

Early intravenous nutrition for the prevention of neonatal jaundice (Review)

Faber BM, Mills JF



**THE COCHRANE
COLLABORATION®**

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2007, Issue 4

<http://www.thecochranelibrary.com>



TABLE OF CONTENTS

ABSTRACT	1
PLAIN LANGUAGE SUMMARY	1
BACKGROUND	2
OBJECTIVES	2
CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW	2
SEARCH METHODS FOR IDENTIFICATION OF STUDIES	2
METHODS OF THE REVIEW	3
DESCRIPTION OF STUDIES	3
METHODOLOGICAL QUALITY	3
RESULTS	3
DISCUSSION	3
AUTHORS' CONCLUSIONS	3
POTENTIAL CONFLICT OF INTEREST	4
ACKNOWLEDGEMENTS	4
SOURCES OF SUPPORT	4
REFERENCES	4
TABLES	5
Characteristics of excluded studies	5
GRAPHS AND OTHER TABLES	5
INDEX TERMS	5
COVER SHEET	5

Early intravenous nutrition for the prevention of neonatal jaundice (Review)

Faber BM, Mills JF

This record should be cited as:

Faber BM, Mills JF. Early intravenous nutrition for the prevention of neonatal jaundice. *Cochrane Database of Systematic Reviews* 2003, Issue 3. Art. No.: CD003846. DOI: 10.1002/14651858.CD003846.

This version first published online: 21 July 2003 in Issue 3, 2003.

Date of most recent substantive amendment: 15 May 2003

ABSTRACT

Background

The early institution of enteral feeding in the first few days of life is known to impact on the development of unconjugated hyperbilirubinaemia. However, the effect of early intravenous nutrition on neonatal jaundice remains unknown.

Objectives

To determine the effect of early intravenous nutrition on neonatal jaundice.

Search strategy

The standard search strategy of the Cochrane Neonatal Review Group was used including searches of the Cochrane Controlled Trials Register (Cochrane Library: Issue 3, 2002), MEDLINE (1966-December 2002), and EMBASE (1974-December 2002).

Selection criteria

Randomised or quasi-randomised controlled trials evaluating the effect of early intravenous nutrition on unconjugated bilirubin.

Data collection and analysis

The search strategy identified no eligible studies, thus no data were collected.

Main results

No studies were identified.

Authors' conclusions

Decisions regarding the institution of early intravenous nutrition must continue to be based upon factors other than its effect on neonatal jaundice.

PLAIN LANGUAGE SUMMARY

Synopsis pending.

BACKGROUND

Approximately 65% of newborn infants develop clinically evident jaundice in the first week of life (Maisels 1992). In the majority of cases, the jaundice results from the increased production and decreased excretion of bilirubin which occurs in all newborns ('physiological' jaundice). In some infants however, jaundice is due to significant underlying disease such as infection, haemolysis or an inborn error of metabolism ('pathological' jaundice). If the hyperbilirubinaemia is principally unconjugated, and if it exceeds the binding capacity of albumin, the unbound fraction can cross the blood brain barrier and have a direct neurotoxic effect on the brain. This can cause a neonatal encephalopathy which may have significant neurodevelopmental sequelae.

Bilirubin metabolism is affected by caloric intake (Barrett 1971). The effect of timing of introduction of enteral feeds on neonatal jaundice is well recognised; Goodhart et al advocated early feeding of low birthweight infants as a treatment for neonatal jaundice in the early 20th century (Goodhart 1913). Subsequently, the early institution of enteral feeds was shown to decrease the severity and duration of neonatal jaundice (Wharton 1965; Wennberg 1966). This is due to a reduction in intestinal transit time with a resulting decrease in the enterohepatic circulation of bilirubin (Wennberg 1966), and may also be related to the effect of positive nitrogen balance on the hepatic conjugation of bilirubin.

