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EFFICACY AND SAFETY OF PROCALCITONIN GUIDANCE IN REDUCING DURATION OF ANTIBIOTIC TREATMENT IN NEONATAL INTENSIVE CARE UNIT

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ABSTRACT

Background: Procalcitonin has emerged as a valuable biomarker in guiding antibiotic therapy duration for patients with sepsis, aiding clinicians in optimizing treatment and reducing antibiotic resistance risks.

Objective: To determine the efficacy and safety of procalcitonin guidance in reducing duration of antibiotic treatment in neonatal intensive care unit.

Study design: A cross-sectional study design was used.

Settings: The study was conducted at Department of Pediatrics CMH, Multan From November 2023 to February 2024.

Methods: Neonates included in the study were ≤ 28 days old and required antibiotic therapy for suspected infections. The process of randomization was carried out using computer-generated random numbers. The procalcitonin group received antibiotic therapy guided by procalcitonin levels, whereas the standard group received antibiotic therapy according to prevailing clinical guidelines. Primary outcomes were the duration of hospitalisation in the intensive care unit (ICU) and the length of time antibiotics were administered. The data collected was analysed using IBM SPSS, specifically version 27.0.

Results: The gender distribution was similar between groups: females were 44.8% (Procalcitonin) and 45.9% (Standard), and males were 55.2% (Procalcitonin) and 54.1% (Standard). Mean gestational age was 38.31 ± 2.41 weeks (Procalcitonin) and 38.08 ± 2.03 weeks (Standard). ICU stay was shorter in Procalcitonin (9.88 ± 4.83 days) vs. Standard (11.3 ± 3.68 days), p=0.002. Antibiotic duration was shorter in Procalcitonin (5.91 ± 2.99 days) vs. Standard (7.28 ± 3.26 days), p<0.001. Procalcitonin mortality was lower (16.0%) vs. Standard (27.4%), p=0.013. Reinfection

rates were similar: Procalcitonin (10.4%) vs. Standard (8.9%), p=0.648. Antibiotic complications were comparable: Procalcitonin (2.5%) vs. Standard (4.5%), p=0.325.

Conclusion: In conclusion, our study supports the use of a serum procalcitonin-based algorithm in critically ill neonates, demonstrating reductions in antibiotic duration, ICU stay, and secondary infection rates

Keywords: Procalcitonin, antibiotic therapy, neonatal intensive care unit, antimicrobial stewardship, clinical outcomes

INTRODUCTION

Infections are the leading cause of neonatal mortality worldwide. Neonatal sepsis is categorized into early onset, typically presenting experiencing breathing difficulties within 72 hours after being born, and late onset, manifesting as septicemia after 72 hours [1]. It continues to be a significant contributor to illness and death, with fatality rates ranging from 3% to as high as 50%, especially in cases involving gram-negative organisms. Globally, neonatal sepsis is a significant due to morbidity and mortality, with a probable 3 million cases happening annually [2]. Neonatal sepsis has been reported to cause a significant number of neonatal mortalities in Pakistan; it's estimated incidence is 7%. It hence entails 8 deaths per 1,000 live births. Neonatal sepsis is extremely prevalent in countries with middle- and low-income levels emphasizes the necessity for reasonable and secure antibiotic management programs [3].

The irrational use of antibiotics (ABs) has negative effects and thus plays a huge role in escalating the problem of antibiotic resistance around the world. This problem led to an estimated 700,000 deaths in the year 2014 and it is projected to get worse and could be the leading cause of death in the globe with an approximate of 10 million lives taken every year by the year 2050 [4]. ICU patients are at higher risk of acquiring infections by MDROs because they are critically ill, immunocompromised and are exposed to more devices and staff, which significantly increase the rates of morbidity and mortality [5]. This article shows that neonates, especially those born prematurely are at a very high risk of acquiring infections due to their immune inexperience. Hence, knowledge of certain precise characteristics implying infection clearance could greatly assist physicians to make better decisions on antibiotic therapy in regard to the specific patient [6]. Markers that are frequently used to this end are the C-reactive protein and the leukocyte count. These biomarkers provide significant roles in evaluating the inflammatory state and the course of infection therapy, while the results allow understanding the time of antibiotics, safe termination depending on the clinical improvement and flaring of biomarkers [7].

