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Zinc supplementation as an adjuvant treatment in neonatal sepsis.

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Abstract

Aim: The aim of this study is to detect the effect of zinc as an adjuvant treatment in the management of neonatal sepsis.

Method: A prospective clinical trial study was conducted on 200 neonates with neonatal sepsis diagnosed clinically and by laboratory investigation. The studied neonates were divided into two groups. Intervention group (n=100) which was treated by zinc and antibiotics, while the control group (n=100) was received antibiotics only. Zinc was administered as 3 mg/kg/ twice a day of zinc sulfate monohydrate orally for 15 day along with antibiotics according to a standard protocol. Both groups were compared using a predefined sepsis score through clinical and laboratory examination.

Results: According to sepsis score there was no significant difference between intervention and control groups before starting zinc (p-value=1.00), while there was significant difference in sepsis score between groups after 5 days,10 days and 15 days of starting zinc with (p-value=0.008, 0.006, 0.002, respectively). The sepsis score improvement is significant in both groups but better in the intervention group.

Conclusion: The use of zinc as an adjuvant treatment of sepsis in neonate is associated with better outcome both clinically and laboratory.

Keywords: Neonates, Sepsis, Zinc.

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Introduction

Sepsis in neonates is defined as a syndrome of bacteremia with clinical picture of infection in the first 28 days of life. Neonatal sepsis may cause overwhelming infection without much localization (septicemia) or may get localized predominantly to meninges (meningitis) or to the lung (pneumonia) [1].

Neonatal sepsis is a main cause of disability and death especially in severe cases [2]. Antimicrobial administration especially if it is according to culture and sensitivity is associated with a better prognosis and outcome [3,4]. Zinc is a cofactor for many enzymes and essential for optimal immune function and reduces bacterial infections, common cold and diarrhea [5]. It has been reported that preterm neonates require more zinc than term neonates as 60% of fetal zinc is acquired during the third trimester of pregnancy. Preterm neonates have poor intestinal absorption due to their immature digestive system [6]. Studies have reported a strong correlation between zinc deficiency and poor weight gain and increased incidence of neonatal sepsis among low birth weight and preterm babies [7]. A randomized double- blind, placebo controlled trial conducted by Bhatnagar et al. showed improved outcome with supplementation of 10 mg zinc given orally in infants aged 7–120 days with serious bacterial infections [8]. Zinc plays a main role in the immunity. It is essential for normal development and function of all the cells of the immune system from innate immunity to neutrophils and phagocytes. Phagocytic function, intracellular destruction of microorganism, cytokine production and T and B cell function are all affected by zinc deficiency [9,10]. Zinc supplementation is associated with decrease rates of infection in several population-based studies of different diseases, especially diarrhea, pneumonia [11]. Some trials have stated that zinc supplementation as co-treatment could be used as an adjuvant treatment in neonatal sepsis [12,13]. We suggested that using zinc in neonatal sepsis will lead to better inflammatory parameters in the serum. Including (TLC, ANC Hs-CRP and I/T) and better clinical course in neonatal sepsis.

Aim

The aim of this study is to detect the effect of zinc

supplementation as an adjuvant treatment in neonatal sepsis.

Patients and Methods

This is a prospective clinical trial study after taking informed consent, we included 200 neonates with neonatal sepsis on the basis of both clinical and laboratory criteria. Patients were included if diagnosed as high probable sepsis according to criteria employed for defining the sepsis score (Table 1).

Exclusion criteria: major congenital anomalies, hypoxic ischemic encephalopathy, intra cranial hemorrhage and respiratory distress syndrome, inborn error of metabolism, candida infection.

Enrolled infants were divided into two groups. Intervention group (n=100) and control group (n=100). Patients were enrolled from the Neonatal Intensive Care Unit of Tanta University Hospital from July 2013 to May 2015.

Table 1A. *Sepsis score definitions*

Sepsis Score	Definition
High Probable Sepsis (HPS):	• At least 3 sepsis-related clinical signs • Hs-CRP more than 5 mg/ml • At least 2 other altered serum parameters • Blood culture: Positive or negative
Probable Sepsis (PRS):	• Less than 3 sepsis-related clinical signs • Hs-CRP more than 5 mg/ml • Less than 2 other altered serum parameters • Blood culture: Negative
Possible Sepsis (POS):	• Less than 3 sepsis-related clinical signs • Hs-CRP less than 5 mg/ml • Less than 2 other altered serum parameters • Blood culture: Negative
No Sepsis (NS):	• No sepsis-related clinical signs • Hs-CRP less than 5 mg/ml • No altered serum parameters • Blood culture: Negative

Evaluation

All neonates were exposed to careful history taking, clinical and laboratory examination. Blood culture was drawn in both groups as a routine work before starting medications. Both groups had laboratory examination in the form of Complete blood count (CBC) including (TLC, ANC, Platelet count and I/T ratio) and high sensitive CRP (hs-CRP).