In some newborn infants, enteral feeds cannot be commenced. This is most often due to concurrent illness (e.g. respiratory failure requiring ventilatory support) but may also be necessary if some gastrointestinal pathology precludes feeding (e.g. gastroschisis, oesophageal atresia). In these infants, the institution of enteral feeds may be delayed for many days and caloric support is achieved by the use of intravenous nutrition solutions. Such solutions contain dextrose, electrolytes, amino acids, fats and vitamins. The side-effects of chronic intravenous nutrition administration on the liver (cholestasis) are well known (Brown 1986); however, the short term effect on the rate of bilirubin conjugation in the first few days of life is unclear.

This systematic review examined the impact of early intravenous nutrition on the subsequent development of unconjugated hyperbilirubinaemia. Randomised controlled trials comparing intravenous nutrition which included amino acids and/or fats with routine intravenous fluids were included. The review also separately examined trials including preterm infants.

OBJECTIVES

The primary objective of this systematic review was to answer the question:

Does the introduction of intravenous nutrition compared with routine intravenous fluids to newborn infants less than 72 hours

old who are not being enterally fed decrease the severity, duration and need for treatment of neonatal jaundice?

The same question was also examined in a subset of trials enrolling preterm infants.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomised and quasi-randomised controlled trials

Types of participants

Newborn infants, less than 72 hours of age, who were not receiving enteral feeds. Preterm infants were defined as those less than 37 weeks gestational age

Types of intervention

Parenteral nutrition, defined as any combination of dextrose and electrolytes plus amino acids and/or fats, versus routine intravenous fluids, defined as any combination of dextrose and electrolytes. The fluid regimen to which an infant had been allocated was required to have been instituted prior to 72 hours of age and continued for at least 72 hours.

Types of outcome measures

Primary outcomes:

- Death at 28 days (%)
- Abnormal neurodevelopment (Bayley score less than or equal to 1 standard deviation below the mean)
- Hearing loss requiring aids (%)
- Kernicterus (%; defined and staged using the criteria of Dennery et al [Dennery 2001])
- Cost benefit (ratio)

Secondary outcomes:

- Absolute change in SBR at 24, 48, 72 hours (micromoles/L/h)
- Relative change in SBR at 24, 48, 72 hours (%/h)
- Peak SBR (micromoles/L)
- Use of phototherapy (%)
- Duration of phototherapy (h)
- Use of exchange transfusion (%)
- Length of hospital stay (d)

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

The standard search strategy of the Neonatal Review Group, as outlined in the Cochrane Library, was used. The following sources were searched for eligible reports in any language:

- Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 3, 2002)
- MEDLINE electronic search (1966-December 2002): Medical Subject Headings - jaundice, jaundice/neonatal, clinical trials, infant/newborn, parenteral nutrition
- EMBASE electronic search (1974- December 2002): Medical Subject Headings - jaundice, jaundice/neonatal, clinical trials, infant/newborn, parenteral nutrition

Reference lists from identified studies were to have been searched, as well as the reference lists of review articles, but none were identified. Accordingly, there were no primary authors to contact.

METHODS OF THE REVIEW

The standard methods of the Cochrane Neonatal Review Group were used. The methodological quality of each eligible trial was to have been assessed by both authors, with the second author blinded to trial author and institution. The following criteria were to have been used to assess trial methodology: blinding of randomisation, blinding of intervention, completeness of follow up and blinding of outcome assessment. It was planned that both authors would have independently extracted the data and compared results, resolving disagreements by consensus. Contact was to have been made with the primary author of each eligible trial to review the eligible trial list for completeness and to provide additional data if required. The standard statistical methods of the Cochrane Collaboration were to have been used. For categorical data, the relative risk (RR), risk difference (RD) and number needed to treat (NNT) were to have been calculated. For outcomes measured on a continuous scale, the weighted mean difference (WMD) was to have been calculated. 95% confidence intervals were to have been used. A fixed effects model was to have been assumed for the meta-analysis. A subgroup analysis, restricted to preterm infants, was planned.