Other compounds that have received concern as candidates for biomarkers to be used as markers include procalcitonin (PCT). Meanwhile, procalcitonin is a precursor of the hormone calcitonin and is customarily produced in response to bacterial infection. This substance rises to a high level during conditions of generalized bacterial infections while it is at a low level during inflammation or viral disease not involving bacterial organisms. In this respect, the specificity of PCT makes it a useful marker in deciding between the bacterial and non-bacterial origin of inflammation – a factor which might help improve the overall clinic management of antibiotic use [8, 9].

For one, neonates are subjected to both birth related stress as well as non-infectious inflammatory conditions that can potentially affect the levels of PCT in their blood. Moreover, neonates, especially preterm infants, present quite distinct characteristics of absorption, distribution, metabolism and excretion of antibiotics as compared to individuals of older age groups. However, it is noteworthy to measure other aspects, namely clinical outcomes, as well as the safety of the therapy prescribed in patients with severe infections according to PCT. Preventing the rebirth of this uncontrolled bug with the reduction of antibiotic usage is another measure that has to be observed keenly to ensure it does not cause other complications such as treatment failure, re-infection or adverse neonatal effects [10].

This study seeks to fill a gap found in literature in the making of appropriate antibiotic therapy in neonatal intensive care unit using the procalcitonin as a guide. As such, the study objectives seek to compare treatment duration and clinical results in order to optimize practices and redeem dangers of antibiotics for at-risk neonates. It brings new thoughts into the comparison and evaluation of the effectiveness of procalcitonin-guided therapy within NICU environment, and can progress the worldwide guidelines for neonatal care. The present knowledge on the effectiveness of applying procalcitonin based therapy in Pakistan particularly in neonatal patients is critically limited. This study tries to address this gap by including localized data which may contribute to optimizing antimicrobial stewardship and consequently the status of Pakistani NICUs.

MATERIALS AND METHODS

The present study was conducted at Department of Pediatrics CMH, Multan From November 2023 to February 2024. The sample size of 320 patients in our study was determined based on the study by Nobre et al. In their study, antibiotic therapy duration was approximately 9.5 days in the control group and 6 days in the group of procalcitonin, with a mean difference of 3.2±4.5 days. With a desired power of 90% and a significance level of 5%, our study included 163 neonates in the procalcitonin-guided antibiotic therapy group and 157 neonates in the standard therapy group to detect clinically significant differences in antibiotic duration and ICU stay [11]. The study received permission from the IRB of hospital and informed consent obtained from guardians. This research utilized a randomized controlled trial design.

Neonates included in the study were ≤ 28 days old and required antibiotic therapy for suspected infections. Exclusion criteria comprised major congenital anomalies, known immune deficiency disorders, and chronic infections necessitating prolonged antibiotic treatment. The process of randomization was carried out using computer-generated random numbers. The procalcitonin group received antibiotic therapy guided by procalcitonin levels, whereas the standard group received antibiotic therapy according to prevailing clinical guidelines.

Baseline characteristics, such as gestational age, gender distribution, birth weight, mode of delivery (cesarean section, vacuum/forceps, spontaneous vaginal,), Apgar scores assessed at 1, 5, and 10 minutes after childbirth, presence of risk factors (Group B streptococcus-positive mothers, chorioamnionitis), clinical symptoms upon admission, and findings of laboratory (C-reactive protein, WBC count, levels of procalcitonin) were documented for each participant.

Primary outcomes included the length of stay in (ICU) and the duration of antibiotic treatment. Secondary outcomes encompassed mortality rates, rates of reinfection, and incidence of antibiotic complications (rash, neutropenia, thrombocytopenia, acute kidney injury, hepatotoxicity).