Blood cultures were tested using Bactalert blood culture system. High sensitive C-reactive protein (hs-CRP) was quantitatively measured by Latix particles coated with specific anti-human CRP were agglutinated when mixed with samples containing CRP. The agglutination causes an absorbance change which depends upon the CRP content in the sample, hs-CRP more than 5 mg/ml is considered positive.

Sepsis score was assigned on admission and daily for 15 days of life. All study patients were classified into high probable sepsis (HPS) or probable sepsis (PRS) or possible sepsis (POS) or no sepsis (NS) according to Criteria employed for defining the sepsis score (Table 1) [14,15].

Intervention

In the intervention group, 100 neonates with sepsis received zinc as 3 mg/kg/twice a day of zinc sulfate monohydrate orally for 15 day along with antibiotics according to the standard protocol. In the Control group, 100 neonates with sepsis did not receiving zinc but only received antibiotics according to the standard protocol. Zinc was given through the oro/naso-gastric tube. The standard antibiotics protocol is Ampicillin plus Gentamycin.

The ethics committee of faculty of medicine, Tanta University had approved this study. Written informed consent was done from the parents of all neonates. The duration of the study was 22 months.

Statistical Analysis

It was performed by using SPSS for Windows, version 20. Data were expressed as range and mean ± standard deviation (SD). Differences between groups in continuous variables were tested for significance with independent

Table 1B. *Sepsis score definitions (continued)*

Sepsis related clinical signs: • General pallor or icterus. • Cardiovascular manifestations: tachycardia or bradycardia, poor perfusion or shock. • Variability in temperature (hypothermia or hyperthermia). • Respiratory manifestations: grunting, intercostal retractions, apnea or cyanosis. • Neurological manifestations: hypotonia, lethargy, irritability or seizures. • Gastrointestinal manifestations: abdominal distension, hepatosplenomegaly.
Serum parameters other than hs-CRP: • White blood cells (WBC) count. • Absolute neutrophil count (ANC). • Platelet (PLT) count. • The ratio of immature to total neutrophils (I/T ratio).

t-test while Chi-square test(X^2) used to compare categorical variables. For all statistical tests done, *p* value <0.05 was considered significant.

Results

200 neonates were examined, 100 in intervention group and 100 in control group. There was no difference between the intervention and control group as regards gestational age (weeks), weight in (kg), mode of delivery and sex (p>0.05) (Table 2).

The organisms isolated from blood cultures in septic neonates in this study were Klebesiella 16%, Coagulative negative staph (CONS) 6%, *E. coli* 24%, GBS 22% and *Candida albicans* 4%, while there is 28% with negative blood cultures (Table 3).

No significant difference was detected in sepsis score between intervention group and control group before starting zinc, while there was significant difference in sepsis score between groups after 5 days, 10 days and 15 days of starting zinc. There was significant improvement in both groups with more improvement of sepsis score in intervention group than control group (Table 4).

No significant difference was detected in hs-CRP between intervention group and control group before starting zinc, while there was significant difference in hs CRP between both groups after 5 days, 10 days and 15 days of starting zinc. There was significant decrease of hs-CRP towards the normal range in both groups with more decrease in hs-CRP in Intervention group than Control group (Table 5).

No significant difference was detected in I/T ratio between intervention group and control group before starting zinc and there was no significant difference in I/T ratio between groups after 5 days of starting zinc, while there was significant difference in I/T ratio after 10 days and 15 days of starting zinc. There was significant improvement in I/T ratio (I/T ratio less than 20%) with more improvement in intervention group than Control group (Table 6).

The mortality rate was lower in intervention group (10%) compared with control group (18%) with statistical significance between both groups (P<0.05) (Table 7).

Discussion

Neonatal sepsis is considered a very big problem in neonates, with a major disability and increased incidence of death despite the progress in neonatal treatment modalities. The neonatal immunity against infections is immature especially in premature neonates, and this makes the neonates especially the premature ones are more susceptible to multiple recurrent infections [16].

Zinc is known to play a central role in the immune system. It is crucial for normal development and function of cells mediating innate immunity, neutrophils, macrophages

Table 2. *Comparison between intervention group and control group as regard gestational age (weeks), weight in (kg), mode of delivery, sex and onset of sepsis*

		Intervention group		Control group		t. test	P. value
Gestational Age (Weeks)	**Mean ± SD**	36.3 ± 1.98		36.5 ± 2.2		0.342	0.737
Weight(kg)	**Mean ± SD**	2.44 ± 0.74		2.45 ± 0.82		0.053	0.964
		N	**%**	**N**	**%**	X^2	P. value
Mode of delivery	**NVD**	40	40	40	40	0.000	1.00
	CS	60	60	60	60		
Sex	**Male**	56	56	56	56	0.000	1.00
	Female	44	44	44	44		
Onset of sepsis	**Early onset**	60	60	60	60	0.000	1.00
	Late onset	40	40	40	40		

*P value is significant if <0.05
NVD: Normal Vaginal Delivery; CS: Cesarean Section

