Management of neonatal hyperbilirubinemia

CRD summary
This review investigated the efficacy of treatments for neonatal hyperbilirubinaemia, namely phototherapy. The authors concluded that phototherapy combined with cessation of breast-feeding was the most effective treatment for healthy infants with jaundice. These conclusions should be interpreted with caution as they are based on a few studies in which the definition of hyperbilirubinaemia and the time of bilirubin measurement varied.

Authors' objectives
To establish the efficacy of treatments (namely phototherapy) for neonatal hyperbilirubinaemia in the reduction of peak bilirubin levels, reduction in duration of hyperbilirubinaemia, and improvement of neurodevelopmental outcomes (question 3 in the review). Question 3 will be abstracted below.

Other issues addressed in the review, but not abstracted here, were: the association between the level and duration of hyperbilirubinaemia and neurodevelopmental outcomes (question 1), and other factors that may act as effect modifiers (question 2); the accuracy of diagnostic strategies (biological indicators) for identifying hyperbilirubinaemia (question 4); and the accuracy of transcutaneous bilirubin measurements (question 5).

Searching
MEDLINE (from 1966 to September 2001) and PREMEDLINE were searched using the MeSH terms and textwords listed in the review. The search was restricted to English language papers of studies conducted in humans. Field experts were contacted and the reference lists of relevant reviews were checked.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and non-randomised controlled trials, with a minimum of 10 patients per treatment arm, were eligible for inclusion.

Specific interventions included in the review
All treatments for neonatal hyperbilirubinaemia were eligible for inclusion. The included studies all investigated the effect of phototherapy, some of which also looked at the effects of exchange transfusion.

Participants included in the review
Healthy infants of at least 34 weeks' gestation, or with a birthweight of at least 2,500 g, were eligible for inclusion.

Outcomes assessed in the review
Serum bilirubin level of at least 20 mg/dL, frequency of exchange transfusion for bilirubin level of at least 20 mg/dL, and neurodevelopmental outcomes were eligible for inclusion.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Study quality was assessed using the authors' own scale, which comprised three categories.

Category A: RCT with complete methods and results (including inclusion and exclusion criteria) described and with proper randomisation and/or blinding, and correct analyses performed.
Category B: non-randomised controlled trial or other prospective design (cohort or case-control study) with proper selection of the control group. Some deficiencies, but unlikely to cause major bias.

Category C: retrospective or no control group with significant design or reporting errors, large amount of missing information, or significant potential bias.

The authors did not state how the papers were assessed for quality, or how many reviewers performed the quality assessment.

**Data extraction**

Data extraction forms were provided. These collected information on the study characteristics, treatments, study design, demographic characteristics, outcomes and study quality. There was no indication of how many reviewers extracted the data, or whether a second reviewer checked the abstraction.

The number-needed-to-treat (NNT) was calculated to quantify treatment efficacy for neonatal hyperbilirubinaemia in each of the studies.

**Methods of synthesis**

How were the studies combined?
The findings were presented in a narrative summary, with the studies grouped by outcome.

How were differences between studies investigated?
The differences between the studies were not formally investigated.

**Results of the review**

Twenty studies (n=1,941) were identified: 3 RCTs (n=444, range: 43 to 276), 2 non-randomised controlled trials (n=633, range: 141 to 492), 6 prospective cohorts (n=497, range: 20 to 220), 1 retrospective cohort (n=112) and 8 within-group comparison studies (n=255, range: 6 to 90).

Three studies investigated the efficacy of phototherapy in preventing the total serum bilirubin (TSB) levels from rising above 20 mg/dL. One RCT (n=276) found that infants with hyperbilirubinaemia, secondary to non-haemolytic causes, receiving phototherapy had a 14.3% risk reduction of blood exchange transfusion than infants not receiving any treatment. The NNT to prevent the need for exchange transfusion, or a TSB above 20 mg/dL, was 7 (95% confidence interval, CI: 6, 8). A second RCT (n=125) found that phototherapy in infants with continued breast-feeding had an absolute risk reduction rate of 10.1%; the NNT to prevent a TSB level of above 20 mg/dL was 10 (95% CI: 9, 12). Phototherapy with discontinued breast-feeding was found to be more effective, with a 16.6% absolute risk reduction rate and an NNT of 6 (95% CI: 5, 7). The non-randomised controlled trial (n=492) found phototherapy to have an 11.2% risk reduction of exchange transfusion; the NNT for preventing the TSB from rising above 20 mg/dL was 9 (95% CI: 8, 10).

Eight within-group comparison studies examined Brain Stem Auditory Evoked Responses (BAER) after treatment for neonatal hyperbilirubinaemia. Three of these studies investigated phototherapy and/or exchange transfusion. Two of these studies found all the infants to have normal BAER after treatment, while the third found 10% of the infants to have an abnormality. Four studies examined the effect of exchange transfusion on BAER. One of these studies found all the infants to have a normal BAER after treatment, while another found 83% of the infants to have a normal BAER after treatment; the other 2 studies did not measure the BAER. Another study identified did not state which treatment it investigated.

Nine studies examined the effect of treatments for hyperbilirubinaemia on neurodevelopmental outcomes, of which seven focused on phototherapy. In these studies, no changes in neurodevelopmental outcomes, including orientation, motor responses and IQ, were found with phototherapy.

Three studies (one of which also reported neurodevelopmental outcomes) evaluated the effect of phototherapy on visual
outcomes. All 3 studies found no change in visual function after phototherapy.

**Authors' conclusions**
The most effective treatment for healthy infants with jaundice was phototherapy in addition to cessation of breast-feeding. The authors stated that abnormal BAER improved with treatments for neonatal hyperbilirubinaemia in healthy infants with jaundice and those with haemolytic disease. They also concluded that phototherapy does not have any long-term adverse effects on the neurodevelopment of healthy or haemolytic jaundiced infants.

**CRD commentary**
The inclusion criteria were clearly defined, although broad. It was stated that the study design was restricted to randomised and non-randomised controlled trials, but studies of less rigorous design were included. The search for relevant literature was limited to MEDLINE and PreMEDLINE, and the authors made no attempt to identify any unpublished literature. It is therefore possible that the search strategy has not identified all potentially eligible studies, which may lead to retrieval and publication bias. The authors' quality assessment of the included studies was not comprehensive and did not fully consider differences in quality between studies with the same design. The included studies varied in their focus, quality and outcome measures. As the authors noted, their conclusions were drawn from a few studies in which the definition of hyperbilirubinaemia and the time of bilirubin measurement might have varied. Thus, the conclusions should be interpreted with caution.

**Implications of the review for practice and research**
The authors did not state any implications for practice or further research.

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**Other publications of related interest**

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.