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[Intervention Review]

Fluid supplementation for neonatal unconjugated hyperbilirubinaemia

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ABSTRACT

Background

Neonatal hyperbilirubinaemia is a common problem which carries a risk of neurotoxicity. Certain infants who have hyperbilirubinaemia develop bilirubin encephalopathy and kernicterus which may lead to long-term disability. Phototherapy is currently the mainstay of treatment for neonatal hyperbilirubinaemia. Among the adjunctive measures to compliment the effects of phototherapy, fluid supplementation has been proposed to reduce serum bilirubin levels. The mechanism of action proposed includes direct dilutional effects of intravenous (IV) fluids, or enhancement of peristalsis to reduce enterohepatic circulation by oral fluid supplementation.

Objectives

To assess the risks and benefits of fluid supplementation compared to standard fluid management in term and preterm newborn infants with unconjugated hyperbilirubinaemia who require phototherapy.

Search methods

We used the standard search strategy of Cochrane Neonatal to search the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 5), MEDLINE via PubMed (1966 to 7 June 2017), Embase (1980 to 7 June 2017), and CINAHL (1982 to 7 June 2017). We also searched clinical trials databases, conference proceedings, and the reference lists of retrieved articles for randomised controlled trials and quasi-randomised trials**.**

Selection criteria

We included randomised controlled trials that compared fluid supplementation against no fluid supplementation, or one form of fluid supplementation against another.

Data collection and analysis

We extracted data using the standard methods of the Cochrane Neonatal Review Group using the Covidence platform. Two review authors independently assessed the eligibility and risk of bias of the retrieved records. We expressed our results using mean difference (MD), risk difference (RD), and risk ratio (RR) with 95% confidence intervals (CIs).

Main results

Out of 1449 articles screened, seven studies were included. Three articles were awaiting classification, among them, two completed trials identified from the trial registry appeared to be unpublished so far.

There were two major comparisons: IV fluid supplementation versus no fluid supplementation (six studies) and IV fluid supplementation versus oral fluid supplementation (one study). A total of 494 term, healthy newborn infants with unconjugated hyperbilirubinaemia were evaluated. All studies were at high risk of bias for blinding of care personnel, five studies had unclear risk of bias for blinding of outcome assessors, and most studies had unclear risk of bias in allocation concealment. There was low- to moderate-quality evidence for all major outcomes.

In the comparison between IV fluid supplementation and no supplementation, no infant in either group developed bilirubin encephalopathy in the one study that reported this outcome. Serum bilirubin was lower at four hours postintervention for infants who received IV fluid supplementation (MD -34.00 μmol/L (-1.99 mg/dL), 95% CI -52.29 (3.06) to -15.71 (0.92); participants = 67, study = 1) (low quality of evidence, downgraded one level for indirectness and one level for suspected publication bias). Beyond eight hours postintervention, serum bilirubin was similar between the two groups. Duration of phototherapy was significantly shorter for fluid-supplemented infants, but the estimate was affected by heterogeneity which was not clearly explained (MD -10.70 hours, 95% CI -15.55 to -5.85; participants = 218; studies = 3; I^2 = 67%). Fluid-supplemented infants were less likely to require exchange transfusion (RR 0.39, 95% CI 0.21 to 0.71; RD -0.01, 95% CI -0.04 to 0.02; participants = 462; studies = 6; I^2 = 72%) (low quality of evidence, downgraded one level due to inconsistency, and another level due to suspected publication bias), and the estimate was similarly affected by unexplained heterogeneity. The frequencies of breastfeeding were similar between the fluid-supplemented and non-supplemented infants in days one to three based on one study (estimate on day three: MD 0.90 feeds, 95% CI -0.40 to 2.20; participants = 60) (moderate quality of evidence, downgraded one level for imprecision).

One study contributed to all outcome data in the comparison of IV versus oral fluid supplementation. In this comparison, no infant in either group developed abnormal neurological signs. Serum bilirubin, as well as the rate of change of serum bilirubin, were similar between the two groups at four hours after phototherapy (serum bilirubin: MD 11.00 μmol/L (0.64 mg/dL), 95% CI -21.58 (-1.26) to 43.58 (2.55); rate of change of serum bilirubin: MD 0.80 μmol/L/hour (0.05 mg/dL/hour), 95% CI -2.55 (-0.15) to 4.15 (0.24); participants = 54 in both outcomes) (moderate quality of evidence for both outcomes, downgraded one level for indirectness). The number of infants who required exchange transfusion was similar between the two groups (RR 1.60, 95% CI 0.60 to 4.27; RD 0.11, 95% CI -0.12 to 0.34; participants = 54). No infant in either group developed adverse effects including vomiting or abdominal distension.

