Fluid restriction and prophylactic indomethacin versus prophylactic indomethacin alone for prevention of morbidity and mortality in extremely low birth weight infants (Review)

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TABLE OF CONTENTS

[Intervention Review]

Fluid restriction and prophylactic indomethacin versus prophylactic indomethacin alone for prevention of morbidity and mortality in extremely low birth weight infants

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ABSTRACT

Background

Although survival of extremely low birth weight (ELBW) infants has dramatically improved over the last decades, the rate of bronchopulmonary dysplasia (BPD) has not changed. The use of indomethacin prophylaxis in ELBW infants results in improved short-term outcomes with no effect on long-term outcomes. The addition of fluid restriction to the indomethacin prophylaxis policy could result in a reduction of BPD and improve long-term survival without neurosensory impairment at eighteen months corrected age.

Objectives

To determine the effect of a policy of fluid restriction compared with a policy of no fluid restriction on morbidity and mortality in ELBW infants receiving indomethacin prophylaxis.

Search strategy

We used the standard search strategy for the Cochrane Neonatal Review Group (CNRG). This included searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 1), MEDLINE (1966 to December 2010), and EMBASE (1980 to December 2010). Additional searches included conference proceedings, references in articles and unpublished data.

Selection criteria

We planned to include all randomized or quasi-randomized trials that compared fluid restriction and indomethacin prophylaxis versus indomethacin prophylaxis alone in ELBW infants.

Data collection and analysis

If we had identified any eligible studies, we would have assessed the methodological quality of the trials using the standard methods of the CNRG. We planned to use Review Manager 5 software for statistical analysis.

Main results

We did not identify any eligible trials.

Authors' conclusions

We found no randomized controlled trials to investigate the possible interaction between fluid restriction and indomethacin prophylaxis versus indomethacin prophylaxis alone in ELBW infants. A well-designed randomized trial is needed to address this question.

PLAIN LANGUAGE SUMMARY

Fluid restriction and prophylactic indomethacin versus prophylactic indomethacin alone for prevention of morbidity and mortality in extremely low birth weight infants

Respiratory and long-term neurosensory outcomes are common morbidities among extremely low birth weight (ELBW),(birth weight less than 1000 g) survivors. Patent ductus arteriosus (PDA), a connection between vessels of the heart, is one of the known causes of respiratory morbidity. Indomethacin (a drug given early to close PDA) prophylaxis studies fail to show an improvement in the incidence of respiratory and long-term outcomes, although there is a 50% reduction in the incidence of PDA. The addition of fluid restriction to indomethacin therapy might prove helpful. However, our review found no studies to answer this question.

BACKGROUND

Description of the condition

Extremely low birth weight (ELBW) infants have a high incidence of significant morbidities and mortality. Bronchopulmonary dysplasia (BPD) is a common morbidity among ELBW survivors (Lemons 2001). The pathogenesis of BPD is multifactorial (Bancalari 2003). Excessive fluid intake in these high-risk neonates during the early postnatal period has been suggested as a risk factor for the development of BPD (Van Marter 1990; Costarino 1992; Hartnoll 2000). High fluid intake with increased extracellular fluid (ECF) is associated with a higher incidence of symptomatic patent ductus arteriosus (PDA) (Bell 1980), which is associated with an increased risk of BPD (Brown 1979). The retention of ECF and the presence of PDA with left-to-right shunt may lead to a higher fluid content in the pulmonary interstitial tissue causing decreased lung compliance and increase the need for greater respiratory support in the form of oxygen administration and mechanical ventilation. These may result further in lung inflammation, lung injury and BPD (Oh 2005).

Body water content is very high in the ELBW infant, with a large proportion of the water in the extracellular fluid compartment (Friis-Hansen 1957; Friis-Hansen 1961). During the first week of life, there is a physiologic contraction of the ECF with negative fluid balance (Stonestreet 1983; Bauer 1989). Negative fluid balance allows for the physiologic contraction of ECF, which is associated with weight loss during the early neonatal period. This is achieved by fluid intake that is less than the amount of water excreted through the kidney and via insensible water loss (Bidiwala 1988; Bauer 1989).

Description of the intervention

In the published systematic review by Bell and colleagues (Bell 2001), fluid restriction was shown to significantly reduce the risks of PDA, necrotizing enterocolitis (NEC) and death along with a trend towards decreasing BPD that did not reach statistical significance. No significant increase in adverse effects was noted (Bell 2001). Caution should be used in extrapolating these results to extremely premature infants. Most of the included studies in this systematic review were old, enrolled a small number of infants, and included very few ELBW infants.

