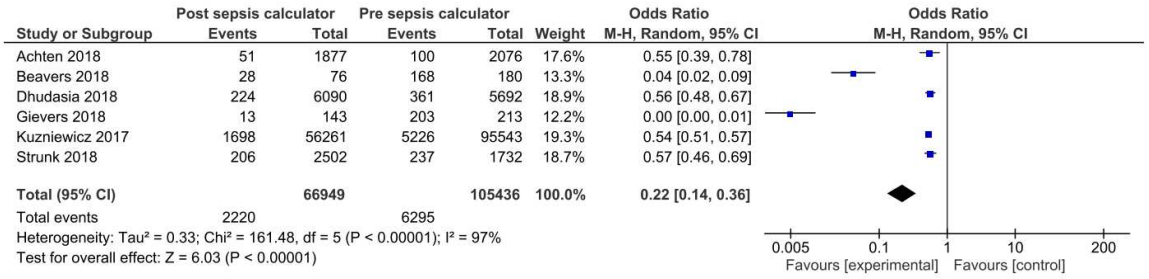

Fig. 2. Forest plot results of sepsis calculator for use antibiotics in neonatal with EOS

There are 6 journals reporting prenatal outcomes with antibiotics usage of 6,03 (95% CI 0,22; 0,36), p< 0,00001. This indicates that the p-value <0.05, means a significant correlation was found between sepsis calculator with antibiotics usage in neonatal with EOS. This study is heterogeneous because it can be seen in the results of 97% Tau^2 heterogeneity, so a random-effects model is used as the results merger.

4. Discussion

Suspected sepsis in one of the most common diagnoses made in the NICU. However, the signs of sepsis are non-specific, most infants with suspected sepsis recover with supportive care with or without antibiotics. The sepsis calculator is a validated tool for predicting early onset sepsis. The program combines existing data on the mother and the condition of the baby as a consideration in the management of early onset sepsis. The sepsis calculator can be used for newborns over 34 weeks with the probability of early onset sepsis per 1000 infants born of specific risk factors from the mother and the condition of the baby. The risk of sepsis at birth was divided into three groups, namely low risk, medium risk and high risk. And the risk score is combined with clinical examination of the newborn during the first 12 hours of life [14].

There are 6 journals reporting prenatal outcomes with antibiotics usage of 6,03 (95% CI 0,22; 0,36), p< 0,00001. This indicates that the p-value <0.05, means a significant correlation was found between sepsis calculator with antibiotics usage in neonatal with EOS. This study is in line with the research done by Gievers (2018) where 356 infants met the inclusion criteria, 203 of the 213 infants in the pre sepsis calculator received antibiotics, 13 of the 143 infants in the post sepsis calculator received antibiotics with p<0,01. In a study conducted by Beavers (2018), there were 180 babies before the implementation of the sepsis calculator who received 158 antibiotics, and there were 76 babies who used the sepsis calculator in which 28 babies received antibiotics with a p value <0,01. A study conducted by Achten (2017) states 100 of 2076 babies from the control group received antibiotics, while 51 of 1877 babies received antibiotics after using a sepsis calculator with p<0,001. A study conducted by Dhudasia (2018) states, 361 of 5692 babies in the group control received antibiotics, while 224 of 6090 babies received antibiotics after the use of a sepsis calculator with p<0.01.

The strengths of our review include its robust methodology, large sample size, inclusion of only prospective studies, exploration of heterogeneity, and useof STROBE guidlines for summarizing the level of evidence. The precision of our results is supported by the tight confidence intervals, and the p values suggesting small role of chance. The limitations of our review include the fact that the data originated from non-RCTs which are prone to biases and overestimate the effect size. Furthemore, all included studies wre conducted in high income

countries. It is important to note that the EOS related mortality is particularly high in low and middle income countries. The lack of data from such setting thus limits the external validity of our results. Irrespective of the set up, the ability to provide adequate monitoring is important for implementation of sepsis calculator.

5. Conclusions

In summary, moderate quality evidence indicates that the implementation of the sepsis calculator for management of EOS was associated with significant reduction in usage of antibiotics in neonates born >34 weeks gestation.

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