Table 3. *Frequency of isolated organisms from blood culture in septic neonates*

		Intervention group		Control group		X^2	P value
		N	**%**	**N**	**%**		
Organism	Klebsiella	20	20	12	12	4.619	0.464
	Coagulative Negative Staph (CONS)	4	4	8	8		
	Group B streptococci(GBS)	24	24	20	20		
	Listeria monocytogenes	0	0	8	8		
	E-coli	24	24	24	24		
	Negative	28	28	28	28		
	Total	100	100	100	100		

*P value is significant if <0.05

Table 4. *Comparison between intervention group and control group as regard sepsis score*

Sepsis score		Intervention group		Control group		X^2	P. value
		N	%	N	%		
Before	High propalbe	100	100	100	100	0.000	1.00
After 5 days	Propable	92	92	60	60	7.018	0.008*
	High propable	8	8	40	40		
After 10 days	Possible	24	24	0	0	10.1	0.006*
	Propable	76	76	84	84		
	High propable	0	0	16	16		
After 15 days	No	48	48	20	20	**14.437**	**0.002***
	Possible	36	36	12	12		
	Propable	16	16	56	56		
	High propable	0	0	12	12		

*P value is significant if <0.05

Table 5. *Comparison between intervention group and control group as regard hs CRP*

Hs CRP (mg/ml)		Intervention group	Control group	t test	P. value
Before	**Mean ± SD**	51.05 ± 22.5	50.4 ± 15.3	0.119	0.905
After 5 days	**Mean ± SD**	20.04 ± 10.25	32.4 ± 22.4	2.508	0.015*
After 10 days	**Mean ± SD**	10.9 ± 4.95	22.8 ± 9.09	5.748	0.001*
After 15 days	**Mean ± SD**	5.50 ± 2.27	21.6 ± 12.7	6.239	0.001*

*P value is significant if <0.05

Table 6. *Comparison between intervention group and control group as regard immature/total (I/T) ratio*

I/T		Intervention group		Control group		X^2	P. value
		N	%	N	%		
Before	<20%	-	-	-	-	0.000	1.00
	>20%	100	100	100	100		
After 5 days	<20%	20	20	12	12	.595	0.440
	>20%	80	80	88	88		
After 10 days	<20%	56	56	28	28	4.023	0.044*
	>20%	44	44	72	72		
After 15 days	<20%	80	80	48	48	5.555	0.018*
	>20%	20	20	52	52		

*P value is significant if <0.05, I/T (Immature to Total)

Table 7. *Outcome of the intervention and control group*

Outcome		Group		Total
		Intervention group	Control group	
Improved	**N**	90	82	172
	%	90.0%	82.0%	86.0%
Death	**N**	10	18	28
	%	10.0%	28.0%	14.0%
Total	**N**	100	100	200
	%	100.0%	100.0%	100.0%
Chi-square	**X^2**	2.326		
	P-value	0.017*		

*P value <0.05 is significant

and natural killer cells. Phagocytosis, intracellular killing, cytokine production and T and B cell function are all affected by zinc deficiency [17,18]. Decreased rates of infection have been observed following zinc supplementation in several population-based studies of different diseases, notably diarrhea, pneumonia [11]. The organisms isolated from blood cultures in septic neonates in this study were Klebesiella 16%; Coagulative negative staph (CONS) 6%, *E. coli* 24%, GBS 22% and *Candida albicans* 4%, while there is 28% with negative blood cultures.

The present study showed that zinc had improved serum inflammatory parameters and also improved the clinical course of septic newborns as judged by Criteria employed

for defining the sepsis score. This was in agreement with Bhatnagar et al. [8] who had shown that zinc has anti-inflammatory effect in neonates suffering from neonatal sepsis if it is added as an adjuvant therapy and revealed a lesser incidence of treatment failure with antibiotics only without zinc administration.

The present study found that there was no significant difference in hs-CRP between Intervention group and Control group before starting zinc, while there was significant difference in hs-CRP between both groups after 5 days, 10 days and 15 days of starting zinc. There was significant decrease of hs-CRP towards the normal range in both groups with more decrease in Intervention group than Control group and in agreement with this study Rashidi et al. [19] who found that hs-CRP in septic group treated by antibiotics and zinc decreased towards the normal ranges more rapid than those who treated with antibiotics only with better prognosis.

In our study, there was no significant difference in I/T ratio between Intervention group and Control group before starting zinc and there was no significant difference in I/T ratio between Intervention group and Control group after 5 days of starting zinc, while there was significant difference in I/T ratio after 10 days and 15 days of starting zinc.

There was significant improvement in I/T ratio (I/T ratio less than 20%) with more improvement in Intervention group than Control group, and this was in agreement with Gulani et al. [20] who stated that neonatal zinc supplementation can be used for prevention of mortality and morbidity in septic neonates.

There are no limitations to discuss the lack of masking and possibly other problems with the design of the trial.

Conclusion

Administration of zinc as an adjuvant therapy in the treatment of neonatal sepsis is associated with improvement of clinical and laboratory outcome.

Human Research Statement

Written informed consent from the parents was obtained.

Authors Contribution

Elfarargy MS participated in the sequence alignment and drafted the manuscript, participated in the design of the study. Neama AS performed the statistical analysis, participated in the sequence alignment. All authors read and approved the final manuscript.

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