The data that was gathered was analysed using IBM SPSS, specifically version 27.0. Categorical variables are given as frequency and percentage and then compared using the Chi-square test. Continuous variables are represented using the mean and standard deviation (SD) and are compared using the Mann-Whitney U test. The assessment of normality was conducted using measures such as skewness, kurtosis, Q-Q plots, and the Shapiro-Wilk's test. The results were graphically represented whenever possible to facilitate interpretation. The level of significance was established at 5%, and a p-value of less than 0.05 (with a 95% confidence interval) was deemed statistically significant.

STUDY RESULTS

The study included 320 neonates who met the criteria for participation. They were randomly divided into two groups: one group received antibiotic therapy guided by procalcitonin levels, while the other group received normal medication. The procalcitonin group consisted of 163 infants, while the standard group contained 157 neonates. There were a total of 163 patients in the Procalcitonin group, and there were 157 patients in the Standard group. The major characteristics of these individuals are indicated in Table 1.

The gender distribution was comparable between the two groups, with females comprising 44.8% and 45.9% of the Procalcitonin and Standard groups, respectively, and males comprising 55.2% and

54.1%. The mean gestational age was 38.31 ± 2.41 weeks for the Procalcitonin group and 38.08 ± 2.03 weeks for the Standard group. The mean weight was similar between the groups (3.37 ± 0.74 kg in the Procalcitonin group and 3.41 ± 0.50 kg in the Standard group).

The mode of delivery was also similar between the groups. In the Procalcitonin group, 78 (47.9%) deliveries were spontaneous vaginal, 23 (14.1%) involved vacuum or forceps, and 62 (38.0%) were cesarean sections. In the Standard group, these percentages were 45.9%, 15.9%, and 38.2%, respectively. The average Apgar ratings at 1, 5, and 10 minutes after birth were similar in both groups.

The risk variables, including Group B streptococcus-positive women, chorioamnionitis, early rupture of membranes lasting 18 hours or more before birth, and gestational age less than 37 weeks, were evenly distributed among the groups. The occurrence of clinical symptoms, such as difficulty breathing or cessation of breathing, rapid or slow heart rate, low blood pressure or inadequate blood flow, abnormally low or high body temperature, seizures, and difficulty with vomiting or feeding, were similarly comparable. The laboratory results showed that there was no significant difference in the proportion of patients with a white blood cell count less than 5 x 10^9 cells/L, C-reactive protein levels greater than 10 mg/L, and initial procalcitonin levels less than 0.5 μg/L and greater than or equal to 0.5 μg/L between the groups. The probability of infection being confirmed, likely, potential, or unlikely was also similar between the groups.

Table 1: Baseline characteristics of the patients included in this study

	Procalcitonin group (n=163)		**Standard group (n=157)**	
	n	**%**	**n**	**%**
Gender				
Female	73	44.8%	72	45.9%
Male	90	55.2%	85	54.1%
Gestational age (weeks), mean ± SD	38.31 ± 2.41		38.08 ± 2.03	
Weight (kg), mean ± SD	3.37 ± 0.74		3.41 ± 0.50	
Mode of delivery				
Spontaneous vaginal	78	47.9%	72	45.9%
Vacuum or forceps	23	14.1%	25	15.9%
Cesarian section	62	38.0%	60	38.2%
Apgar score, mean ± SD				
1 min post-partum	6.94 ± 2.30		6.92 ± 2.25	
5 min post-partum	7.94 ± 1.16		7.98 ± 1.42	
10 min post-partum	8.90 ± 0.87		8.80 ± 1.13	
Risk factors				
Group B streptococcus-positive mother	23	14.1%	24	15.3%
Chorioamnionitis	33	20.2%	32	20.4%
Premature rupture of membranes 18 h or longer before birth	40	24.5%	36	22.9%
Gestational age less than 37 weeks	32	19.6%	24	15.3%
Clinical symptoms				
Respiratory distress or apnea	100	61.3%	90	57.3%
Tachycardia or bradycardia	21	12.9%	20	12.7%
Arterial hypotension or poor perfusion	15	9.2%	15	9.6%
Hypothermia or hyperthermia	26	16.0%	27	17.2%
Seizure and/or floppy infants and/or irritability and/ or lethargy	15	9.2%	16	10.2%
Vomiting and/or feeding intolerance and/or ileus	13	8.0%	11	7.0%
Laboratory findings				
WBC count < 5 x 10^9 cells/L	7	4.3%	3	1.9%
C-reactive protein > 10 mg/L	53	32.5%	40	25.5%
Initial PCT level < 0.5 μg/L	70	42.9%	66	42.0%
Initial PCT level ≥ 0.5 μg/L	93	57.1%	91	58.0%