DESCRIPTION OF STUDIES

Eight studies were identified using the described search strategy. Four of these were ineligible for inclusion in the review (Alvear 1974; Closa 1976; Ogata 1983; Yu 1979). The first, Closa et al (Closa 1976), was an uncontrolled case series. In two (Alvear 1974; Yu 1979), intravenous nutrition was compared with enteral feeds rather than with routine intravenous fluids, and in a further study (Ogata 1983) two different intravenous nutrition solutions were compared.

This left four trials which were eligible for inclusion (Black 1981; Pildes 1973; Rivera 1993; Van Lingen 1992). Two (Rivera 1993; Van Lingen 1992) were excluded as no outcomes relevant to this review were reported. The study of Black et al (Black 1981) reported relevant outcomes but was excluded because the infants were randomised after 72 hours of age. The study of Pildes et al (Pildes 1973) was excluded because some infants in both arms of the study received enteral feeds but no data were separately reported for the subgroup who did not.

METHODOLOGICAL QUALITY

Not applicable

RESULTS

No studies were included.

DISCUSSION

Bilirubin metabolism is affected by caloric intake. For infants receiving enteral feeds this may be mediated by a direct effect on nitrogen balance, as well as the indirect effect of decreased intestinal transit time on the enterohepatic circulation of bilirubin. Intravenous nutrition is commonly used in newborn infants who cannot be enterally fed, and is often commenced within the first few days of life at a time when unconjugated hyperbilirubinaemia is almost invariably present. Although the early institution of intravenous nutrition might be expected to result in lower levels of unconjugated hyperbilirubinaemia, no controlled or uncontrolled data have been published investigating this potential benefit. Future clinical trials investigating the merits of early institution of intravenous nutrition should include outcomes related to neonatal jaundice.

AUTHORS' CONCLUSIONS

Implications for practice

Many factors determine the optimum timing of institution of intravenous nutrition in newborn infants. These include the gestational age of the infant, the perceived adequacy of intrauterine nutrition, and the presence of co-existing morbidities such as sepsis, thrombocytopenia and respiratory disease. There is no evidence from clinical trials regarding the effect of early intravenous feeding on the prevention of neonatal jaundice. Decisions regarding the institution of early intravenous nutrition must therefore continue to be based upon these other factors.

Implications for research

Future randomised trials investigating the early institution of intravenous nutrition should include outcomes related to neonatal jaundice.

POTENTIAL CONFLICT OF INTEREST

None

ACKNOWLEDGEMENTS

Nil

SOURCES OF SUPPORT

External sources of support

- No sources of support supplied

Internal sources of support

- Royal Women's Hospital, Melbourne AUSTRALIA
- Murdoch Childrens Research Institute AUSTRALIA
- Royal Children's Hospital, Melbourne AUSTRALIA

REFERENCES

References to studies excluded from this review

Alvear 1974

Alvear DT, Morris N, Pilling GP, Cresson SL. Total parenteral hyperalimentation versus conventional techniques. *Pa Med* 1974;**77**: 34–37.

Black 1981

Black DD, Suttle EA, Whittington PF, Whittington GL, Korones SD. The effect of short-term total parenteral nutrition on hepatic function in the human neonate: a prospective randomized study demonstrating alteration of hepatic canalicular function. *J Pediatr* 1981;**99**: 445–449.

Closa 1976

Closa SJ, Meredith C, Rio ME, Serramalera ME. Parenteral nutrition in infants: biochemical findings. *Acta Chir Scand Suppl* 1976;**466**: 110–111.

Ogata 1983

Ogata ES, Boehm JJ, Deddish RB, Wiringa KS, Yanagi RB, Bussey ME. Clinical trial of a 6.5% amino acid infusion in appropriate-for-gestational-age premature neonates. *Acta Chir Scand Suppl* 1983; **517**:39–48.

Pildes 1973

Pildes RS, Ramamurthy RS, Cordero GV, Wong PW. Intravenous supplementation of L-amino acids and dextrose in low-birth-weight infants. *J Pediatr* 1973;**82**:945–950.

Rivera 1993

Rivera A Jr, Bell EF, Bier DM. Effect of intravenous amino acids on protein metabolism of preterm infants during the first three days of life. *Pediatr Res* 1993;**33**:106–111.

