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Pentoxifylline in Preterm Neonates

A Systematic Review

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Abstract

Sepsis, necrotizing enterocolitis (NEC), and chronic lung disease (CLD) in preterm neonates are associated with significant mortality and morbidity, including long-term neurodevelopmental impairment and socioeconomic burden. Safe and effective drugs for the prevention and treatment of these conditions are urgently needed.

Pentoxifylline, a synthetic theobromine derivative, is a non-steroidal immunomodulating agent with unique hemorrheologic effects which has been used in a range of infectious, vascular, and inflammatory conditions in adults and children. The unique properties of pentoxifylline explain its potential benefits in preterm neonates with sepsis, NEC, and CLD, conditions characterized by activation of the inflammatory cytokine cascade, free radical toxicity, and impaired microcirculation. Pentoxifylline has anti-inflammatory properties resulting from inhibition of erythrocyte phosphodiesterase. It lowers blood viscosity and improves microcirculation and tissue perfusion. As a phosphodiesterase inhibitor, pentoxifylline down-regulates pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin-6, and interferon-γ. Methylxanthines, including caffeine, theophylline, and theobromine are relatively non-toxic drugs; of these, theobromine is the least toxic. Pentoxifylline-related significant adverse events are thus very rare. Unlike other methylxanthines, pentoxifylline does not have significant cardiac and bronchodilating effects at therapeutic doses. Although it is contraindicated in adults with recent cerebral hemorrhage due to its effect

on platelets, red blood cells, and plasma fibrinogen levels, no significant adverse effects including thrombocytopenia and bleeding have been reported in critically ill preterm neonates with sepsis or NEC after treatment with pentoxifylline.

Based on data from pilot randomized trials and observational studies, our systematic review suggests that pentoxifylline may reduce mortality and/or morbidity in preterm neonates with sepsis, NEC, and CLD. Results of experimental studies also indicate that pentoxifylline may potentially be beneficial in meconium aspiration syndrome and hypoxic ischemic encephalopathy.

Given the substantial burden of sepsis, NEC, and CLD in high-risk preterm neonates, and the findings of this systematic review, pentoxifylline needs to be evaluated urgently as a preventative and therapeutic agent for these conditions in randomized controlled trials that can detect minimal clinically significant effect sizes. Further clinical and experimental studies are also necessary to evaluate whether pentoxifylline is safe and effective in meconium aspiration syndrome and hypoxic ischemic encephalopathy.

We aimed to conduct a systematic review of pentoxifylline as prevention or rescue treatment in preterm neonates with sepsis, necrotizing enterocolitis (NEC), or chronic lung disease (CLD). Literature was also reviewed to evaluate the potential of pentoxifylline in other neonatal conditions.

1. Clinical Context

Survival of preterm and very low birthweight (VLBW) neonates has improved significantly following advances in neonatal intensive care in the surfactant era. However, sepsis, NEC, and CLD, conditions where activation of the cytokine cascade is common, remain major contributors towards the significant mortality and morbidity, including long-term neurodevelopmental impairment and socioeconomic burden associated with this high-risk population.[1-3]

Late-onset sepsis (LOS, sepsis after 72 hours of age) occurs in 21% of VLBW neonates with a mortality of 18%, and is associated with longer hospital stay and a higher incidence of CLD and NEC.[1] LOS has also been linked with up to a 4-fold increased risk of cerebral palsy in preterm neonates.[2] Excessive pro-inflammatory cytokines such as interleukin (IL)-8 and tumor necrosis factor (TNF)-α are seen in septic shock, especially with Gram-negative organisms, and are associated with a higher mortality.[4] Therapies such as granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, and immunoglobulin have not shown a significant benefit in improving outcomes in preterm neonates with sepsis.[5-7]

Definite (greater than or equal to stage II) NEC occurs in approximately 5–10% of neonates with gestation <32 weeks, and is associated with significant mortality (30–50%) and morbidity, including long-term hospitalization, dependency on parenteral nutrition, recurrent sepsis, growth failure related to short bowel syndrome, long-term neurodevelopmental impairment, and economic burden.[3,8,9] The outcomes are worst in those who are extremely preterm (gestation <28 weeks) and/or need surgical intervention.[9] The pathogenesis of NEC remains poorly understood despite extensive research. Endogenous production of proinflammatory cytokines is considered to play an important role in the process that ultimately leads to gut necrosis in NEC, with TNFα playing a significant role.[10] Elevated levels of TNFα have been demonstrated in neonates with NEC.[11] Given its poorly understood pathogenesis, there is no single specific strategy for either prevention or treatment of this condition. The treatment of NEC thus continues to be mainly supportive, including provision of antibacterials, bowel rest, ventilatory and cardiovascular support, and surgical intervention as needed.

