Fluid Restriction and Prophylactic Indomethacin in Extremely Low Birth Weight Infants

Jasim A. Anabrees, Khalid M. AlFaleh[1]
Neonatal Care, Sulaiman Al Habib Medical Group, [1]Department of Pediatrics (Division of Neonatology), King Saud University, College of Medicine, Riyadh, Saudi Arabia

ABSTRACT

Although survival of extremely low birth weight (ELBW) infants dramatically improved over last decades, bronchopulmonary dysplasia (BPD) rate 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 18 months corrected age. 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. The standard search strategy for the Cochrane Neonatal Review Group was used. This included search of OVID MEDLINE-National Library of Medicine, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 8, 2011). Additional search included conference proceedings, references in articles, and unpublished data. All randomized or quasi-randomized trials that compared fluid restriction and indomethacin prophylaxis vs. indomethacin prophylaxis alone in ELBW infants were included. Standard methods of the Cochrane Neonatal Review Group were planned to assess the methodological quality of the trials. Review Manager 5 software was planned to be used for statistical analysis. We found no randomized controlled trials to investigate the possible interaction between fluid restriction and indomethacin prophylaxis vs. indomethacin prophylaxis alone in ELBW infants. A well-designed randomized trial is needed to address this question.

Key words:
Extremely low birth weight infants, fluid restriction, indomethacin

INTRODUCTION

Extremely low birth weight (ELBW) deliveries are associated with high incidence of many significant morbidities and mortality. Bronchopulmonary dysplasia (BPD) is a common morbidity among ELBW survivors.[1] The pathogenesis of BPD is multifactorial.[2] 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.[3-5] High fluid intake with increased extracellular fluid (ECF) is associated with a higher incidence of symptomatic patent ductus arteriosus (PDA),[6] which is associated with an increased risk of BPD.[7] 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.[8]

Body water content is very high in ELBW infant, with a large proportion of the water in the ECF compartment.[9,10] During the first week of life, there is a physiologic contraction of the ECF with negative fluid balance.[11,12] 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 through insensible water loss.[12,13]

In the published systematic review by Bell and colleagues, fluid restriction was shown to significantly reduce the risks of PDA, necrotizing enterocolitis (NEC), and death. In addition, there was a trend toward decreasing BPD that did not reach statistical significance and no significant increase in adverse effects.[14] Caution should be used in extrapolating these results to extremely premature infants. Most of the included studies in this systematic review were

Address for correspondence:
Dr. Jasim A. Anabrees,
Neonatal Care, Arrayan Hospital, Sulaiman Al Habib Medical Group,
P. O. Box 272069, Riyadh 11352, Saudi Arabia.
E-mail: jasim1800@yahoo.com

Access this article online	
Quick Response Code:	Website: www.jcnonweb.com
	DOI: 10.4103/2249-4847.92228

old, enrolled small number of infants, and included very few ELBW infants.

The efficacy of prophylactic indomethacin for 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 found that in ELBW infants, indomethacin prophylaxis reduces the risk of significant PDA by 56% (typical relative risk (RR), 0.44; 95% CI, 0.38-0.50), surgical ligation of the PDA by 49% (typical RR, 0.51; 95% CI, 0.37-0.71), serious intraventricular hemorrhage (IVH) by 34% (typical RR, 0.66; 95% CI, 0.53-0.82)[15], and serious pulmonary hemorrhage during the first week of life.[16] 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.[15] These results have led to a controversy among neonatal practitioners that has resulted in a decrease in the use of indomethacin prophylaxis in ELBW infants after the publication of the large trial of indomethacin prophylaxis in preterm infants (TIPP) in 2001.[17,18]

In a secondary analysis of TIPP trial data,[19] 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 of 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 outcome. Strict fluid management protocols or prophylactic fluid restriction in indomethacin-treated infants could ameliorate the consequences of this anticipated side-effect.

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. The secondary objective is to evaluate the effect of this combination in a subgroup analysis of the most vulnerable infants with birth weight <750 g.

MATERIALS AND METHODS

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 first week of life) *vs* indomethacin prophylaxis alone in ELBW infants were planned to be included. Cross-over trials were planned to be excluded.