Van Lingen 1992

Van Lingen RA, Van Goudoever JB, Luijendijk IH, Wattimena JL, Sauer PJ. Effects of early amino acid administration during total parenteral nutrition on protein metabolism in pre-term infants. *Clin Sci* 1992;**82**:199–203.

Yu 1979

Yu VY, James B, Hendry P, MacMahon RA. Total parenteral nutrition in very low birthweight infants: a controlled trial. *Arch Dis Child* 1979;**54**:653–661.

Additional references

Barrett 1971

Barrett PVD. Hyperbilirubinaemia of fasting. *JAMA* 1971;**217**: 1349–1353.

Brown 1986

Brown MR, Thunberg BJ, Golub L, Maniscalco WM, Shapiro DL. Decreased cholestasis with oral instead of intravenous protein in the very low birth weight infant. *Pediatr Res* 1986;**20**:236A.

Dennery 2001

Dennery PA, Seidman DS, Stevenson DK. Neonatal hyperbilirubinaemia. *N Engl J Med* 2001;**344**:581–590.

Goodhart 1913

Goodhart JF. In: StillG F editor(s). *The Diseases of Children*. 10th Edition. London: Churchill, 1913:36.

Maisels 1992

Maisels MJ. Neonatal jaundice. In: SinclairJC, BrackenMB editor(s). *Effective Care of the Newborn Infant*. New York: Oxford University Press, 1992:507–561.

Wennberg 1966

Wennberg RP, Schwartz R, Sweet AY. Early versus delayed feeding of low birth weight infants: Effects on physiological jaundice. *J Pediatr* 1966;**68**:860–866.

Wharton 1965

Wharton BA, Bower BD. Immediate or later feeding for premature babies? A controlled trial. *Lancet* 1965;**2**:969–972.

T A B L E S**Characteristics of excluded studies**

Study	Reason for exclusion
Alvear 1974	Infants randomised to intravenous nutrition or enteral feeding (rather than routine intravenous fluids).
Black 1981	Infants randomised after 72 hours of age.
Closa 1976	Uncontrolled case series
Ogata 1983	Infants randomised to two different TPN solutions.
Pildes 1973	Some infants were receiving enteral feeds. No separate data reported for exclusive intravenous nutrition group.
Rivera 1993	Eligible trial but no outcomes relevant to this review reported.
Van Lingen 1992	Eligible trial but no outcomes relevant to this review reported.
Yu 1979	Infants randomised to intravenous nutrition or enteral feeding (rather than routine intravenous fluids).

G R A P H S A N D O T H E R T A B L E S

This review has no analyses.

I N D E X T E R M S**Medical Subject Headings (MeSH)**

Infant, Newborn; Jaundice, Neonatal [*prevention & control]; Parenteral Nutrition [*methods]

MeSH check words

Humans

C O V E R S H E E T**Title**

Early intravenous nutrition for the prevention of neonatal jaundice

Early intravenous nutrition for the prevention of neonatal jaundice (Review)
Copyright © 2007 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd

Authors	Faber BM, Mills JF
Contribution of author(s)	Brenda Faber was the primary author of the review. She specified the objectives of the review and decided on the types of studies, participants, interventions and outcomes that would be included. She subsequently executed the search strategy. John Mills acted as co-reviewer. He collaborated with Ms Faber in writing the protocol and review.
Issue protocol first published	2002/4
Review first published	2003/3
Date of most recent amendment	27 May 2003
Date of most recent SUBSTANTIVE amendment	15 May 2003
What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
Contact address	Brenda Faber Research Nurse Intensive and Special Care Nurseries Royal Women's Hospital 132 Grattan Street Carlton Vic 3053 AUSTRALIA E-mail: brendamf@unimelb.edu.au Tel: 61+3-9344 2089
DOI	10.1002/14651858.CD003846
Cochrane Library number	CD003846
Editorial group	Cochrane Neonatal Group
Editorial group code	HM-NEONATAL