CLD (commonly defined as a requirement for supplemental oxygen at 36 weeks postmenstrual age) occurs in 23% of VLBW neonates and is associated with significant mortality and morbidity.[12] The pathogenesis of CLD relates mainly to pulmonary immaturity (including surfactant deficiency), injury related to mechanical ventilation (baro/volutrauma), production of free oxygen radicals, inflammation following sepsis, and suboptimal nutrition at a critical stage of development. Activation of the cytokine cascade also plays an important role in the pathogenesis of CLD. A pulmonary infiltration of inflammatory cells is seen, and is associated with increased pro-inflammatory cytokines such as IL-8, intracellular adhesion molecule-1 (ICAM-1), and TNFα.[13] Despite their short-term benefits, the utility of anti-inflammatory agents such as glucocorticoids (e.g. dexamethasone) is limited because of their association with long-term neurodevelopmental impairment.[14-16] Glucocorticoids are therefore currently used only as a part of research or under exceptional circumstances for neonates on maximal life support.[17] Caffeine, when used for apnea of prematurity in infants with a birthweight of 500–1250 g, reduces the risk of

CLD (odds ratio [OR] 0.63; 95% CI 0.52, 0.76) and improves survival without neurodisability at 18–21 months of age (OR 0.77; 95% CI 0.64, 0.93).[18,19]

Thus, neonatal sepsis, NEC, and CLD have in common their inflammatory etiology and the lack of a safe and effective therapy. Other neonatal illnesses also associated with an inflammatory cascade and with a need for safe treatment include meconium aspiration syndrome and persistent pulmonary hypertension of the newborn which can be associated with sepsis. The latter condition is also associated with impaired circulation in the lungs.[20]

2. Pentoxifylline

Pentoxifylline is a synthetic theobromine derivative, structurally related to the methylxanthines, theophylline, and caffeine (figure 1). It has unique hemorrheologic effects not seen with other methylxanthines. Over the last 2 decades, this nonsteroidal immunomodulating agent has been used in a range of infectious, vascular, and inflammatory conditions, including sepsis and multi-organ failure in adults[21-23] and in children with Kawasaki's disease.[24] The unique properties of pentoxifylline explain its potential benefits in preterm neonates with sepsis, NEC, and CLD, conditions characterized by activation of the inflammatory cytokine cascade, free radical toxicity, and impaired microcirculation, as discussed in section 1.

2.1 Mechanisms of Action

The mechanisms of action of pentoxifylline in septic shock and inflammation are summarized in figure 2. Pentoxifylline has anti-inflammatory properties; it inhibits erythrocyte phosphodiesterase (PDE), resulting in increased intracellular cyclic adenosine monophosphate activity. Pentoxifylline also produces unique dose-related hemorrheologic effects; it increases erythrocyte flexibility, fibrinolytic and tissue plasminogen activator activity,[25] and inhibits platelet adhesion. These effects lower blood viscosity and improve microcirculation and tissue perfusion. As a PDE inhibitor, pentoxifylline downregulates powerful pro-inflammatory cytokines such as TNFα, IL-6, and interferon-γ. It may also potentiate endogenous prostacyclin, which has antiaggregatory and vasodilatory actions.[23,26] Pentoxifylline has been reported to have a dual effect on neutrophil function, including the superoxide respiratory burst; low doses enhance and high doses inhibit the burst.[26,27] It prevents endothelial cell dysfunction in sepsis.[28]

Numerous other effects have been reported as a consequence of the action of pentoxifylline on cyclic adenosine monophosphate, including preservation of the protein C and S anticoagulant systems in sepsis,[29] and increased leukocyte and erythrocyte deformity.[30] Importantly, its action on platelets does not increase platelet adhesion[29] or impair their function.[25] Recent studies using intestinal cell monolayer have shown that pentoxifylline helps to preserve the disruption in the tight junction barrier after an insult with cytokines TNFα, interferon-γ, and IL-1.[31] Similarly, pentoxifylline seemed to effectively attenuate burn-induced intestinal permeability in a mouse model of severe burn injury.[32] These studies may indicate why pentoxifylline may be particularly useful in conditions associated with disturbed intestinal integrity/permeability such as NEC.

2.2 Pharmacokinetics

Pentoxifylline is soluble in water and ethanol and is 70% protein bound in blood, with an elimination half-life of 0.4–0.8 hours. Bioavailability information is available mainly in adults in whom the peak drug concentration occurs 5 minutes after an intravenous injection. Metabolism is primarily by reduction to metabolite I and oxidation to metabolites III and IV (table I). Renal excretion of metabolite IV (45%) and, to a lesser extent, metabolite III (5%), occurs rapidly.[36]

There are limited data on the pharmacokinetics of pentoxifylline in neonates and children. Szymura-Oleksiak et al.[37] reported that an intravenous infusion of pentoxifylline at 30 mg/kg/day over 6 hours in neonates with septic shock resulted in serum pentoxifylline concentrations comparable to those in adults with septic shock treated with a similar dose. However, clinical improvement was transient, lasting for only a

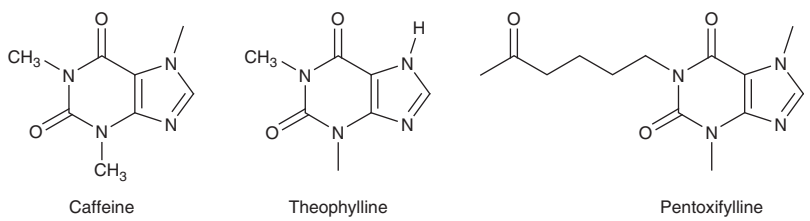

Fig. 1. Chemical structure of pentoxifylline ($C_{13}H_{18}N_4O_3$) and two structurally related methylxanthines that are widely used for apnea of prematurity: caffeine ($C_8H_{10}N_4O_2$) and theophylline ($C_7H_8N_4O_2$).