All strategies for fluid restriction and all indomethacin dosing regimens and rates of infusion were planned to be accepted.

Primary outcome was BPD defined as oxygen requirement at 36 weeks of postmenstrual age.[20]

Secondary outcomes include death before discharge, Neurosensory impairment defined as rates of cerebral palsy, cognitive delay, deafness, blindness at 18 to 24 months corrected age as per Baley's score.[21]

The composite of death or neurosensory impairment at 18 to 24 months corrected age, IVH as per Papile criteria[22] by cranial ultrasound, Symptomatic PDA diagnosed by echocardiogram, and Stage II and III NEC as defined by Bell's criteria[23,24] were measured.

Other important outcomes like serious pulmonary hemorrhage defined as endotracheal bleeding requiring increased ventilatory or oxygen support and/or transfusion of blood products,[16] retinopathy of prematurity (ROP) defined by International Classification of Retinopathy of Prematurity classification:[25,26] (a) any stage; (b) severe ROP (stage 3 or more), duration of hospital stay (days), Late bacterial sepsis defined as positive bacterial blood or cerebrospinal fluid cultures taken beyond five days of age, Periventricular Leukomalacia, Serum Creatinine level, and Urine output were assessed.

Search methods for identification of studies

The standard search strategy for the cochrane neonatal review group (CNRG) was used. Randomized and quasi-randomized controlled trials that compare indomethacin prophylaxis and fluid restriction *vs* indomethacin prophylaxis alone in ELBW infants were planned to be identified from OVID MEDLINE-National Library of Medicine (1966 to August, 2011) using the following subject headings (MeSH) and text word terms: Patent ductus arteriosus or PDA, indomethacin, and publication type "controlled trial," limited to infants. No language restrictions were applied. Other databases were searched including EMBASE (1980 to August, 2011) and the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 8, 2011). Authors performed the electronic database search independently. A manual search of the abstract books published from the society of pediatric research (SPR) and the european society of pediatric research (ESPR) for the period of 1995 to 2010 was

performed. Additional citations were planned to be sought using references in articles retrieved from searches. Subject experts and trials registration sites (clinicaltrials.gov) were contacted to identify the unpublished and ongoing studies. Authors of the published trials were planned to be contacted to clarify or provide additional information. Authors independently were planned to screen candidate articles to check the eligibility for inclusion in the review. Unpublished data and abstracts were eligible for inclusion provided adequate information regarding primary and/or secondary outcomes can be obtained.

Standard methods of the CNRG were planned to be used to assess the methodological quality (validity criteria) of the trials. For each trial, information were planned to be sought regarding the method of randomization, blinding, and reporting of all outcomes of all the infants enrolled in the trial. Each criteria was planned to be assessed as yes, no, can't tell. Retrieved articles were planned to be assessed for eligibility and data abstracted independently by two reviewers. Discrepancies were planned to be resolved by discussion and consensus. Where data are incomplete, the primary investigator was planned to be contacted for further information and clarifications.

For dichotomous outcomes, RR and its associated confidence interval was planned to be calculated. For continuous outcomes, treatment effect was planned to be expressed as mean difference and its calculated standard deviation. If appropriate, meta-analysis of pooled data was planned to be performed assuming a fixed effect model. Review Manager 5 software was planned to be used for statistical analysis. A sensitivity analysis was planned to be carried out to assess the effect of trials methodological quality on results of the meta-analysis. A subgroup analyses was planned to be carried out to investigate the effect of prophylactic indomethacin and fluid restriction in high-risk infants with birth weight <750 g. Heterogeneity was defined as a significant test of heterogeneity (P<0.1) and differences in the treatment effects across studies. Tests for between-study heterogeneity (including the I squared test) were planned to be applied. We hypothesize 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 (<1 000 g *vs* <750 g infants), and study quality.

RESULTS

No studies that fulfilled the eligibility criteria were found.

DISCUSSION

Our review found no randomized controlled trials to investigate the possible interaction between fluid restriction and indomethacin prophylaxis *vs* indomethacin prophylaxis alone in ELBW infants.

