Neonatal pearls : safety and efficacy of medication use in fetus and neonate

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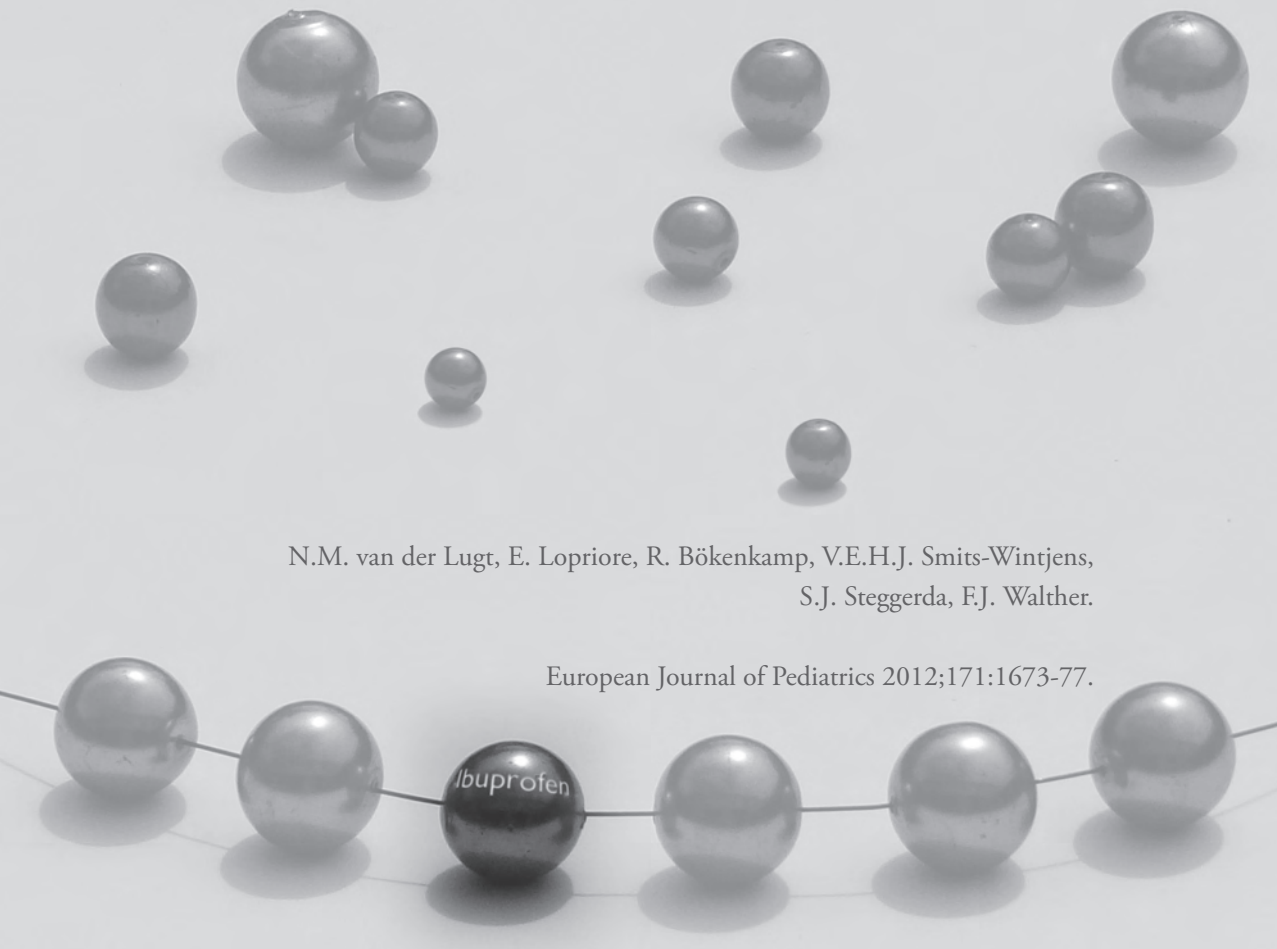
Chapter 4

Repeated courses of ibuprofen are effective in closure of a patent ductus arteriosus



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European Journal of Pediatrics 2012;171:1673-77.

Abstract

Patent ductus arteriosus (PDA) is a frequent complication in preterm infants. Ibuprofen and indomethacin (both COX-inhibitors) are used for pharmacological closure of PDA. In most centers a failed second course of COX-inhibitors is followed by surgical closure.

Our aim was to estimate the closure rate of clinically significant PDA after second and third courses of ibuprofen and record possible side effects.

A study population, consisting of 164 preterm infants (<32 weeks' gestational age) with PDA admitted at our tertiary care center between November 2005 and September 2011, was retrospectively analyzed. Primary outcome was the closure rate after repeated courses of ibuprofen. The closure rate was similar after the first (109/164), second (24/43) an d third (6/11) course of ibuprofen ($X^2 = 2.1$, $p = 0.350$). Late start of the first course of ibuprofen was a predictive factor for increased need of a second course ($X^2 = 4.4$, $p = 0.036$). No additional side effects of multiple courses of ibuprofen were detected.

Conclusion

Repeated courses of ibuprofen are an effective and safe alternative for surgical closure and should be considered after failure of the first course of ibuprofen.