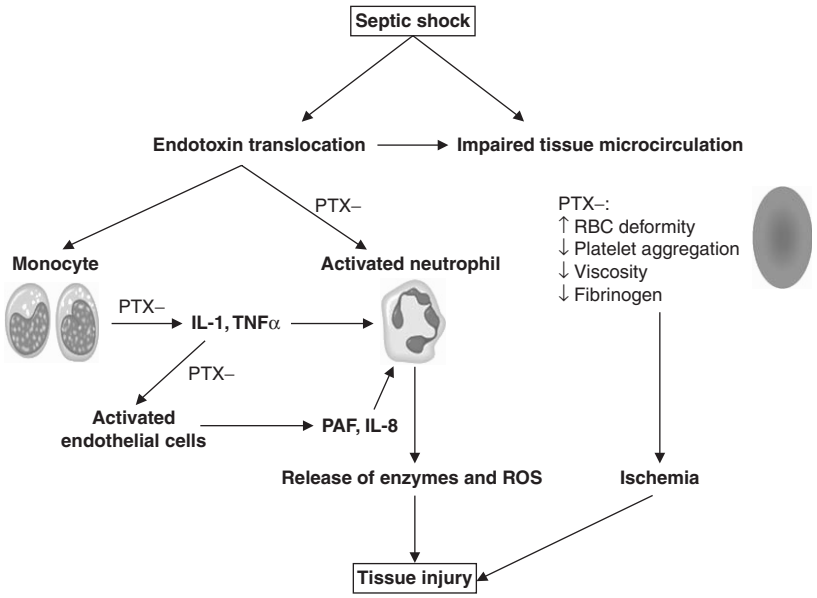

Fig. 2. Mechanisms of action of pentoxifylline (PTX) in septic shock and inflammation. **IL** = interleukin; **PAF** = platelet activating factor; **PTX–** indicates PTX inhibition; **RBC** = red blood cell; **ROS** = reactive oxygen species; **TNFα** = tumor necrosis factor-α; ↑ indicates increase; ↓ indicates decrease.

few hours. The authors therefore went on to use 60 mg/kg/day over 12 hours, resulting in a significant increase in serum concentrations of pentoxifylline and its important active metabolites as well. This dose was tolerated with no adverse effects reported. Such a high initial dose may be necessary to inhibit high levels of TNFα. Lauterbach et al.[38] and Hinshaw[39] suggested that impaired microcirculation in sepsis can inhibit the distribution of antibacterials to the infection site. This problem can be overcome if pentoxifylline, which improves microcirculation, is given before the antibacterials. Lauterbach and Szymura-Oleksiak[40] reported plasma pentoxifylline concentrations in preterm neonates (mean gestation, birthweight, and postnatal age: 28.6 weeks, 1088 g, and 53.6 days, respectively) receiving nebulized pentoxifylline (20 mg/kg and 10 mg/kg per dose 6 hourly for 3 days if spontaneously breathing and mechanically ventilated, respectively). The plasma pentoxifylline level on day 6 following nebulized pentoxifylline was approximately 20-fold less than that in neonates receiving the drug intravenously (60 mg/kg/day) over 6 days for sepsis.[40]

2.3 Adverse Effects

The methylxanthines caffeine, theophylline, and theobromine are relatively non-toxic drugs, and theobromine is the least toxic. With pentoxifylline being a theobromine derivative, pentoxifylline-related significant adverse events are thus unlikely in preterm neonates.[37-47] Unlike other methylxanthines, pentoxifylline does not have significant cardiac and bronchodilating effects.[48] Theobromine is considerably weaker than caffeine and theophylline, having about one-tenth of the

Table I. Metabolism of pentoxifylline (adapted from Aviado and Dettelbach[33])

Drug/metabolite	Site of formation	Urinary excretion (%)	Platelet aggregation[34]	Anti-TNFα[35]
Pentoxifylline		Trace	+	++
Metabolite I	Erythrocytes	<1	+	++
Metabolite II	Liver	12	NA	NA
Metabolite III	Liver	12	NA	NA
Metabolite IV	Liver	8	+/–	–
Metabolite V	Liver	50–60	–	–
Metabolite VI	Liver	<1	NA	NA
Metabolite VII	Liver	<1	NA	NA

NA = not applicable; **TNF** = tumor necrosis factor; + indicates positive effect; ++ indicates very positive effect; – indicates no effect; +/– indicates possible effect.

stimulating effect of either. CNS (irritability, tremors, and convulsions) and cardiovascular (hypotension, arrhythmia) side effects are thus rare with therapeutic doses of the drug.

