The Effect of Pentoxifylline in the Treatment of Neonatal Sepsis

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Abstract: **Objective.** Evaluation of the therapeutic efficiency of pentoxifylline as adjuvant therapy in the treatment of neonatal sepsis. **Patients and Methods**: A prospective case -control study was conducted on 50 neonates with neonatal sepsis on the basis of both clinical and laboratory criteria. They were collected from the Neonatal Intensive Care Unit of Tanta University Hospital from June 2013 to June 2014, and were divided into two groups:Group 1(G1):25 neonates with sepsis received pentoxifylline (Trental, Boehring-Hoechst, Germany) intravenously in a dose of 5 mg/kg per hour for 6 h. the infusion was repeated on the 2nd and 3rd day of therapy and received also antibiotics according to the standard protocol and Group 2(G2): 25 neonates with sepsis not receiving pentoxifylline but received antibiotics according to the standard protocol. So, the two groups given antibiotics according to the standard protocol (Ampicillin plus Gentamycin). **Results.** Shows that there is a significant reduction in CRP level in PTX group than control group with statistical significance between both groups (P<0.05). **Conclusion** Administration of pentoxifylline as adjuvant therapy in the treatment of sepsis in neonates is associated with improvement of clinical and laboratory outcome of septic neonate with better prognosis and outcome.
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1. Introduction

Neonatal sepsis is an invasive infection, usually bacterial, occurring during the neonatal period. Signs are multiple and include diminished spontaneous activity, poor suckling, apnea, bradycardia, temperature instability, respiratory distress, vomiting, diarrhea, abdominal distention, jitteriness, seizures, and jaundice. The highest rates occur in low birth weight (LBW) infants, those with depressed respiratory function at birth, those with maternal perinatal risk factors, males, and those with congenital anomalies ***(1).***

Suspected infection should be treated promptly and with appropriate antibiotics. Each antibiotic has benefits and side effects which must be evaluated every time antibiotics are prescribed ***(1,2)***

The mortality and morbidity for both early and late onset sepsis still remains high despite the use of potent antimicrobials and there is a global emergence of antibiotic resistance. This has led to the search for modalities to enhance neonatal host defense mechanisms, which could be used as adjuncts to antibiotics in treating neonatal sepsis. Some of these agents help to re-establish the balance between pro and anti-inflammatory influences which may affect clinical outcome. ***(2,3)***

Pentoxifylline, a xanthine derivative and a phosphodiesterase inhibitor, has attracted fresh attention since the discovery that inhibition of tumor necrosis factor (TNF) gene transcription reduces mortality from sepsis. TNF acts as an early and important mediator of inflammation Pentoxifylline has been shown to have numerous potential beneficial effects in sepsis ***(4,5).***

Pentoxifylline suppresses production of inflammatory mediators e.g. TNF, Interleukin-8 (IL-8), it has been shown that pentoxifylline decrease TNF alpha, IL-1, and IL-10 but not IL-6 or IL-8.***(6,8)***

Pentoxifylline delays the release of endothelin-1, abolishes TNF burst and suppresses IL-6 and lactate and cause improving survival in cases of neonatal sepsis ***(7,9).*** Pentoxifylline may prevent the development of necrotizing enterocolitis by preserving small intestinal micro-vascular blood flow ***(5,11).*** Pentoxifylline also augments haemodynamic performance during sepsis, improving renal blood flow during bacteraemia and preventing the progression of sepsis ***(4,10).***

2. Patients and methods

The Study was done on 50 neonate who admitted in NICU at Tanta University Hospital from June 2013 to June 2014. All of them were suspected to be septic based on the presence of 2 or more clinical signs of sepsis in association with high CRP value >10 mg. **(*12*).**

The studied neonates were divided into 2 groups:-

1. ***Group (I) (PTX group):*** this group includes 25 neonates who received antibiotics as well as Pentoxifylline IV in a dose of 5mg/kg/h for 6 hrs. for 3 consecutive days.
2. ***Group (II)(control group):***this group includes 25 neonate received antibiotics only.

The inclusion criteria were:

1. Signs suggestive of sepsis.

2. Elevated serum CRP level.
3. Hematological sepsis score > 3***(13)***

The exclusion criteria were:

1. Congenital anomalies.
2. Chromosomal abnormalities.
3. Inborn error of metabolism.

All study neonates were subjected to the following:

1. History-taking, including:

- **Antenatal history**
- **Natal history including:**

- Prolonged rupture of membranes (PROM) (> 18 hours).