Authors' conclusions

There is no evidence that IV fluid supplementation affects important clinical outcomes such as bilirubin encephalopathy, kernicterus, or cerebral palsy in healthy, term newborn infants with unconjugated hyperbilirubinaemia requiring phototherapy. In this review, no infant developed these bilirubin-associated clinical complications. Low- to moderate-quality evidence shows that there are differences in total serum bilirubin levels between fluid-supplemented and control groups at some time points but not at others, the clinical significance of which is uncertain. There is no evidence of a difference between the effectiveness of IV and oral fluid supplementations in reducing serum bilirubin. Similarly, no infant developed adverse events or complications from fluid supplementation such as vomiting or abdominal distension. This suggests a need for future research to focus on different population groups with possibly higher baseline risks of bilirubin-related neurological complications, such as preterm or low birthweight infants, infants with haemolytic hyperbilirubinaemia, as well as infants with dehydration for comparison of different fluid supplementation regimen.

PLAIN LANGUAGE SUMMARY

Giving additional fluid to newborn infants having phototherapy for serious jaundice

Review question: does giving additional fluid improve outcomes in newborn infants with jaundice who require phototherapy?

Background: jaundice in newborn infants is common, because the infants' livers are unable to fully process bilirubin, the breakdown product of red blood cells. Some infants develop serious jaundice, and though uncommon, a small number suffer major complications as excessive bilirubin crosses from the blood to the brain. The complications include acute (short-term or sudden onset) brain injuries and long-term disability in the form of cerebral palsy (which affects movement and co-ordination). The extent of jaundice is commonly assessed by looking at the infants' skin and eyes, and confirmed by checking the blood bilirubin level. Phototherapy (light treatment)

is the main treatment, and if bilirubin remains very high after phototherapy, exchange transfusion (transfusing with new blood while removing blood containing high levels of bilirubin) is recommended. Several other treatments have also been evaluated. Among them, giving infants additional intravenous (into a vein) fluid to dilute the blood and increasing feeding to enhance bilirubin excretion in bowel movements have been practised. We examined whether fluid supplementation confers any additional benefit on top of phototherapy for infants with serious jaundice.

Search date: we searched medical databases in February 2016.

Study characteristics: we included seven studies (total participants = 494). All studies were on full-term, healthy infants who were breastfeeding fully or partially. There were two main comparisons: fluid supplementation via intravenous route versus no fluid supplementation and fluid supplementation via intravenous route versus oral route (by increasing feeding by mouth). Most studies did not provide enough information on certain key aspects of the methods employed. Notably, in all studies, care personnel could not be masked from knowing whether or not the infants received additional fluid, and if so through which route, and this might have affected the interpretation of results, especially those that required a person to make a judgement.

Study funding sources: none of the included studies reported funding.

Key results: no infant in either the fluid supplementation or no fluid supplementation group developed clinical complications related to excessive bilirubin. Serum bilirubin was slightly lower at four and eight hours after treatment in fluid-supplemented infants. Beyond eight hours, bilirubin levels were very similar whether or not additional fluid was given. Infants who received additional fluid appeared to have shorter duration of phototherapy (on average 10.70 hours shorter, participants = 218, studies = three) and lower risk of requiring exchange transfusion (on average 1% lower, participants = 462, studies = six), but in both analyses, inconsistent results among the included studies have weakened our confidence in the overall estimates. There were no differences in breastfeeding frequencies in the first three days between infants who received additional fluid and infants who did not.

In another comparison, one study showed that there were no clear differences between infants who received intravenous and oral fluid supplementation in all measurements (called outcomes), including blood bilirubin and the rate of change of bilirubin levels after four hours of study, as well as the number of infants who required exchange transfusion.

Quality of evidence: there was no evidence on the major clinical outcomes of bilirubin-associated brain problems, as no infants in either group developed these problems. There was low- to moderate-quality evidence for all major outcomes. Three main factors affected the quality of evidence: first, the use of bilirubin, a laboratory measurement, as the main outcome, rather than direct clinical outcomes that matter to patients; second, inconsistent study results; and third, unpublished studies that might change the review findings for the relevant outcomes.

Conclusions: there is no evidence that intravenous fluid supplementation affected major clinical outcomes such as acute- or long-term brain problems associated with excessive bilirubin in healthy, full-term newborn infants, mainly because the baseline risk of developing such problems was very low in this group of infants. Intravenous fluid supplementation may reduce serum bilirubin at certain time points but it is unclear whether this translates into important clinical benefits. Future research should focus on higher-risk populations such as preterm infants or infants with haemolysis (increased red blood cell breakdown which causes a rapid rise in bilirubin).