Given its effect on platelets, red blood cells, and plasma fibrinogen levels,[48] pentoxifylline is contraindicated in adults with recent cerebral and retinal hemorrhage. Intraventricular hemorrhage associated with preterm birth has thus been raised as a potential concern during treatment with pentoxifylline in preterm neonates. However, it is reassuring to note that no significant adverse effects, including thrombocytopenia and bleeding, have been reported in critically ill preterm neonates with sepsis (n = 117) after treatment with pentoxifylline.[37-47,49] The frequency of bleeding was actually lower (pentoxifylline: 0/34 patients vs placebo: 4/30 patients; p = 0.05) in neonates allocated to pentoxifylline.[37] The fact that comparison of cranial ultrasound scans before and after pentoxifylline treatment showed no change in 73% of critically ill neonates with advanced surgical NEC supports the safety of the drug.[47] Nevertheless, given these concerns, neonates treated with pentoxifylline should be monitored for all possible adverse events, including occurrence of new or extension of old intraventricular hemorrhage. Concomitant administration of pentoxifylline and other methylxanthines could theoretically cause an increased incidence of the latter.[48]

2.4 Toxicity

Although a toxic dose of pentoxifylline has not been defined, symptoms of moderate to severe toxicity have been reported in patients taking up to 80 mg/kg per dose.[48] These authors also reported an infant who ingested 80 mg/kg of pentoxifylline along with 6 mg/kg of clobazam and developed life-threatening effects that resolved with supportive care. The toxic effects of pentoxifylline include flushing, fever, hypothermia, agitation, myoclonus, somnolence, loss of consciousness, seizures, and hypotension. Bradycardia, atrioventricular block, and asystole have also been reported. There are no reports of chronic toxicity. Treatment of pentoxifylline toxicity is supportive and symptomatic. Hypotension is likely due to peripheral vasodilatation, therefore α-adrenergic vasopressors are likely to be useful.[50]

3. Systematic Review of Pentoxifylline in Preterm Neonates

3.1 Search Methods

The standard search strategy of the Cochrane Neonatal Review Group (http://www.cochrane.org) was followed. Electronic databases, including MEDLINE/PubMed (1980 onwards), CINAHL, EMBASE, Cochrane CENTRAL, and Google, were searched. References and cross references of review articles and proceedings of the Pediatric Academic Societies Annual Meeting 2007 were manually searched. The search terms consisted of ('infant, newborn' [MeSH] OR Neonat* OR Newborn*) AND ('sepsis' [MeSH] OR sepsis OR septicaemia OR septicemia OR septic OR 'necrotizing enterocolitis' [MeSH] OR 'necrotising enterocolitis' OR 'chronic lung disease' OR 'bronchopulmonary dysplasia' [MeSH]) AND ('Pentoxifylline' [MeSH] OR Trental OR Pentoxif*).

3.2 Inclusion Criteria

All articles (e.g. systematic reviews, randomized controlled trials [RCTs], observational studies) in preterm neonates with gestation <37 weeks were included in the review with no restriction on the design. Assessment of the quality of the trials included in the review was based on the standard Cochrane methodology (http://www.cochrane.org). Clinical and experimental data on conditions other than sepsis, NEC, and CLD were also included to evaluate the potential of the drug in other conditions.

3.3 Results

Table II outlines the methodological characteristics of the studies included in the systematic review. Table III presents the primary outcomes of the studies, excluding case series.

3.3.1 Sepsis

Two RCTs (n = 140),[41,42] one quasi-RCT (n = 50),[45] and two further cohort/observational studies (n = 37)[38,46] have evaluated the use of pentoxifylline in sepsis in preterm neonates. The pilot clinical trial by Lauterbach and Zembala[41] evaluated the safety and efficacy of pentoxifylline in 40 preterm (gestation <36 weeks) neonates with suspected sepsis after the first week of life. The inclusion criteria were presence of respiratory or cardiovascular dysfunction and signs, such as apnea, tachycardia, bradycardia, or shock. Neonates with major congenital malformations, congenital infection, or high-grade intraventricular hemorrhage (grade III or IV) were excluded. Enrolled neonates were randomly allocated to receive intravenous infusion of pentoxifylline or an equal volume of normal saline as placebo at 5 mg/kg/hour for 6 hours per day for 3 days, starting 30 minutes before the administration of antibacterials. Double blinding was assured but the method of generating random sequence and concealment of allocation was not clear. All neonates also

Table II. Characteristics of the included studies

Study (y)	Design	No. of pts	No. of centers	Population	Birth year	Adequacy of randomization	Allocation concealment	Blinding of caregivers	Blinding of assessors	Follow-up rate (%)
Sepsis										
Lauterbach and Zembala[41] (1996)	RCT	40	1	PT <36 wk GA	1994	Unclear	Unclear	Yes	Yes	73
Lauterbach et al.[42] (1999)	RCT	100	2	PT <36 wk GA	1995–1996	Yes	Yes	Yes	Yes	78
Ali et al.[45] (2006)	CT	50	1	PT <37 wk GA	2004–2005	NA	NA	No	No	100
Selim et al.[46] (2004)	CT	20	1	PT and T <1 mo	NA	NA	No	No	No	100
Lauterbach et al.[38] (1994)	CS	30	1	PT <36 wk GA	1992	NA	NA	NA	NA	NA
Chronic lung disease										
Lauterbach et al.[43] (2006)	RCT	150	1	VLBW at 72 h	2000–2003	Yes	Yes	No	No	65
Lauterbach and Szymura-Oleksiak[40] (1999)	CS	5	1	PT 27–31 wk GA	2000	NA	NA	NA	NA	NA
Lauterbach et al.[44] (2004)	RCT	27	1	PT <36 wk GA	2000	Unclear	Unclear	No	No	NA
Necrotizing enterocolitis										
Rossouw et al.[47] (2007)	CS	20	1	Stage III NEC (patient age not given)	2002–2006	NA	NA	NA	NA	NA