- Mode of delivery; vaginal delivery (VD) or cesarean section(C/S)

- **Postnatal history including:** symptoms suggestive of sepsis

- Fever or hypothermia, vomiting,jaundice, abdominal distension lethargy or irritability, tachypnea, apnea

2. Physical examination

3. Investigations: complete blood count (CBC), total white blood cells (WBCs) with differential, C-reactive protein (CRP), liver function tests, kidney function test, blood culture

Pentoxifylline

Apart from the routine therapy of sepsis, all infants in the study group received Pentoxifylline (Trental, Boehring-Hoechst, Germany) intravenously in a dose of 5 mg/kg per hour for 6 h**.** the infusion was repeated on the 2nd and 3rd day of therapy***(5).***

Empirical antibiotic therapy was given to all the studied cases in the form of ampicillin (100mg/kg/d) and gentamycin (5mg/kg/d) as first line antibiotics. After the results of the blood cultures were obtained, antibiotics were adjusted according to the sensitivity of the isolated organisms.

Infants treated with Pentoxifylline were monitored for adverse reactions, for example: hypotension, irritability.

This study was approved by the ethics committee of faculty of medicine, Tanta University. Written informed consent was obtained from the parents of all subject of the study. The duration of the study was 12 months.

Statistical analysis: 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 paired t-test while univariate analysis was done with the *Chi-square*test($\mathbf{X^2}$) For all statistical tests done, *P*value< 0.05 was considered significant.

3. Results

Table (1) shows the demographic data of the studied groups there was no significant differences between both groups as regard gestational age, birth weight and sex.

Table (1): Demographic data of the studied groups.

		Pentoxifylline (PTX) group		Control group		t. test	*p*. value
Gestational age (weeks)	**Range**	30-39		28-39		**1.326**	**0.247**
	Mean±SD	35.6+2.56		36.01+2.38			
		N	%	N	%		
Sex	**Male**	8	32	10	40	0.347	0.521
	Female	17	68	15	60		
Birth weight (kg)	**Range**	1.1-3		1.1-3.9		0.362	0.114
	Mean±SD	2.31+0.57		2.62+0.70			

* P. value < 0.05 is significant

Table (2) shows that there was increase in platelets count in both groups however there was much increase in PTX group than control group with statistical significance between both groups (*P*<0.05).

Table (2):platelets count for both PTX and control groups before (PLT1) and after 3 days treatment(PLT2) with PTX for PTX group and placebo for control group.

.		Pentoxifylline group	Control group	t. test	*p*. value
PLT1 ($\times10^3$/mm^3)	**Range**	26-472	31-392	**2.326**	**0.057**
	Mean±SD	117.9±94.2	160.9±93.5		
PLT2 ($\times10^3$/mm^3)	**Range**	53-499	32-364	**4.629**	**0.009***
	Mean±SD	131.7±70.12	149.6±60.41		
t. test		**3.253**	**2.958**		
***p*. value**		**0.041***	**0.047***		

* *P*. value < 0.05 is significant

Table (3):Organisms causing sepsis of the PTX and control groups.

Organism		Group		Total
		Pentoxifylline group	Control group	
Meningococci	**N**	1		1
	%	4.0%		2.0%
GBS	**N**	5	3	8
	%	20.0%	12.0%	16.0%
Escherichia coli	**N**	4	5	9
	%	12.0%	16.0%	18.0%
Klebsiella pneumonia	**N**	4	5	9
	%	12.0%	16.0%	18.0%
Enterobacter cloacae	**N**	3	3	4
	%	8.0%	8.0%	8.0%
Staphylococcus aureus	**N**	5	5	10
	%	16.0%	16.0%	20.0%
H. Influenza	**N**	1	1	2
	%	4.0%	4.0%	4.0%
Pseudomonas A	**N**	1	1	2
	%	4.0%	4.0%	4.0%
No growth	**N**	1	2	3
	%	4.0%	8.0%	6.0%
Total	**N**	25	25	50
	%	100.0%	100.0%	100.0%
Chi-square	**X^2**	**1.241**		
	P-value	**0.241**		

Table(3)shows that gram -ve organisms frequency was higher in PTX (70%)and control groups(67%) than gram +ve(26%and29%) respectively, but without statistical significance between both groups (P>0.05).

Table (4) shows that there is a significant reduction in CRP level in PTX group than control group with statistical significance between both groups (P<0.05).

Table (4):CRP values for both PTX and control groups before (CRP1) and after 3 days treatment(CRP2) with PTX for PTX group and placebo for control group.