The indomethacin story is indeed a puzzling one to all neonatal practitioners. Although indomethacin prophylaxis resulted in an excellent reduction of important intermediate outcomes, it failed to maintain this effect on the long-term neurosensory outcome. The TIPP trial is by far the largest trial to investigate the efficacy of prophylactic indomethacin in preterm infants.[17] In the published meta-analysis by Fowlie and Davis,[15] the data of the TIPP trial weighed more than 50% in intermediate outcomes and 80% in long-term outcomes. Few possible methodologic and indomethacin-related factors could possibly explain this:

First, 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). Although 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 affect large number of ELBW infants is quite generous. Utilizing a smaller MCD (i.e., 5-10%) could translate in a positive long-term outcomes, but it will require double or triple the number of infants enrolled in the TIPP trial.

Second, the use of a composite outcome in order to evaluate related clinical outcomes or increase precision of the trial is common in medical literature.[27] Unfortunately, use of composite end points 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 end points 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 end point is dependent on similarity in patient importance, treatment effect, and number of events across the components. Experts in research methodology strongly advised to abandon the use of composite endpoints when large variations exist between the composite endpoint components.[28] The composite end point of the TIPP trial included five components, some of which are very rare, e.g., blindness which affects only one percent and other more common outcomes, e.g., cognitive delay which affects up to 25% of enrolled ELBW infants.

Third, indomethacin prophylaxis reduces urine output

(Number need to harm 1 in 7). In an ancillary analysis of TIPP trial data,[19] 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 outcome. Stringent fluid management protocol or prophylactic fluid restriction in indomethacin-treated infants could ameliorate the consequences of this anticipated side effect.

Fourth, although 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.[29]

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 reduction of important intermediate neonatal outcomes without proven long-term benefits or harms. Patient's decision aids are increasingly used in various fields of medicine over the last ten years. Prior to withholding prophylactic indomethacin, clinicians need to explain (utilizing a 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 of highest risk and the possible interaction between fluid restriction to prophylactic indomethacin.

CONCLUSIONS

We found no randomized controlled trials to investigate the possible interaction between fluid restriction and indomethacin prophylaxis *vs* indomethacin prophylaxis alone in ELBW infants.