Infection likelihood				
Infection proven	7	4.3%	4	2.5%
Infection probable	18	11.0%	16	10.2%
Infection possible	73	44.8%	69	43.9%
Infection unlikely	65	39.9%	68	43.3%

The primary and secondary outcomes are presented in Table 2. The mean length of ICU stay was significantly shorter in the Procalcitonin group (9.88 ± 4.83 days) compared to the Standard group (11.3 ± 3.68 days), with a p-value of 0.002. Similarly, the duration of antibiotic treatment was significantly shorter in the Procalcitonin group (5.91 ± 2.99 days) compared to the Standard group (7.28 ± 3.26 days), with a p-value of less than 0.001.

Mortality was significantly lower in the Procalcitonin group (16.0%) compared to the Standard group (27.4%), with a p-value of 0.013. The rates of reinfection were not significantly different between the Procalcitonin group (10.4%) and the Standard group (8.9%), with a p-value of 0.648. Antibiotic complications, including rash, neutropenia, thrombocytopenia, acute kidney injury, or hepatotoxicity, were also not significantly different between the groups (2.5% in the Procalcitonin group and 4.5% in the Standard group), with a p-value of 0.325.

Table 2: Primary and secondary outcome measures

	Procalcitonin group (n=163)		**Standard group (n=157)**		**p value**
	n	**%**	**n**	**%**	
Length of ICU stay (days), mean ± SD	9.88 ± 4.83		11.3 ± 3.68		0.002 [a]
Duration of antibiotic treatment (days), mean ± SD	5.91 ± 2.99		7.28 ± 3.26		< 0.001 [a]
Mortality	26	16.0%	43	27.4%	0.013 [b]
Reinfection	17	10.4%	14	8.9%	0.648 [b]
Antibiotic complication [c]	4	2.5%	7	4.5%	0.325 [b]

[a] Mann-Whitney U test; [b] Chi square test.

[c]An antibiotic complication is characterised as a rash, neutropenia, thrombocytopenia, acute renal damage, or hepatotoxicity that can be ascribed to the usage of antibiotics.

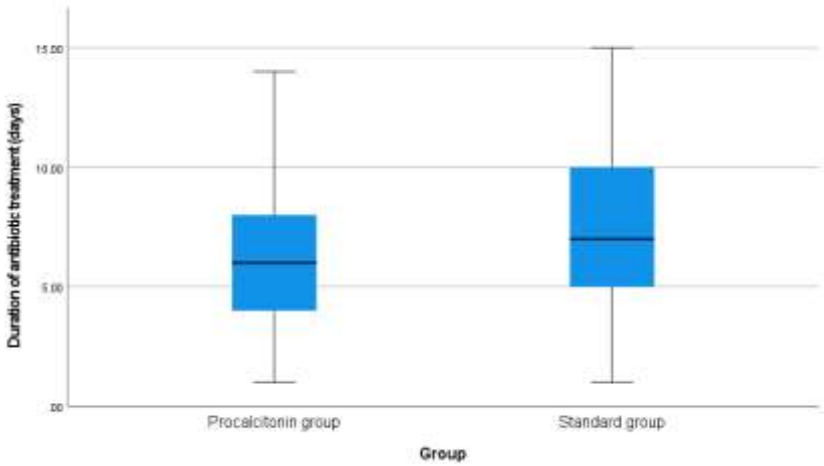

Figure 2: Duration of antibiotic treatment in both groups.

