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TABLE OF CONTENTS

HEADER 1
ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
BACKGROUND 3
OBJECTIVES 4
METHODS 4
RESULTS 6
DISCUSSION 9
AUTHORS' CONCLUSIONS 9
ACKNOWLEDGEMENTS 10
REFERENCES 11
CHARACTERISTICS OF STUDIES 13
DATA AND ANALYSES 18
Analysis 1.1. Comparison 1 Cyst(e)ine vs. placebo in added to cysteine-free PN, Outcome 1 Weight gain during the study (g/kg/day). 20
Analysis 1.2. Comparison 1 Cyst(e)ine vs. placebo in added to cysteine-free PN, Outcome 2 Increase in length (cm/ 6 days). 20
Analysis 1.3. Comparison 1 Cyst(e)ine vs. placebo in added to cysteine-free PN, Outcome 3 Increase in head circumference (cm/ 6 days). 20
Analysis 1.4. Comparison 1 Cyst(e)ine vs. placebo in added to cysteine-free PN, Outcome 4 Nitrogen retention (mg/kg/day). 20
Analysis 1.5. Comparison 1 Cyst(e)ine vs. placebo in added to cysteine-free PN, Outcome 5 Plasma level of free cyst(e)ine (micromoles/100 ml). 22
Analysis 1.6. Comparison 1 Cyst(e)ine vs. placebo in added to cysteine-free PN, Outcome 6 Total plasma cyst(e)ine level (micromoles/ 100 ml). 23
Analysis 2.1. Comparison 2 N-acetylcysteine vs. placebo added to cysteine-containing PN, Outcome 1 Weight gain during the study (g/kg/day). 24
Analysis 2.2. Comparison 2 N-acetylcysteine vs. placebo added to cysteine-containing PN, Outcome 2 Weight (g) at 36 weeks of postmenstrual age. 24
Analysis 2.3. Comparison 2 N-acetylcysteine vs. placebo added to cysteine-containing PN, Outcome 3 Death by 36 weeks of postmenstrual age. 24
Analysis 2.4. Comparison 2 N-acetylcysteine vs. placebo added to cysteine-containing PN, Outcome 4 Bronchopulmonary dysplasia among survivors at 36 weeks of postmenstrual age. 25
Analysis 2.5. Comparison 2 N-acetylcysteine vs. placebo added to cysteine-containing PN, Outcome 5 Death or Bronchopulmonary Dysplasia (36 weeks postmenstrual age). 25
Analysis 2.6. Comparison 2 N-acetylcysteine vs. placebo added to cysteine-containing PN, Outcome 6 Retinopathy of prematurity (any stage) among those examined. 25
Analysis 2.7. Comparison 2 N-acetylcysteine vs. placebo added to cysteine-containing PN, Outcome 7 Severe (stage 3 or more) retinopathy of prematurity among those examined. 25
Analysis 2.8. Comparison 2 N-acetylcysteine vs. placebo added to cysteine-containing PN, Outcome 8 Necrotizing enterocolitis (operated). 26
Analysis 2.9. Comparison 2 N-acetylcysteine vs. placebo added to cysteine-containing PN, Outcome 9 Periventricular leukomalacia in all examined. 26
Analysis 2.10. Comparison 2 N-acetylcysteine vs. placebo added to cysteine-containing PN, Outcome 10 Intraventricular hemorrhage (any grade). 26
Analysis 2.11. Comparison 2 N-acetylcysteine vs. placebo added to cysteine-containing PN, Outcome 11 Severe intraventricular hemorrhage (grade 3-4). 27
Analysis 2.12. Comparison 2 N-acetylcysteine vs. placebo added to cysteine-containing PN, Outcome 12 Plasma level of free cyst(e)ine (micromoles/ 100 ml). 27
FEEDBACK 27
WHAT'S NEW 27
HISTORY 28
CONTRIBUTIONS OF AUTHORS 28
DECLARATIONS OF INTEREST 28
SOURCES OF SUPPORT 28
INDEX TERMS 28

[Intervention Review]

Cysteine, cystine or N-acetylcysteine supplementation in parenterally fed neonates

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ABSTRACT

Background

Cysteine is a precursor of glutathione, an antioxidant that may reduce oxidation injury. The addition of cysteine to parenteral nutrition (PN) allows for the reduction of the amount of methionine in PN, thereby limiting hepatotoxicity and acidifies the solution, thereby increasing calcium and phosphate solubility and potentially improving bone mineralization.

Objectives

To determine the effects of supplementing PN with cysteine, cystine or its precursor N-acetylcysteine on neonatal growth and short and long-term outcomes.

Search methods

The standard search method of the Cochrane Neonatal Review Group was used. MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (*The Cochrane Library*) and recent abstracts from the Society for Pediatric Research/ American Pediatric Society, Eastern Society for Pediatric Research, and Society for Parenteral and Enteral Nutrition were originally searched in 2005. In August 2009 updated searches were done of *The Cochrane Library,* MEDLINE (search via PubMed), CINAHL and EMBASE from 2006 to 2009.