CS = case series; **CT** = controlled trial; **GA** = gestational age; **NA** = data not available; **NEC** = necrotizing enterocolitis; **PT** = preterm neonates; **pts** = patients; **RCT** = randomized controlled trial; **T** = term neonates; **VLBW** = very low birthweight infants (<1500 g).

received immunoglobulin on day 1 of the study along with conventional treatment in the form of antibacterials. The analysis was not on an intention-to-treat basis because neonates with a negative blood culture (n = 11) were excluded from the analysis. Outcomes assessed included mortality and plasma TNFα levels before and after the infusion on the first and third day of treatment. Plasma TNFα levels were also compared with those of ten healthy age- and weight-matched neonates. There was a statistically significant difference in TNFα levels between the pentoxifylline and placebo groups after the last infusion (41.0 vs 246.9 pg/mL; $p < 0.001$; CI values not given). Data regarding the TNFα levels in the healthy neonates were not stated. The difference in mortality (pentoxifylline: 0/16 vs placebo: 3/13) was not significant. There were significantly fewer infants with NEC (1/16 vs 5/13) in the pentoxifylline group (no evidence of definite NEC [greater than stage II] was present prior to treatment). No significant adverse effects were noted. Data on the development of new or extension of existing intraventricular hemorrhage were not reported.

Lauterbach et al.[42] have also reported results of a larger RCT of pentoxifylline involving 100 preterm neonates (gestation <36 weeks) with presumed sepsis after the first week of life. Strategies for allocation concealment and double blinding were reported adequately. The daily dose of pentoxifylline and placebo was similar to that in the pilot trial but the duration of treatment was extended to 6 days. The first dose of pentoxifylline was administered either with the first dose of antibacterials or 30 minutes prior to this if there was suggestion of abnormal peripheral circulation. Other immunomodulating agents such as immunoglobulin or corticosteroids were not used. Antibacterial treatment was standardized and consisted of amoxicillin/clavulanic acid (augmentin) and amikacin. The analysis was again not based on an intention-to-treat principle as neonates with a negative blood culture (n = 22) were excluded from the analysis. The baseline characteristics, including gestational age and birthweight, of the neonates in both groups were similar (mean birthweight 1690 vs 1749 g; gestation 32 vs 32 weeks). Plasma IL-6 and TNFα levels were significantly lower on day 6 in the pentoxifylline versus placebo group (TNFα, pentoxifylline vs placebo: 68.1 pg/mL vs 452.3 pg/mL; IL-6, pentoxifylline vs placebo: 13.6 vs 197.5 pg/mL; $p = 0.04$). Mortality was significantly lower (1/40 vs 6/38; $p = 0.043$) in the pentoxifylline versus placebo group. There were indications of an improved clinical course in those receiving pentoxifylline, including significantly less metabolic acidosis, anuria, or oliguria, disseminated intravascular coagulation, hypotension, and development of NEC. A significant difference was found on subanalysis of infants with septic shock; only one of four

Table III. Primary outcomes of included studies (excluding case series)

Study (y)	Primary outcome (no. of pts)[a]		p-Value
	PTX	placebo	
Sepsis			
Lauterbach and Zembala[41] (1996)	0/16	3/13	>0.05
Lauterbach et al.[42] (1999)	1/40	6/38	0.046
Ali et al.[45] (2006)	4/25	10/25	<0.02
Selim et al.[46] (2004)	3/7	0/13	>0.05
Prevention of CLD			
Lauterbach et al.[43] (2006)	12/37	16/27	0.039

a The primary outcome for sepsis was mortality; the primary outcome for prevention of CLD was the incidence of CLD.

CLD = chronic lung disease; **pts** = patients; **PTX** = pentoxifylline.

infants receiving placebo survived, whereas all five receiving pentoxifylline survived ($p < 0.04$). These infants all had Gram-negative sepsis and infants with Gram-negative sepsis had significantly higher TNFα levels compared with those with Gram-positive sepsis. No adverse effects were noted. Data on intraventricular hemorrhage and long-term neurodevelopment were not provided.

A meta-analysis[49] of the two trials by Lauterbach et al.[41,42] discussed above reported a significant decrease in mortality from sepsis in preterm neonates when treated with pentoxifylline; the typical relative risk was 0.14 (95% CI 0.03, 0.76) with a number needed to treat of 6 (95% CI 4, 25). Subgroup analysis indicated a borderline significant reduction in mortality in those with Gram-negative sepsis receiving pentoxifylline. No other outcomes were reported from the meta-analysis. The reviewer concluded that pentoxifylline is promising in the treatment of neonatal sepsis but further well designed RCTs are necessary.[49]