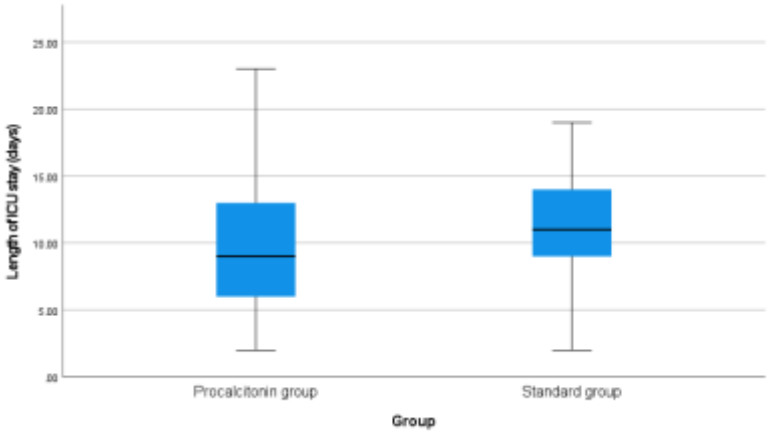

Figure 3: Length of ICU stay in both groups.

DISCUSSION

Thus, as a tool for guiding antibiotic therapy, procalcitonin has proved to be effective in NICUs. Thus, the determination of procalcitonin has shown to provide a better indication of bacterial infection presence and the required antibiotic therapy intensity. This approach assists to tackle issue of resistance in antibiotic usage and helps avoid side effects that may be attended by premature infants. Thus, procalcitonin, as a biomarker, has a potential to improve the antimicrobial stewardship approaches for neonates that would meet the needs of this particular group of patients [12].

Findings of the impotent study can therefore be compared with other similar study demographics as partly same and partly different. The distribution of gender in the NeoPInS trial by Stocker et al. (2021) was also slightly imbalanced with the subject pool of 1,710 infants, 912 of which were females, and 798 males. However, their mean gestational age was slightly lower at a mean of 37. 5 weeks; this makes the inclusion of preterm infants wider. It should be noted though that in this study, the mean birth weight was slightly lower and was recorded to be at 2. 9 kg, that would point to a fact that a larger percentage of the LBWI is made up of newborns that have low birth weights [7]. This was a case series of 171 neonates comprising 87 (50. 9%) female neonates taken with a mean age of 7. 5 ± 6. Six of days showed the cohort included 46. There are also high incidences of Low Birth Weight infants; 2% of them being either LBW or pre-term. 9% of patients with prior PROM indicated that their membranes ruptured prior to labor in this study. These demographics align with Habib et al. (2021), who found that 50.3% of neonates had positive blood cultures. Median PCT levels in our study were comparable to Habib et al.'s findings, emphasizing its potential role in infection diagnosis and management. This parallels their observation of significantly higher PCT levels (median 7.10 ng/ml) in culture-positive cases compared to negatives, supporting biomarker utility in clinical decision-making for neonatal infections [14].

In comparing our study findings with those of Zihlmann et al. (2021), both studies highlight the potential benefits of biomarker-guided antibiotic therapy in neonates. While Zihlmann et al. focused on early-onset sepsis (EOS), reporting a reduction in antibiotic duration from 4 to 3 calendar days using a procalcitonin-guided approach, our study expands on these benefits. Specifically, our findings demonstrate not only a shorter duration of antibiotic therapy (5.91 ± 2.99 days vs. 7.28 ± 3.26 days, $p < 0.001$) but also reduced ICU stays (9.88 ± 4.83 days vs. 11.3 ± 3.68 days, $p = 0.002$) and lower mortality (16.0% vs. 27.4%, $p = 0.013$) in the procalcitonin-guided group compared to standard therapy. These findings support the application of procalcitonin to enhance antibiotic stewardship and enhance the newborn’s health outcomes [15]. Analyzing the difference between current study and Baer et al. (2013) it can also be seen that this study does not aim at changing the antibiotic prescription rates but rather uses PCT to inform the optimal duration of antibiotic therapy. Baer et al. proved that implementation of PCT led to decrease of time on antibiotic therapy in