How the intervention might work

The efficacy of prophylactic indomethacin for the prevention of important intermediate and long-term outcomes has been tested in more than 19 randomized controlled trials. Although included studies did not report the fluid policy in their methodology, their systematic review Fowlie et al found that in ELBW infants, indomethacin prophylaxis reduces the risk of significant PDA by 56% (typical risk ratio (RR) 0.44; 95% confidence interval (CI) 0.38 to 0.50), surgical ligation of the PDA by 49% (typical RR 0.51; 95% CI 0.37 to 0.71), serious intraventricular hemorrhage (IVH) by 34% (typical RR 0.66; 95% CI 0.53 to 0.82) (Fowlie 2010) and serious pulmonary hemorrhage during the first week of life (Alfaleh 2008). However, these positive effects did not translate to a reduction of BPD or improve long-term survival without neurosensory impairment at 18 months corrected age (Fowlie 2010). These results have led to a controversy among neonatal practitioners that has resulted in a decrease in the use of indomethacin pro-

phylaxis in ELBW infants after the publication of the large Trial of Indomethacin Prophylaxis in Preterm infants (TIPP) in 2001 (Schmidt 2001; Clyman 2007).

In a secondary analysis of the TIPP trial data (Schmidt 2006), it was noted that infants treated with indomethacin had a lower urine output and a slightly higher oxygen requirement during the first week of life. This may indicate that indomethacin-treated infants might have been disadvantaged with fluid overload secondary to an anticipated treatment side-effect (decreased glomerular filtration rate). This disadvantage could have resulted in increased rates of BPD, which might mask a beneficial effect of indomethacin therapy on long-term neurosensory outcomes. Strict fluid management protocols or prophylactic fluid restriction in indomethacin-treated infants could ameliorate the consequences of this anticipated side-effect.

Why it is important to do this review

This review examines the role of fluid restriction for the prevention of morbidity and mortality in ELBW infants who received prophylactic indomethacin compared with no fluid restriction.

OBJECTIVES

To determine the effect of a policy of fluid restriction compared with a policy of no fluid restriction on morbidity and mortality in ELBW infants receiving indomethacin prophylaxis.

We planned to carry out a subgroup analysis to investigate the effect of prophylactic indomethacin and fluid restriction in high-risk infants with birth weight < 750 g.

METHODS

Criteria for considering studies for this review

Types of studies

We planned to include all randomized or quasi-randomized trials that compared indomethacin prophylaxis (starting within the first 24 hours of life) and fluid restriction (to achieve at least 10% weight loss in the first week of life) versus indomethacin prophylaxis alone in ELBW infants. We planned to exclude cross-over trials.

Types of participants

ELBW < 1000 g at birth who received prophylactic indomethacin in the first 24 hours of life.

Types of interventions

Fluid restriction (to achieve at least 10% weight loss in the first week of life) plus indomethacin prophylaxis (starting within the first 24 hours for three doses) versus indomethacin prophylaxis alone.

We planned to accept all strategies for fluid restriction and all indomethacin-dosing regimens and rates of infusion.

Types of outcome measures

Primary outcomes

Bronchopulmonary dysplasia defined as oxygen requirement at 36 weeks postmenstrual age (Shennan 1988).

Secondary outcomes

1. Death before discharge.
2. Neurosensory impairment defined as rates of cerebral palsy, cognitive delay, deafness, blindness at 18 to 24 months corrected age as per Baley's score (Bayley 1993).
3. The composite of death or neurosensory impairment at 18 to 24 months corrected age.
4. Intraventricular hemorrhage as per Papile criteria (Papile 1978) by cranial ultrasound: (a) any IVH; (b) severe IVH (grades III and IV).
5. Symptomatic PDA diagnosed by echocardiogram.
6. Stages II and III NEC as defined by Bell's criteria (Bell 1978; Walsh 1986).
7. Serious pulmonary hemorrhage defined as endotracheal bleeding requiring increased ventilatory or oxygen support and transfusion of blood products, or both (Alfaleh 2008).
8. Retinopathy of prematurity (ROP) defined by ICORP classification (ICROP 1984; ICROP 2005): (a) any stage; (b) severe ROP (stage 3 or more).
9. Duration of hospital stay (days).
10. Late bacterial sepsis defined as positive bacterial blood or cerebrospinal fluid cultures taken beyond five days of age.
11. Periventricular leukomalacia (PVL).
12. Serum creatinine level.
13. Urine output.