Ali et al.[45] reported a small quasi-RCT of pentoxifylline in preterm neonates (gestation <37 weeks; n = 50) with culture-proven sepsis and clinical signs of sepsis, and respiratory or cardiovascular dysfunction. Neonates with intracranial hemorrhage, congenital infection, and negative blood cultures were excluded. Enrolled neonates received either pentoxifylline or routine treatment (no placebo). The method of randomization, strategies for allocation concealment, and blinding were not reported. The dosing of pentoxifylline was 5 mg/kg/hour over 6 hours for 3 consecutive days. The baseline characteristics of enrolled neonates in each group were similar. No neonates were below 950 g birthweight or <32 weeks' gestation. Mortality was significantly reduced (4/25 vs 10/25; $p < 0.02$) in those receiving pentoxifylline; this benefit was significant in those with Gram-negative sepsis ($p < 0.04$) and those with clinical shock ($p < 0.002$). Fewer neonates (8% vs 28%) developed NEC after receiving pentoxifylline as an adjunct to routine treatment. No adverse effects were reported.

A small (n = 20) poor quality cohort study of neonates with sepsis has also been reported.[46] Pentoxifylline was used for the first 'block' of 13 neonates and the subsequent 'block' of seven served as the controls who received standard management (no placebo). No difference was found in TNFα or IL-6 levels between the groups, and there was no significant difference in mortality (0 vs 3 deaths, pentoxifylline vs control). No adverse effects were reported. The poor design and small sample size make it difficult to derive any conclusions from this study.

Lauterbach et al.[38] earlier reported an observational study involving 17 preterm neonates with sepsis who were treated with pentoxifylline. They retrospectively compared this group with 13 preterm neonates with sepsis not treated with pentoxifylline and found significantly reduced mortality ($p < 0.04$), and a reduced incidence of hypotension ($p < 0.006$) and metabolic acidosis ($p < 0.01$) in those who received pentoxifylline. These authors also reported that pentoxifylline at a dose of 5 mg/kg/hour over 6 hours for 3 days is safe with no adverse effects.

3.3.2 Chronic Lung Disease

We found one RCT evaluating early use of pentoxifylline for preventing CLD (n = 150),[43] one observational study of late use (n = 5),[40] and one interim report of an RCT evaluating a different protocol of pentoxifylline as a rescue for established CLD (n = 27).[44] Lauterbach et al.[43] reported the results of their RCT evaluating whether early pentoxifylline (compared with placebo or dexamethasone) would prevent the development of CLD. A total of 150 VLBW neonates were recruited at 72 hours of age if they required ventilatory support or inspired oxygen concentration of more than 30%. Exclusion criteria were congenital anomaly, infection, or intraventricular hemorrhage grade III or IV. Neonates in the pentoxifylline arm received nebulized pentoxifylline (at 20 mg/kg/dose if breathing spontaneously or at 10 mg/kg/dose if intubated) four times a day for 3 consecutive days. The dexamethasone dosage was 0.25 mg/kg/dose twice daily for 3 days. The course would be repeated every 7 days if the neonate continued to meet the recruitment criteria. There was no blinding as the route of drug administration was different. The primary outcome was the incidence of CLD as defined by requiring supplemental oxygen for at least 27 days and at the postmenstrual age of 36 weeks. Secondary outcomes included pneumothorax, intraventricular hemorrhage, persistent ductus arteriosus, and periventricular leukomalacia during the trial period. Of the neonates recruited,

the actual number of cases analyzed was 37, 33, and 27 neonates in the pentoxifylline, dexamethasone, and placebo groups, respectively. Mortality was similar between groups (pentoxifylline, n = 10; dexamethasone, n = 12; placebo, n = 12). There was significantly less CLD in the neonates receiving pentoxifylline ($p = 0.039$) or dexamethasone ($p = 0.07$) compared with placebo. The reduction in risk was 27% in the pentoxifylline group and 23% in the dexamethasone group. However, it is important to note that the intention-to-treat analysis of all 150 neonates revealed no significant differences. This makes the weighting of this study less significant. The only adverse effect noted with pentoxifylline was 'occasional feeding intolerance'.

Lauterbach and Szymura-Oleksiak[40] reported an observational study of nebulized pentoxifylline in five preterm neonates (postnatal age >43 days, gestation 27–31 weeks) with established CLD. The neonates were spontaneously breathing with supplemental oxygen concentration of 40–70% and had no clinical improvement during the previous 7 days. Pentoxifylline was administered via a nebulizer at 10 mg/kg/dose over 10 minutes four times a day for 6 days. By day 6, there was a significant reduction in oxygen requirement ($p = 0.043$). Only one of the five neonates needed oxygen at the end of day 6. This neonate also had a reduction in supplemental oxygen concentration from 70% to 25%. There was no rebound in oxygen requirement after completion of the treatment course. Additionally, there was a significant improvement in respiratory mechanics over the treatment period.

Lauterbach et al.[43] have also reported an interim analysis of their RCT evaluating pentoxifylline compared with dexamethasone as late 'treatment'/rescue of CLD in preterm neonates. Preterm neonates needing oxygen at day 30 were recruited to either receive pentoxifylline or dexamethasone at the same dosage as in the prevention trial described previously,[43] except each drug was given for 10 (not 3) days and repeat courses were given after 5 days until the neonate was ventilator and oxygen independent. Only 27 neonates had been recruited at the time of the report. There was a trend to less oxygen dependency in the pentoxifylline group. Detailed results of the statistical analysis were not reported. The median time on oxygen was less in pentoxifylline versus dexamethasone recipients (12 [range 5–51] vs 16.5 [2–89] days). No firm conclusions could be made from this report.