Selection criteria

All randomized (RCTs) and quasi-randomized trials that examined the effects of cysteine, cystine or N-acetylcysteine supplementation of neonatal PN were reviewed.

Data collection and analysis

The standard methods of the Cochrane Collaboration and its Neonatal Review Group were used. Statistical analysis included relative risk, risk difference, and weighted mean difference (WMD).

Main results

Six trials fulfilled entry criteria. The majority of patients in these trials were preterm. Five small trials evaluated short-term cysteine supplementation of cysteine-free PN. One large multicenter RCT evaluated short-term N-acetylcysteine supplementation of cysteine-containing PN in extremely low birth weight infants (≤ 1000 grams).

Growth was not significantly affected by cysteine supplementation (1 trial) or by N-acetylcysteine supplementation (1 trial). Nitrogen retention was significantly increased by cysteine supplementation (4 trials) (WMD 31.8 mg/kg/day, 95% confidence interval +8.2, +55.4, n = 95, including 73 preterm infants).

Plasma levels of cysteine were significantly increased by cysteine supplementation but not by N-acetylcysteine supplementation. N-acetylcysteine supplementation did not significantly affect the risks of death by 36 postmenstrual weeks, bronchopulmonary dysplasia (BPD), death or BPD, retinopathy of prematurity (ROP), severe ROP, necrotizing enterocolitis requiring surgery, periventricular leukomalacia, intraventricular hemorrhage (IVH), or severe IVH.

Authors' conclusions

Available evidence from RCTs shows that routine short-term cysteine chloride supplementation of cysteine-free PN in preterm infants improves nitrogen balance. However, there is insufficient evidence to assess the risks of cysteine supplementation, especially regarding metabolic acidosis, which has been reported during the first two weeks of cysteine chloride administration. Available evidence from a large RCT trial does not support routine N-acetylcysteine supplementation of cysteine-containing PN in extremely low birth weight infants.

PLAIN LANGUAGE SUMMARY

Cysteine, cystine or N-acetylcysteine supplementation in parenterally fed neonates

Sick or preterm newborn infants may require intravenous nutrition, including intravenous administration of solutions containing amino acids. Newborn infants need cysteine (an amino acid) for growth under certain conditions. Cysteine may decrease the chance of liver disease and brittle bones. This systemic review was done to analyze whether adding cysteine (or related compounds) to intravenous nutrition affects growth and other outcomes in newborn infants. Five trials studied the effects of adding cysteine to intravenous nutrition that did not contain cysteine. Addition of cysteine significantly improved the babies' ability to build body proteins (analyzed in four studies); however, it did not improve growth (analyzed in one study); no other outcomes were available. One large randomized trial studied the effect of adding another chemical, N-acetyl-cysteine, to intravenous nutrition that already contained cysteine. This study showed no benefit and no toxicity of this intervention. We conclude that present data are insufficient to justify routine addition of cysteine to the intravenous nutrition of newborn infants that does not contain cysteine. Available evidence does not support routine addition of N-acetylcysteine to intravenous nutrition of newborn infants containing cysteine.

BACKGROUND

Description of the condition

The inability of sick term and preterm infants to feed enterally frequently leads to the use of total parenteral nutrition (TPN) in order to provide adequate calories and nutrients to promote growth. Most commercial parenteral solutions contain a mixture of both essential and non-essential amino acids. Low plasma levels of any essential amino acid indicate a relative deficiency state and this may be detrimental to nitrogen balance and growth (Rose 1955).

Description of the intervention

Several facts suggest that the addition of L-cysteine, cystine or N-acetylcysteine to TPN may be beneficial in neonates, especially very low birth weight (VLBW) infants (infants with birth weight < 1500 g) .

Several publications have suggested that L-cysteine could be a conditionally essential (i.e., essential under certain conditions) amino acid for very preterm but not for borderline preterm or full-term neonates (Uauy 1993; Brunton 2000; Heird 1998; Riedijk 2006). In contrast, one randomized trial comparing various intakes of cyst(e)ine in enterally fed very low birth weight infants did not support the hypothesis that cyst(e)ine is a conditionally essential amino acid in these infants. (Riedijk 2007; Riedijk 2008).