Search methods for identification of studies

We used the standard search strategy of the Cochrane Neonatal Review Group (CNRG). We searched for randomized and quasi-randomized controlled trials that compared indomethacin prophylaxis and fluid restriction with indomethacin prophylaxis alone in ELBW infants. We searched the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library* 2010, Issue 1); MEDLINE (1966 to December 2010) using the following

subject headings (MeSH) and text word terms: patent ductus arteriosus or PDA, indomethacin, and publication type 'controlled trial', limited to infants; and EMBASE (1980 to December 2010). We did not apply any language restrictions. Two review authors independently performed the electronic database search. We also performed a manual search of the abstract books published by the Society of Pediatric Research (SPR) and the European Society of Pediatric Research (ESPR) for the period 1995 to 2010.

We planned to seek additional references from the bibliography of any articles retrieved that met the inclusion criteria. We contacted subject experts and searched trials registration sites (clinicaltrials.gov) to identify unpublished and ongoing studies.

Data collection and analysis

Selection of studies

Both review authors planned to screen independently all potential articles to check eligibility for inclusion in the review. Unpublished data and abstracts were eligible for inclusion provided we could obtain adequate information regarding primary and/or secondary outcomes. We planned to resolve discrepancies by discussion and consensus.

Data extraction and management

Both review authors planned to independently extract data from included studies. We planned to resolve discrepancies by discussion and consensus. Where data were incomplete, we planned to contact the primary investigator for further information and clarifications.

Assessment of risk of bias in included studies

We planned to use the standard methods of the CNRG to assess the methodological quality (validity criteria) of the trials. For each trial, we planned to seek information regarding the method of randomization, blinding and reporting of all outcomes of all the infants enrolled in the trial. We planned to assess each criteria as 'yes', 'no', 'unclear'.

Measures of treatment effect

For dichotomous outcomes, we planned to calculate the RR and its associated CI. For continuous outcomes, we planned to express treatment effect as mean difference (MD) and its calculated standard deviation (SD).

Assessment of heterogeneity

Heterogeneity was defined as a significant test of heterogeneity ($P < 0.1$) and differences in the treatment effects across studies. We planned to apply tests for between-study heterogeneity (including the I^2 test).

Data synthesis

If appropriate, we planned to perform a meta-analysis of pooled data using a fixed-effect model. We planned to use Review Manager 5 software for statistical analysis.

Subgroup analysis and investigation of heterogeneity

If we had identified relevant studies for inclusion, we planned to perform subgroup analyses to investigate the effect of prophylactic indomethacin and fluid restriction in high-risk infants with birth weight < 750 g. We hypothesized that heterogeneity, if present, might be due to differences in the dose of indomethacin, rate of infusion used, degree of fluid restriction, population under study (< 1000 g versus < 750 g infants) and study quality.

Sensitivity analysis

We planned to conduct a sensitivity analysis to assess the effect of the methodological quality of the trials on the results of the meta-analysis.

RESULTS

Description of studies

We did not find any studies that fulfilled the eligibility criteria.

Risk of bias in included studies

Not applicable as we did not find any studies that fulfilled the eligibility criteria.

Effects of interventions

Not applicable as we did not find any studies that fulfilled the eligibility criteria.

DISCUSSION

We did not find any randomized controlled trials to investigate the possible interaction between fluid restriction and indomethacin prophylaxis versus indomethacin prophylaxis alone in ELBW infants.

The indomethacin story is indeed a puzzling one to all neonatal practitioners. Although indomethacin prophylaxis has resulted in an excellent reduction of important intermediate outcomes, indomethacin prophylaxis has not demonstrated an effect on long-term neurosensory outcomes. The TIPP trial is by far the largest trial to investigate the efficacy of prophylactic indomethacin in preterm infants (Schmidt 2001). In the published meta-analysis by Fowlie et al (Fowlie 2010), the data of the TIPP trial weighed more than 50% in intermediate outcomes and 80% in long-term outcomes. A few possible methodologic and indomethacin-related factors could possibly explain this:

1. Readers of any research should always think of power when faced with a negative study. The TIPP trial report showed that a post-hoc power calculation was done and reveals that the study would have had a power of 90% to detect a 20% difference in the primary composite outcome (i.e. death or survival without neurosensory impairment). While there are no current standards of minimal clinical difference (MCD) determination by neonatal researchers, the choice of 20% in the TIPP trial for such an important outcome that affects a large number of ELBW infants is quite generous. Utilizing a smaller MCD (i.e. 5% to10%) could translate in positive long-term outcomes, but it will require double or triple the number of infants enrolled in the TIPP trial.