3.3.3 Necrotizing Enterocolitis

Our literature search did not reveal any published RCTs of pentoxifylline as a treatment for NEC; however, a report of a series of cases with advanced surgical NEC was identified.[47] Given the limited clinical data, we also searched for relevant experimental studies.

Rossouw et al.[47] reported a series of critically ill neonates with severe NEC treated with pentoxifylline as an adjunct therapy at their regional surgical referral center. Over a 4-year period there were 204 cases of definite NEC. A total of 20 with advanced stage III NEC were treated with pentoxifylline. All of these neonates had multi-system organ failure (4–6 organs) and all required inotrope infusion. Pentoxifylline infusion (5 mg/kg/hour over 6 hours for 6 days) was commenced an average of 3 days after inotropes were started; the mean number of infusions was four. The actual mortality was 55% compared with 94% predicted by the Sepsis-related Organ Failure Assessment score. Follow up revealed no significant changes in pre- and post-pentoxifylline cranial ultrasound scans in 73% of cases. Pentoxifylline was well tolerated in this critically ill population with no adverse effects.

Travadi et al.[51] evaluated the effects of pentoxifylline on NEC in a well accepted animal model by conducting a rigorous, randomized, triple-blind, placebo-controlled trial with adequate power to test the proposed hypothesis. Based on their pilot data, the estimated sample size for this trial was 40 rat pups in each group ($\alpha = 0.05$, $\beta = 0.02$) to detect a 50% reduction in the incidence of NEC. The incidence (pentoxifylline: 5/38 vs placebo: 15/36; OR 0.21; CI 0.07, 0.67) as well as the severity of NEC (intestinal injury scores [grade 3–4]: pentoxifylline: 1/5 versus placebo: 10/15; OR 0.06; 95% CI 0.01, 0.79) were significantly lower in the rat pups administered with pentoxifylline.

Erdener et al.[52] had earlier reported that pre-treatment with pentoxifylline did not have a protective effect in their animal model of NEC, which relied on hypoxia/reoxygenation (H/R) to induce the intestinal injury. Twenty-one newborn rabbits were divided into three groups: group 1 (control), group 2 (H/R), and group 3 (H/R plus pentoxifylline). Five minutes of reoxygenation following 5 minutes of hypoxia was performed three times a day for 3 days. Before each H/R procedure in the H/R plus pentoxifylline group, the rabbits were administered intraperitoneal pentoxifylline 25 mg/kg. The animals were sacrificed on day 3, and ileum samples were preserved for histopathology and biochemical measurements. There was a significant difference in the grade and number of the intestinal lesions between controls and the H/R and H/R plus pentoxifylline groups ($p < 0.001$), but no significant difference was found between the H/R and the H/R plus pentoxifylline groups ($p > 0.05$). Intestinal superoxide dismutase, glutathione reductase, and glutathione S-transferase activities in the H/R and H/R plus pentoxifylline groups were significantly higher than in the control group ($p < 0.05$); however, there was no significant difference between the H/R and H/R plus pentoxifylline groups ($p > 0.05$). Rabbits are not the most appropriate species to study

NEC and, apart from H/R, the role of prematurity and feeding is also important in the pathogenesis of NEC. These 'negative' results by Erdener et al.[52] may thus relate to selection of the wrong species, the wrong insult, and, importantly, to a small sample size.

Two multicenter RCTs are currently underway evaluating the safety and efficacy of pentoxifylline in NEC in preterm neonates (Australian Clinical Trials Registry Number 012606000257561; ClinicalTrials.gov Identifier NCT00271336). The results of these trials are not expected for several years.

3.3.4 Persistent Pulmonary Hypertension of the Newborn

Persistent pulmonary hypertension of the newborn (PPHN), also referred to as persistent fetal circulation, is a rare but life-threatening condition that occurs when a neonate's circulation does not adequately adapt to extrauterine conditions at birth. PPHN is characterized by elevated pulmonary arterial pressures and open ductus arteriosus, resulting in poor pulmonary blood flow and hypoxemia. PPHN often results from birth complications such as asphyxia, meconium aspiration syndrome, or sepsis.[20] Pentoxifylline has been reported to be beneficial in a case report by improving the oxygenation in a preterm neonate with PPHN, presumably secondary to sepsis.[53] The benefits of pentoxifylline may relate to the pulmonary vasodilatory action of the drug acting as a PDE inhibitor.[54]

3.3.5 Meconium Aspiration Syndrome

Neonatal meconium aspiration syndrome frequently produces severe respiratory distress associated with patchy pulmonary neutrophil influx and inflammatory lung injury. Korhonen et al.[55] have reported beneficial anti-inflammatory effects of pentoxifylline in nine unilaterally meconium-exposed piglet lungs compared with controls. Regional inflammation and ventilatory disturbance was reduced. Meconium instillation increased bronchoalveolar lavage fluid total cell, neutrophil, and macrophage counts, TNFα and protein concentrations, and lung tissue myeloperoxidase activity in the instilled lungs, compared with the non-instilled side. Pentoxifylline prevented the increases in the bronchoalveolar lavage fluid macrophage count and TNFα and protein concentrations in the meconium-instilled lungs but had no significant effect on pulmonary neutrophil accumulation. Ventilation of the meconium-insulted lung was initially disturbed similarly in both study groups, but pentoxifylline prevented the sustained local ventilatory perturbation at 4, 6, and 12 hours after meconium instillation. These results indicate that pentoxifylline treatment may be beneficial in neonatal meconium aspiration syndrome.[55] To our knowledge, no clinical studies have been reported.

