Role of I.V Pentoxifylline as an Adjunct with Antibiotic Therapy in the Management of Neonatal Sepsis

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ABSTRACT

Introduction: Neonatal sepsis is the most important cause of neonatal morbidity and mortality in developing countries like India. Pentoxifylline is a methyl xanthine derivative, a phosphodiesterase inhibitor and an immunomodulating agent. Various studies have suggested an important role of this drug in counteracting the deleterious effects of neonatal sepsis through its inhibitory effects on various inflammatory mechanisms. Study was done to know the role of I.V. Pentoxifylline as an adjunct with antibiotic therapy in the management of neonatal sepsis, adverse effects and comparison of outcome in term and preterm neonates.

Material and Methods: 100 cases of neonatal sepsis who were 0-28 days of life were selected on the basis of clinical criteria who came to pediatrics OPD and were admitted in the NICU of LLRM Medical College, Meerut. Consent was taken from guardians and samples were sent for investigations prior to start of therapy. Then, neonates were divided in two groups as control and study group. Control group was given standard antibiotic therapy and study group was given I.V. Pentoxifylline as an adjunct to antibiotic therapy in form of continuous infusion with I.V. Fluids (5mg/kg/hr × 6hrly) for 6 days. This group was further divided into two groups, Preterm 25 cases and Term 25 cases. The results of use of Pentoxifylline as an adjunct to antibiotic therapy were compared with cases treated with standard antibiotic therapy.

Results: Pentoxifylline has a beneficial role with reference to comparison of number of days of stay in NICU between study and control group showing significant sensitivity ($p<0.001$), need for ventilation in study group as compared to control group was statistically significant ($p<0.0473$), mortality was 20% in study group as compared to 38% in control group which is also statistically significant ($p<0.0473$).Same beneficial results were noted in preterm neonates as compared to term neonates, difference was statistically significant ($p<0.0339$). No adverse effects attributable to pentoxifylline were observed in this study.

Conclusion: In view of following results, Pentoxifylline has a promising future as a tool for management of neonatal sepsis as an adjunct to standard antibiotic therapy.

Keywords: Neonatal sepsis, Preterm, Term, Neonates, Infusion.

INTRODUCTION

Neonatal sepsis is the most important cause of neonatal morbidity and mortality especially among Low Birth weight (LBW), Very low birth weight (VLBW), Preterm and Small for date babies in developing countries like ours. Incidence of neonatal sepsis in the developed world is reported to be between 0.6 to 1.2% of all live births[1], but in the developing world it can be as high as 20 to 40% of all live births.[2]

Mortality rate due to neonatal sepsis in India is reported to be 45/1000 live births.[3] In India 10 to 12 percent babies are born preterm (less than 37 completed weeks) as compared to 5-7 percent incidence in the west. These infants are more prone to develop neonatal sepsis. A variety of adjunctive immunotherapies for sepsis like double volume exchange transfusion, granulocyte infusion, the administration of intravenous immunoglobulin (IVIG) and treatment with granulocyte-colony stimulating factor and granulocyte-macrophage stimulating factor (G-CSF and GM-CSF) have all been studied with variable results.[4]

Neonatal sepsis can be divided into two main sub types depending on whether the onset in during the first 72 hours of life (early onset septicemia) or later (late onset septicemia).

Pentoxifylline (1-[5-oxohexyl]- 3,7 dimethylxanthine; Trental) which is a methyl xanthine derivative, a phosphodiesterase inhibitor and an immunomodulating agent, has been widely used in treatment of intermittent claudication.[5] Pentoxifylline has multiple effects on immune system, but inhibition of proinflammatory cytokine release predominates.[6,7] Being an immunomodulator, Pentoxifylline (PTXF) suppresses production of inflammatory mediators like Tumor Necrosis factor and Interleukin -8, which will in turn reduce the severity of neonatal sepsis. It also inhibits production of interleukin 6 in infants and neonates.[8] Pentoxifylline also suppresses TNF and IL-10 which prevents development of necrotizing enterocolitis in neonatal sepsis by preserving small intestinal micro vascular blood flow.

Thus, it can probably prevent one of the most important causes of mortality in neonatal sepsis. A decreased concentration of fibrinogen may also contribute to latter by improving renal blood flow during bacteremia.[9] Pentoxifylline also protects against endotoxin induced acute renal failure. Pentoxifylline has a number of physiological effects at cellular and endothelial vascular levels. It not only prevents endothelial cell dysfunction in sepsis, but also preserves endothelial thrombomodulin, protein C and protein S anticoagulation system.[10]

Thus, the current evidence suggests that this drug plays an important role in counteracting the deleterious effects of neonatal sepsis through its inhibitory effects on various inflammatory mechanisms. Absence of any significant adverse effects in studies conducted so far is also an additional benefit.[11]

In view of these factors, we conducted a study on Role of Pentoxifylline in the management of neonatal septicemia in order of evaluate the effect of intravenous pentoxifylline as an

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adjunct to antibiotic therapy in neonates with sepsis.