		PTX	control	t. test	*p*. value
CRP1	**Range**	12-96	12-96	**2.326**	**0.241**
	Mean±SD	47.04±22.1	50.4±32.1		
CRP2	**Range**	3-96	12-128	**6.325**	**0.003***
	Mean±SD	26.3±11.3	50.3±15.6		
t. test		**3.158**	**0.956**		
p. value		**0.028***	**0.847**		

* *P.* value < 0.05 is significant

Table (5): WBC values for both PTX and control groups before (WBC1) and after 3 days treatment with Pentoxyfelline (WBC2) for PTX group and placebo for control group.

		PTX	Control group	t. test	*p*. value
WBC 1	**Range**	3.5-18.4	3.1-21.5	**0.635**	**0.241**
	Mean±SD	11.65+4.05	11.85+5.01		
WBC 2	**Range**	3.1-15	3.1-21.5	**3.262**	**0.024***
	Mean±SD	9.43+3.25	11.80+6.32		
t. test		**2.362**	**0.624**		
***p*. value**		**0.043***	**0.417**		

* *P.* value < 0.05 is significant

Table (5) shows that there is a reduction in WBC count in PTX group than control group with statistical significance between both groups (P<0.05).

Table (6): Length of stay for both PTX and control groups.

	Length Of Stay	
	PTX group	**Control group**
Range (days)	11-67	10-67
Mean (days)	30.12	35.2
±SD	10.2	13.4
t. test	**3.958**	
***p*. value**	**0.014***	

* *P.* value < 0.05 is significant

Table (6) shows that mean value of length of stay is lower in PTX group (30) than in control group (35), with statistical significance between both groups (P<0.05).

Table (7):Outcome of the PTX and control groups.

Outcome			Group		Total
			Pentoxifylline group	Control group	
Improved		**N**	21	18	38
		%	80.0%	72.0%	76.0%
Death		**N**	4	7	12
		%	20.0%	28.0%	24.0%
Total		**N**	25	25	50
		%	100.0%	100.0%	100.0%
Chi-square	**X^2**	**2.326**			
	***P*-value**	**0.017***			

* *P*. value < 0.05 is significant

Table (7) shows that mortality rate was lower in PTX group (20%) compared with control group (28%) with statistical significance between both groups (*P*<0.05).

4. Discussion

Neonatal sepsis is defined as a clinical syndrome of bacteremia with systemic signs and symptoms of infection in the first 4 weeks of life. When pathogenic bacteria gain access into the blood stream, they may cause overwhelming infection without much localization (septicemia) or may get predominantly localized to the lung (preumonia) or the meninges (meningitis)***(14)***

Pentoxifylline(PTX) has been shown to have numerous potential beneficial effects by boosting host defenses in sepsis i.e. suppression of TNF alpha, IL-6 and IL-8, and a variety of physiological effects at cellular, vascular and endothelial level. Thus, it seems a promising adjuvant therapy in the treatment of neonatal sepsis (***15)***

Prematurity is an important risk factor for neonatal sepsis with a subsequent increase in the risk of morbidity and mortality (***16,17).***

In the present study there was a significant increase in platelet count in PTX group when compared with control group (P =.041), this was in agreement with ***Adel et al. (2010)*** study who showed that there was an increase in platelet count in PTX group than control group but without statistical significance (*P* =.832).***(11)***

In the present study, there is a significant reduction on CRP level at 3 days after starting PTX when compared with control group (*P* =.028), these results were in agreement with ***Adel et al. (2010)*** who stated that a statistically significant decrease was noticed in CRP serum levels in the PTX group when compared to control group at 3 days after starting PTX. ***(11)***

The present study results were in disagreement with ***Akdag et al. (2014)*** study who stated that no significant differences were observed among the groups regarding CRP***.(7)***

In the present study 4 out of 25 neonate in PTX Group died (20 %) whereas7 of 25neonate in the control group did not survive (28 %),there was a significant statistical difference in mortality rate (p =.017), these results were in agreement with ***Ali et al. (2006)(5)*** who found that 4 of 25 (16%) died due to sepsis, however in control group 10 of 25 (40%) neonates died of sepsis.these results also were in agreement with ***Lauterbach et al. (1999)(15)***. However ***Akdag et al. (2014)(7)*** study stated that PTX therapy did not reduce the rate of morbidity and mortality in neonatal Sepsis.

In this study a significant reduction also observed in length of stay in PTX group when compared with control group (*p* =.014). In agreement with our study ***Adel et al. (2010)(11)*** stated that hospital stay duration of survivors was significantly s shorter (*P* =.044) in the PTX treated-infants, similar results also reported by ***Ali et al. (2006)(5).***

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