3.4 Discussion

The results of our systematic review indicate the potential of pentoxifylline as a safe and effective drug for managing sepsis, NEC, and CLD, conditions that contribute significantly to the substantial health burden associated with preterm VLBW neonates surviving after the first week of life. The limitations of the available clinical data relate mainly to small sample sizes and poor quality of study design and/or reporting. Large and well designed RCTs that can detect the minimal clinically significant effect size with adequate power are urgently needed to evaluate the short- as well as long-term safety and efficacy of pentoxifylline in these conditions. Assessing long-term neurodevelopmental impairment is crucial given its baseline incidence in this high-risk population as well as the neurological adverse effects (and subsequent potential medico-legal issues) possibly associated with glucocorticoids as a rescue strategy for severe CLD. The limited clinical and experimental data, however, support the hypothesis that pentoxifylline may prove to be a steroid-sparing agent in this high-risk population. Designing high quality RCTs is not expected to be difficult given the low cost of pentoxifylline and the suitability of normal saline as a placebo; however, multicenter involvement is necessary given the current rather low incidence of sepsis, NEC, CLD, and long-term neurodevelopmental impairment in preterm VLBW neonates with gestation <32 weeks. Assuring strategies for optimizing follow up of patients (≥80%) is important if survival free of long-term neurodevelopmental impairment is the preferred primary outcome.

Proinflammatory cytokines play an important role in the pathophysiology of sepsis, NEC, and CLD, and prolonged exposure to such cytokines at a critical stage of development is associated with long-term neurodevelopmental impairment in high-risk neonates. It is therefore not unreasonable to expect that pentoxifylline may improve long-term neurodevelopmental outcomes in these neonates by directly suppressing some of the key proinflammatory cytokines, minimizing further injury to a vulnerable brain. Whether the significant benefits of pentoxifylline in sepsis with Gram-negative organisms are retained in LOS with Gram-positive organisms (e.g. coagulase negative staphylococci) remains to be seen.

The current data provide adequate evidence for the protocol (dose and mode of administration) of pentoxifylline. Optimal equipment for drug delivery is critical when pentoxifylline is nebulized. Using a higher dose (60 mg/kg/day) at the start of therapy seems appropriate as plasma levels of proinflammatory cytokines are expected to be high during the initial stage of illnesses such as NEC, sepsis, and CLD. Given its long track record and safety, especially in critically ill preterm neonates, treatment with pentoxifylline should start as soon as possible

after the diagnosis of the condition that needs intervention to optimize its efficacy. Researchers have hypothesized that intermittent infusion with possibly waxing and waning drug levels seems beneficial in keeping a balance between pro- and anti-inflammatory cytokines that is crucial for survival in patients with sepsis.[44] Primary prophylaxis is probably best avoided to minimize exposure of almost the entire population of high-risk neonates to the known/unknown short- and long-term adverse effects of the drug.

In addition to the conditions covered in this systematic review, hypoxic ischemic encephalopathy following birth asphyxia in neonates may be a future target for pentoxifylline therapy. This condition continues to be a significant issue, especially in developing countries. Until recently, there was no proven intervention for neuroprotection of neonates with hypoxic ischemic encephalopathy. Over the last few years, therapeutic hypothermia has emerged as a causative neuroprotective intervention for hypoxic ischemic encephalopathy, based on the encouraging results from several RCTs.[56] Given the role of ischemia-reperfusion injury and oxidative stress in the pathogenesis of hypoxic ischemic encephalopathy, the role of pentoxifylline in this condition also needs to be explored.[57-59] Experimental studies have shown that pentoxifylline treatment improves neurological and neurochemical deficits in rats subjected to transient brain ischemia.[60] The TNFα inhibition and anti-inflammatory actions of pentoxifylline could be responsible, at least in part, for the neuroprotection afforded by the drug.[60] Experts have already suggested the need for studies of therapeutic hypothermia with adjunct pharmacotherapy as a method for neuroprotection in neonates with hypoxic ischemic encephalopathy,[61,62] and pentoxifylline is one of the most promising candidate drugs that need to be trialled.

4. Conclusions

Given the substantial burden of disease associated with sepsis, NEC, and CLD in the high-risk population of preterm neonates, and based on the efficacy and safety profile of pentoxifylline as summarized in this article, pentoxifylline appears to be a promising preventative and therapeutic agent for these conditions. Well designed, multicenter, randomized trials are warranted. Experimental research is necessary in order to evaluate whether pentoxifylline is safe and effective in meconium aspiration syndrome and hypoxic ischemic encephalopathy.

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