MATERIAL AND METHODS

We conducted this study at the Neonatal Unit of Department of Pediatrics, LLRM Medical College, Meerut, which is the main referral centre for critically sick neonates in this area. All neonates with culture proved sepsis admitted in the department from Oct 2013 to Oct 2015 were enrolled for this study. Observations were recorded according to a predesigned proforma and at the end of the study; the results were compiled and were analyzed statistically.

The study population was further subdivided into two groups depending upon the therapy administered:

1. Control Group

These patients received standard antibiotic therapy for neonatal sepsis.

2. Study Group

Patients in this group received pentoxifylline in addition to standard antibiotic therapy.

Study group patients were again divided into two categories according to the gestational age:

(a) Preterm neonates (born before 37 completed weeks of gestation).

(b) Term neonates (born at/after 37 completed weeks of gestation).

Written informed consent was obtained from parents/guardians of all patients before enrolling the babies for the study. A detailed clinical history covering antenatal, natal and postnatal periods was obtained for all cases. Socio-economic status of mothers was determined using BJ Prasad Classification. This was followed by a thorough physical examination to collect baseline data, apart from recording vital parameters like heart rate, respiratory rate, blood pressure and temperature.

Following tests were conducted as and when needed:

- Hemoglobin. TLC, DLC, Absolute neutrophil count, Band cells, platelet count and presence of toxic granules in peripheral blood smear.
- C-reactive protein
- Blood culture- Bactec method
- CSF: Cytology, biochemistry, culture and sensitivity testing.
- Urine: routine and microscopic examination, culture and sensitivity testing.
- Pus: Gram stain, Culture and sensitivity testing.
- Diarrhoeal stools were cultured and were tested for drug sensitivity.
- X-Ray chest PA view
- Cranial CT Scan.

Newborn babies in the study population received treatment according to the following plan:

(a) Control group- Patients in this group were given standard antibiotic therapy. All babies with presumed sepsis received cefotaxim and amikacin in appropriate doses according to blood culture / sensitivity report.

(b) Study group- Patients in this group received intravenous pentoxifylline in addition to standard antibiotic therapy.

Pentoxifylline was given by intravenous route in the dose of 5mg/kg/hr×6hrly for 6 days.

The patients were carefully monitored during their hospital stay for their response to therapy. In addition, they were also evaluated for any possible adverse effects to administration of pentoxifylline.

Sample size

The study was conducted on 100 newborn babies of either sex in the age group of 0-28 days, diagnosed as neonatal sepsis on the basis of clinical criteria, subject to confirmation by blood culture.

STATISTICAL ANALYSIS

The difference between study and control groups as well as between preterm and term infants was calculated using fisher exact test. The p value of <0.05 was considered significant.

RESULTS

Comparative study of duration of stay in NICU in study group and control group

Study group infants stayed for 10.18±3.373 days in NICU, whereas control group infants stayed for 14.88±4.843 days in NICU (p<0.001). The difference between the study and control group is statistically significant, which showed that study group infants had a shorter stay in NICU as compared to control group.

Comparative study of duration of stay in NICU in preterm and term infants

Preterm infants in study group stayed for 8±l.633 days in NICU, whereas term infants in study group stayed for I2.36±3.264 days in NICU (p <0.001) which is statistically significant, which showed that preterm infants in study group had a shorter stay in NICU as compared to term infants in study group.

Comparison of need for ventilation in study and control group

Table-1 shows the comparison of need for ventilation (NFV) in study and control group. Study group infants had a smaller (20%) need for ventilation, whereas, control group infants had larger (38%) need for ventilation. The difference between the two groups is (2=3.934, p<0.0473) statistically significant

Comparison of need for ventilation in preterm and term infants

Table-2 shows the comparison of need for ventilation (NFV) in preterm and term infants of study group. Preterm in study group had a smaller (20%) need for ventilation than term infants, who

Group	NFV		No NFV		Total	
	Number	%	Number	%		
Study	10	20	40	80	50	100
Control	19	38	31	62	50	100
Total	29	29	71	71	100	100

Table 1: Comparison of need for ventilation in study and control group

Group	NFV		No NFV		Total	
	Number	%	Number	%		
Preterm	5	20	20	80	25	100
Term	8	32	17	68	25	100
Total	13	26	37	74	50	100