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

REFERENCES

1. Lemons JA, Bauer CR, Oh W, Korones SB, Papile LA, Stoll BJ, *et al.* Very low birth weight outcomes of the National Institute of Child health and human development neonatal research network, January 1995 through December 1996. NICHD Neonatal Research Network. Pediatrics 2001;107:E1.
2. Bancalari E, Claure N, Sosenko IR. Bronchopulmonary dysplasia: Changes in pathogenesis, epidemiology and definition. Semin Neonatol 2003;8:63-71.
3. Van Marter LJ, Leviton A, Allred EN, Paqano M, Kuban KC. Hydration during the first days of life and the risk of bronchopulmonary dysplasia in low birth weight infants. J Pediatr 1990;116:942-9.
4. Costarino AT, Gruskay JA, Corcoran L. Sodium restriction versus daily maintenance replacement in very low birth weight premature neonates: A randomized, blind therapeutic trial. J Pediatr 1992;120:99-106.
5. Hartnoll G, Betremieux P, Modi N. Randomized controlled trial of postnatal sodium supplementation on body composition in 25 to 30 week gestational age infants. Arch Dis Child Fetal Neonatal Ed 2000;82:F24-8.
6. Bell EF, Warburton D, Stonestreet BS, Oh W. Effect of fluid administration of the development of symptomatic patent ductus arteriosus and congestive heart failure in premature infants. N Engl J Med 1980;302:598-604.
7. Brown E. Increased risk of bronchopulmonary dysplasia in infants with patent ductus arteriosus. Pediatrics 1979;95:865-6.
8. Oh W, Poindexter BB, Perritt R, Lemons JA, Bauer CR, Ehrenkranz RA, *et al.* Association between fluid intake and weight loss during the first ten days of life and risk of bronchopulmonary dysplasia in extremly low birth weight infants. J Pediatr 2005;147:786-90.
9. Friis-Hansen B. Changes in body water compartment during growth. Acta Paediatrica Supplement 1957;110:S1-68.
10. Friis-Hansen B. Body water compartments in children: Changes during growth and related changes in body composition. Pediatrics 1961;28:169-81.
11. Stonestreet BS, Bell EF, Warburton D, Oh W. Renal response in low birth-weight neonates. Results of prolonged intake of two different amounts of fluid and sodium. Am J Dis Child 1983;137:215-9.
12. Bauer K, Versmold H. Postnatal weight loss in preterm neonates less than 1,500 g is due to isotonic dehydration of the extracellular volume. Acta Paediatr Scand Suppl 1989;360:37-42.
13. Bidiwala KS, Lorenz JM, Kleinman LI. Renal function correlates of postnatal diuresis in preterm infants. Pediatrics 1988;82:50-8.
14. Bell EF, Acarregui MJ. Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants. Cochrane Database of Systematic Reviews 2001;(3):CD000503. DOI: 10.1002/14651858.CD000503.
15. Fowlie PW, Davis PG. Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants. Cochrane Database of Systematic Reviews 2002;(4):CD000174. DOI: 10.1002/14651858.CD000174.
16. Alfaleh K, Smyth JA, Roberts RS, Solimano A, Asztalos EV, Schmidt B. Trial of indomethacin prophylaxis in preterms investigators. prevention and 18-month outcomes of serious pulmonary hemorrhage in extremely low birth weight infants: results from the trial of indomethacin prophylaxis in preterms. Pediatrics 2008;121:e233-8.
17. Schmidt B, Davis P, Moddemann D, Ohlsson A, Roberts RS, Saigal S, *et al.* Trial of indomethacin prophylaxis in preterms investigators. Long-term effect of indomethacin prophylaxis in extremely-low-birth -weight infants. N Engl J Med 2001;344:1966-72.
18. Clyman RI, Saha S, Jobe A, Oh W. Indomethacin prophylaxis for preterm infants: The impact of 2 multicentered randomized controlled trials on clinical practice. J Pediatr 2007;150:46-50.e2.
19. Schmidt B, Roberts RS, Fanaroff A, Davis P, Kirpalani HM, Nwaesei C, *et al.* TIPP Investigators. Indomethacin prophylaxis, patent ductus arteriosus, and the risk of bronchopulmonary dysplasia: Further analyses from the Trial of Indomethacin Prophylaxis in Preterms

(TIPP). J Pediatr 2006;148:730-4.

20. Shennan AT, Dunn MS, Ohlsson A, Lennox K, Hoskins EM. Abnormal pulmonary outcomes in premature infants: Prediction from oxygen requirement in the neonatal period. Pediatrics 1988;82:527-32.
21. Bayley N. Manual for the Bayley Scales of Infant Development. 2nd Ed. San Antonio: Psychological Corporation; 1993.
22. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: A study of infants with birth weights less than 1,500 gm. J Pediatr 1978;92:529-34.
23. Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, *et al*. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg 1978;187:1-7.
24. Walsh MC, Kliegman RM. Necrotizing enterocolitis: Treatment based on staging criteria. Pediatr Clin North Am 1986;33:179-201.
25. ICROP. An International Classification of Retinopathy of Prematurity. Pediatrics 1984;74:127-33.
26. ICROP. The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol 2005;123:991-9.
27. Freemantle N, Calvert M, Wood J. Composite outcomes in randomized trials: Greater precision but with greater uncertainty? JAMA 2003;289:2554-9.
28. Montori VM, Permanyer-Miralda G, Ferreira-González I. Validity of composite end points in clinical trails. BMJ 2005;330:594-6.
29. Hack M, Taylor HG, Drotar D. Poor predictive validity of the Bayley Scales of Infant Development for cognitive function of extremely low birth weight children at school age. Pediatrics 2005;116:331-41.

How to cite this article: Anabrees JA, AlFaleh KM. Fluid restriction and prophylactic indomethacin in extremely low birth weight infants. J Clin Neonatol 2012;1:1-5.

Source of Support: Nil, **Conflict of Interest:** None declared.