2. The use of a composite outcome in order to evaluate related clinical outcomes or increase the precision of a trial is common in medical literature (Freemantle 2003). Unfortunately, the use of composite endpoints makes the interpretation of the results of randomized trials for clinical decision challenging. Investigators and their sponsors may claim treatment effects over a broad range of outcomes, whereas the effect may in fact be limited to one component. Occasionally, composite endpoints prove useful and informative for clinical decision making. Often, they do not. Researchers frequently generalize the results of the overall composite to its individual components. The validity of the composite endpoint is dependent on similarity in patient importance, treatment effect and number of events across the components. Experts in research methodology are strongly advised to abandon the use of composite endpoints when large variations exist between the composite endpoint components (Montori 2005). The composite endpoint of the TIPP trial included five components, some of which are very rare e.g. blindness, which affects only 1% and other more common outcomes e.g. cognitive delay, which affects up to 25% of enrolled ELBW infants.

3. Indomethacin prophylaxis reduces urine output (number needed to treat to harm (NNTH) one in seven). In an ancillary analysis of TIPP trial data (Schmidt 2006), it was noted that infants treated with indomethacin had a lower urine output and a slightly higher oxygen requirement during the first week of life. This might indicate that indomethacin-treated infants might have been disadvantaged with fluid overload secondary to an anticipated treatment side-effect. This disadvantage could have resulted in increased rates of BPD which might mask a beneficial effect of indomethacin therapy on long-term neurosensory outcomes. A stringent fluid management protocol or prophylactic fluid restriction in indomethacin-treated infants could ameliorate the consequences of this anticipated side-effect.

4. While it is a common practice in neonatal literature to assess neurosensory impairment at 18 to 24 months corrected age, the positive predictive value of such measurement is poor and a longer follow-up period is advised (Hack 2005).

In the era of evidence-based medicine, neonatal practitioners should always evaluate therapies directed to preterm infants within three main domains; clinical experience, research evidence and patient preferences. In neonatal medicine history, indomethacin prophylaxis is one of the most effective therapies in the reduction of important intermediate neonatal outcomes without proven long-term benefits or harms. Patients' decision aids have been increasingly used in various fields of medicine over the last ten years. Prior to withholding prophylactic indomethacin, clinicians need to explain (utilizing structured instruments) the proven short-term benefits of this therapy along with the doubts of its future effect to parents of ELBW infants. Randomized clinical trials are needed to investigate the targeted approach where prophylactic indomethacin is given to a selected subgroup at the highest risk and the possible interaction between fluid restriction to prophylactic indomethacin.

AUTHORS' CONCLUSIONS

Implications for practice

We did not find any randomized controlled trials to investigate the possible interaction between fluid restriction and indomethacin prophylaxis versus indomethacin prophylaxis alone in ELBW infants. Currently, there is no evidence to support one practice over the other.

Implications for research

A well-designed large randomized trial to investigate the possible interaction between indomethacin prophylaxis and fluid restriction in the reduction of BPD and long-term neurosensory outcomes, or both, is needed.

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* *Indicates the major publication for the study*

DATA AND ANALYSES

This review has no analyses.

HISTORY

Protocol first published: Issue 1, 2009

Review first published: Issue 7, 2011

CONTRIBUTIONS OF AUTHORS

Both review authors:

- Prepared the review protocol.
- Searched the literature for eligible trials.

JA wrote the manuscript which then was reviewed by KA.

DECLARATIONS OF INTEREST

None known.

INDEX TERMS

Medical Subject Headings (MeSH)

*Infant, Extremely Low Birth Weight; Anti-Inflammatory Agents, Non-Steroidal [*therapeutic use]; Bronchopulmonary Dysplasia [mortality; *prevention & control]; Fluid Therapy; Indomethacin [*therapeutic use]; Infant, Newborn

MeSH check words

Humans