Table-2: Comparison of need for ventilation in preterm and term infants

Group	NIS		NO NIS		Total	
	Number	%	Number	%		
Study	10	20	40	80	50	100
Control	19	38	31	62	50	100
Total	29	29	71	71	100	100

Table-3: Comparison of inotropic support in study and control group

Group	NIS		NO NIS		Total	
	No	%	No	%		
Preterm	5	20	20	80	25	100
Term	8	32	17	68	25	100
Total	13	26	37	74	50	100

Table-4: Comparison of inotropic support in preterm and term infants

had larger (32%) need for ventilation. The difference between term and preterm infants ("2=0.936. p<0.3334) is statistically significant

COmparison of inotropic support in study and control group

Table-3 shows the comparison for inotropic support in the study and control group infants. Study group had a smaller (20%) need for inotropic support (NIS), whereas, infants in control group had a larger (38%) need for inotropic support. Need for inotropic support was more in the control group (2-3.934. p<0.0473) which is statistically significant.

Comparison of inotropic support in preterm and term infants

Table-4 shows the comparison of inotropic support in preterm and term infants of study group. Preterm in study group had a smaller (20%) need for inotropic support, whereas, term infants had a larger {32%} need for inotropic support. The difference between two groups (2-0.936, p<0.3334) was statistically insignificant.

Comparison of mortality in study and control group

Infants in study group had a smaller (20%) mortality rate than the infants in control group (38%), which showed that study group infants had a lower percentage of mortality than the control group infants (2=3.934. p<0.0473) which was statistically significant.

Comparison of mortality in preterm and term infants

Preterm infants in study group had lesser (8%) mortality rate than the term infants (32%). The difference between the two values (2=4.5. p<0.0339) was statistically significant.

DISCUSSION

In this study, duration of stay in NICU was 10.18+3.373 days in the study group, whereas duration of stay in NICU was 14.88 ±4.843 days in the control group. The difference of results between two groups was statistically significant (p<0. 001). Similar results were seen in study done by Wajid Ali et al.[12] In our study, duration of stay in NICU was 8±1.633 days in preterm and 12.36±3.264 days in term infants. The difference of values between the two groups was statistically significant (p<0.001).

In our study, need for ventilation was recorded to be 20% in the study group, whereas it was 38% in the control group. The difference between the two values was statistically significant (p=0. 0473). Similar datas were recorded in study on Pentoxifylline in treatment of sepsis of premature infants done by Wajid Ali et al 12. In the study group, average duration of ventilation was 72 hours whereas in the control group duration of ventilation was 120 hours.

In our study, need for ventilation was also compared between preterm and term infants. Need for ventilation was found to be 20% in the preterm, whereas it was 32% in term infants. The difference between the two groups was statistically insignificant (p=0.3334).

In this study, need for inotropic support was found to be 20% in the study group, whereas it was recorded to be 38% in the control group, The difference between two groups was statistically significant (p=0.0473).In the study group, need for inotropic support was 20% in preterm infants, whereas it was recorded to be 32% in term infants. The difference between the two values was statistically insignificant (p<0.3334).

In our study, mortality was found to be 20% in the study group, whereas mortality was 38% in the control group. The difference between the two groups was statistically significant (p=0. 0473). Similar statistics were recorded in the study by Wajid Ali et al 12. In study group, 4 of 25 infants (16%) died due to sepsis. However, in control group, 10 to 25 (40%) neonates died due of sepsis. The difference in mortality was quite significant (p<0.02).

Similarly, a statistically significant decrease in mortality rate (0.04) was observed in a study done by Lauterbach et al[13] on role of pentoxifylline in premature infants with sepsis.

Lauterbach et al[14] found that pentoxifylline significantly affects synthesis of TNF and IL-6 when given in dose of 5mg/kg/hr for 6 hours on 6 successive days.Lauterbach et al[15] also found that pentoxifylline reduces plasma tumor necrosis factor alpha concentration infants with sepsis.

In this study, adverse effects attributable to pentoxifylline as –hypertension, irritability and detonation of vital status were looked for. But, no significant adverse effects were recorded in any of the cases of the study group. A similar conclusion was stated in study on Pentoxifylline in treatment of sepsis of premature infants done by Wajid Ali et al.[12] In their study, there was no evidence of toxicity attributable to Pentoxifylline.

CONCLUSION

We finally conclude that the effect of intravenous pentoxifylline as an adjunct to the standard antibiotic therapy in neonates with sepsis is highly beneficial. Outcome of neonatal sepsis in preterm neonates is better as compared to term neonates with the use of intravenous pentoxifylline as an adjunct to standard antibiotic therapy.No significant adverse effects attributable to pentoxifylline were observed.

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