children with LRTI including pneumonia. In the same manner, our study on new born neonates applying PCT-guided antibiotic therapy, reduced the antibiotic treatment duration (5.91 ± 2.99 days from 7.28 ± 3. 26 days, p < 0. 001) and the average staying days in ICU 9.88 ± 4.83 days from the normal 11.3±3. 68 days, p = 0. The results of this study stress the possibility of extending the use of PCT to strengthen antibiotic stewardship, as well as optimize treatment approach to improve clinical outcomes and reduce related risks [16].

As to neonates, the current research compared to Stocker et al. (2015) and Go et al. (2023) shows that further investigation of PCT as a marker for shorter course antibiotic therapy will justify better management of antibiotic therapy. Stocker et al. made quantitative findings proving that there was a decrease in the proportion of newborns to whom antibiotics for 72 hours and more were administered in the framework of the PCT as compared with the control group (55% vs 82%, p = 0. The finding of this study shows that with optimization of factors that influence IV morphine administration, there was a decrease in antibiotic duration by 4 hours out of 17 [4]. Go et al. also presented a significant reduction of antibiotic therapy days per 1000 patient days (82. 0 versus 211. 3, p < 0. 01) and fewer newborns receiving antibiotics (12% versus 38%, p < 0. 01) employing the PCT-based diagnostic criteria, but with no rising of the risk of early on bacterial infection. Our study findings similarly support prior work by documenting a marked reduction in the duration of antibiotic therapy (5.91 ± 2.99 days vs. 7. 28 ± 3. 26 days; p < 0. 001) and stay in the ICU (9.88 ± 4. 83 days vs. 11.3 ± 3.68 days; p = 0. Compared to the study by Li et al. (2022) and Vishalashi et al. (2021) concerning neonates, our study also provided evidence of the effectiveness of procalcitonin (PCT)-based decision for shortening appropriate length of antibiotics administration and clinical prognosis.

Li et al. discovered that using PCT-guided therapy resulted in a significant decrease in the duration of antibiotic treatment for different infectious infections. This aligns with the findings of present study, which showed that neonates had shorter antibiotic durations (5.91 ± 2.99 days vs. 7.28 ± 3.26 days, p < 0.001). Similarly, Vishalashi et al. found that there was a significant reduction in the length of ICU stays (5.98 ± 2.73 days vs. 8.80 ± 3.35 days, p < 0.001) and a lower incidence of secondary infections (4.4% vs. 26.7%, p = 0.014) with PCT-guided therapy in adults, echoing our study's findings of reduced ICU stays (9.88 ± 4.83 days vs. 11.3 ± 3.68 days, p = 0.002) and favorable clinical outcomes in neonates. These collective results underscore the broad applicability and effectiveness of PCT-guided strategies in reducing antibiotic exposure while maintaining or improving clinical outcomes across different patient populations, including neonates. Implementing PCT-guided protocols can thus enhance antibiotic stewardship and patient care practices in diverse clinical settings [19,20]. Limitations of our study include the need for longer-term follow-up to assess sustained outcomes and the necessity for larger multicenter trials to confirm generalizability across diverse neonatal populations and settings.

CONCLUSION

In conclusion, our study supports the use of a serum procalcitonin-based algorithm in critically ill neonates, demonstrating reductions in antibiotic duration, ICU stay, and secondary infection rates. This approach enhances antibiotic stewardship without compromising patient outcomes, highlighting its potential for improving neonatal care practices

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