Cysteine is incorporated into proteins and is a precursor of taurine and glutathione. In adults, cysteine can be synthesized from ingested methionine via the trans-sulfuration pathway and hence is considered one of the non-essential amino acids (Rose 1955). In the fetus, hepatic cystathionase, the rate-limiting enzyme that converts cystathionine to cysteine, is either absent or barely detectable, resulting in decreased synthesis of cysteine from methionine and high serum concentration of cystathionine (Sturman 1970; Pascal 1972; Gaull 1972; Heinonen 1974). Preterm infants have higher plasma cystathionine levels than term infants (Viña 1995). Hepatic cystathionase activity increases with gestational age (Sturman 1970; Heinonen 1974; Zlotkin 1982) and increases rapidly after birth (Zlotkin 1982) reaching mature levels at about three months in term infants. *In vivo* studies have shown that cysteine synthesized in preterm liver may be present in apolipoprotein B but not in plasma, suggesting that endogenous cysteine is used preferentially for hepatic protein synthesis (Miller 1996). In contrast, a recent study showed that cysteine synthesized in the liver was found in plasma of VLBW infants in amounts that increased with maturation (Shew 2005). Extrahepatic cystathionase, which matures earlier than the hepatic enzyme, might account for some conversion of methionine into cysteine even in preterm infants (Uauy 1993).

How the intervention might work

Parenterally fed infants or adults who do not receive cysteine supplements in TPN have low plasma levels of cystine (Zlotkin 1981; Uauy 1993), the oxidized, disulfide form of cysteine. Regression analysis suggests that an intravenous intake of cysteine of 500 micromoles per kg per day is required in preterm infants to reach plasma cysteine levels comparable to those in full-term, breast-fed infants (Van Goudoever 1994). Snyderman found that enteral supplementation of cysteine improved growth in preterm infants at two to four months of age (Snyderman 1971). These data support the possibility that cysteine may be a conditionally essential amino acid in preterm infants; supplementation of cysteine could improve growth and nitrogen retention under certain conditions. Liver toxicity may be induced by high methionine content of commercial parenteral nutritional solutions that do not contain cysteine (Moss 1999; Brunton 2000). Because of this, some manufacturers have added cysteine to commercial TPN and reduced methionine content accordingly. Supplementation of an essential amino acid (in this case cysteine) may not result in any improvement in growth if caloric intake or intake of other essential or conditionally essential nutrients (e.g., tyrosine) is limiting (Helms 1987; Heird 1993).

Studies have suggested that preterm infants have a poorly developed antioxidant system, making various organs more susceptible to oxidation injury, thereby increasing the risk for intracranial hemorrhage, periventricular leukomalacia, retinopathy of prematurity, chronic lung disease, and necrotizing enterocolitis (Thibeault 2000). Cysteine deficiency may be an etiological factor in the limited ability of preterm babies to produce glutathione, a natural antioxidant. The first step of synthesis of glutathione involves gammma-glutamylcysteine synthetase, which mediates a peptide linkage between glutamate and cysteine. Studies have demonstrated a decrease in glutathione synthesis in erythrocytes of neonates when methionine was used as a cysteine precursor (Viña 1995). The effect was more pronounced in preterm infants less than 32 weeks of age. Supplementation of parenteral nutrition with cysteine increases endogenous synthesis of taurine and glutathione (Shew 2000a).

Taurine is present in all cells and is conjugated to biliary pigments, which are excreted into bile as soluble biliary salts. In adults, taurine can be synthesized from cysteine and methionine. However, in preterm infants, taurine is also considered a conditionally essential amino acid. Taurine needs to be included in parenteral solutions to prevent cholestasis (Howard 1992).

Adding cysteine-hydrochloride (cysteine-HCl) to TPN solutions increases calcium and phosphate solubility. Cysteine-HCl reduces the pH of TPN significantly (Laine 1991; Parikh 2005), thereby increasing calcium and phosphate solubility and allowing increased mineral intake, a limiting factor in mineral accretion in preterm infants receiving TPN. Increased mineral accretion could reduce the incidence of osteopenia of prematurity and fractures in VLBW infants. However, acidification of the TPN by cysteine-chloride in the smallest infants (especially those < 1250 g) may be associated with metabolic acidosis for the first two weeks (Uauy 1993; Laine 1991; Heird 1988). Such metabolic acidosis can be prevented by the administration of base (acetate or lactate) at a 2:1 molar (base:cysteine hydrochloride) ratio (Uauy 1993; Laine 1991).

Stability of cysteine in TPN

The poor stability of cysteine in commercial amino acid solutions has led to the development of cysteine substitutes with greater stability. Cysteine is easily oxidized to cystine, which precipitates rapidly and is virtually insoluble in TPN solutions. In solutions containing both cysteine and glucose, the cysteine content of the fluid decreases by 40% within the first 10 hours from both oxidization and formation of D-glucocysteine (Bjelton 1990). N-acetyl-cysteine, a soluble precursor, improves stability in solution, thereby allowing higher total concentrations of cysteine, cystine and its precursor in TPN. However, plasma cystine levels have been shown to be less than one third the lower limit of the reference range when cyst(e)ine intake consisted of small doses and no correlation was found between plasma cystine levels and N-acetyl-cysteine intake at these doses (Van Goudoever 1994).

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