Introduction

Patent ductus arteriosus (PDA) is a frequent complication in preterm infants, with a reported incidence of 28% in preterm infants with a gestational age <32 weeks up to 60-70% in those with a gestational age of <29 weeks.[1,2] PDA is associated with increased neonatal mortality, chronic lung disease and necrotizing enterocolitis. The optimal management of PDA is still not clear as the evidence for and against treatment remains controversial.[1,3-7]

Indomethacin and ibuprofen (both COX-inhibitors) are commonly used for pharmacological closure of PDA and appear to be equally effective.[7-9] However, ibuprofen has shown fewer side effects than indomethacin.[7,10] One course of COX-inhibitors resulted in a closure rate of 68-88% for indomethacin and 45-91% for ibuprofen. A second course led to a lower closure rate of 44-47% for indomethacin and 40-45% for ibuprofen.[10-13]

In most centers, closure failure after a second course of COX-inhibitors is followed by surgical closure. However, surgical closure has been associated with an increased risk of chronic lung disease, retinopathy of prematurity and neurodevelopmental impairment, compared to indomethacin therapy.[14,15] A comparison of morbidity and neurodevelopmental outcome after surgical closure and pharmacological closure with ibuprofen is not available.

Only few studies report on the efficacy and safety of three courses of COX-inhibitors. Two small studies showed a PDA closure rate varying from 16 (3/19) to 43% (10/23) after a third course of indomethacin.[10,16] The effect of a third course of ibuprofen has only been studied in two small studies with a closure rate varying from 19% (7/37) to 66% (2/3), and was associated with more renal complications than first and second courses.[10,13]

The aim of this retrospective study was to estimate the effectiveness and safety of second and third courses of ibuprofen on PDA closure and its potential, as an alternative for invasive and possible harmful surgical closure of the PDA. In addition, possible predicting factors for unsuccessful closure were investigated.

Methods

Study population

We included all preterm infants (gestational age at birth <32 weeks) admitted to the Neonatal Intensive Care Unit (NICU) of the Leiden University Medical Center

between November 2005 and September 2011 with a PDA treated with ibuprofen. We excluded infants with congenital heart disease and infants referred to our center for surgical closure of the PDA. The Medical Ethics Committee of the Leiden University Medical Center did not require approval of this study because it consisted of retrospective chart review, nor did the medical ethics committee require written consent by the parents for their infant's information to be (anonymously) stored in the hospital database and used for research.

Diagnosis of PDA was reached and confirmed using echocardiography (Aloka α10, Biomedic Nederland B.V., Almere, The Netherlands). First echocardiography was made when PDA was suspected, due to clinical symptoms such as widened pulse pressures, cardiac murmur, bounding pulses and/or significant respiratory disease. A PDA was considered clinically significant and requiring treatment, when the ductus was moderate to large in size (>1.5 mm) with evidence of left to right ductal shunting and an increased left atrium to aortic ratio.

Each ibuprofen course was prescribed as 10 mg/kg for the first dose followed by two additional doses of 5 mg/kg on consecutive days. Doses were administered intravenously with a 24 hour interval between each dose. Control echocardiography was routinely performed on the first day after the third dose of ibuprofen. A closed or hemodynamic insignificant ductus was scored as closed. No infants received prophylactic treatment with ibuprofen.

Indications for immediate surgical closure after one or two courses of ibuprofen were congestive heart failure and respiratory instability due to the PDA.

Data collection

Data were collected prospectively throughout the study period and entered in a dedicated database. Data for demographic and perinatal characteristics, as well as postnatal clinical conditions included birth weight, gestational age at birth, gender, intrauterine growth restriction, multiple gestation, pre-eclampsia, chorioamnionitis (defined as smelly amniotic fluid, maternal fever or signs of infection at birth), neonatal sepsis (defined as presence of clinical signs of infection with a positive blood culture), respiratory distress syndrome (RDS)[17], duration of mechanical ventilation, need for postnatal steroids, bronchopulmonary dysplasia (need for oxygen therapy at a gestational age > 36 weeks)[18], hypotension requiring inotropics, necrotizing enterocolitis (NEC)[19], cystic periventricular leukomalacia[20] and intraventricular hemorrhage[21,22], duration of admission (until transfer to another secondary center) and neonatal mortality.

Primary outcome data were closure of the PDA after the first and (if necessary), second or third course of ibuprofen or after surgical ligation. We studied potential risk factors for failure of closure, including general characteristics (gestational age, birth weight), postnatal characteristics possibly pathophysiologic associated with PDA (RDS, duration of mechanical ventilation, NEC, neonatal sepsis) and age at start of ibuprofen for each individual course. Bronchopulmonary dysplasia, duration of admission and mortality were studied as possible consequences of failure of closure. We scored the following potential adverse effects of ibuprofen: oliguria (urine production <1.0 ml/kg/hour) with or without renal failure (serum creatinine level >133 μmol/L[23]), severe thrombocytopenia (platelet count < 50 x 10^9/L after ibuprofen with platelet count > 150 x 10^9/L before).

Statistical analysis

Data are reported as median values and ranges. Statistical analyses were performed with SPSS Version 18.0 (SPSS Inc., Chicago, IL). Data were not normally distributed and therefore analyzed using a Fisher's Exact test. A p-value of <0.05 was considered significant. Study size was determined by the total number of exposed infants in the defined period.

Potential confounders in this study were all demographic and postnatal characteristics, mentioned previously. Confounding was minimized by using regression analysis. Infants with missing characteristics were excluded from regression analyses.

Results

Between November 2005 and September 2011 931 preterm infants with a gestational age <32 weeks were admitted to our NICU. The incidence of PDA was 18% (170/931). Six infants were excluded from analysis because of referral to our center for primary surgical closure of PDA (n=6). A flowchart of the study population can be seen in figure 1. An overview of characteristics of the study population of preterm infants with PDA is shown in table 1.

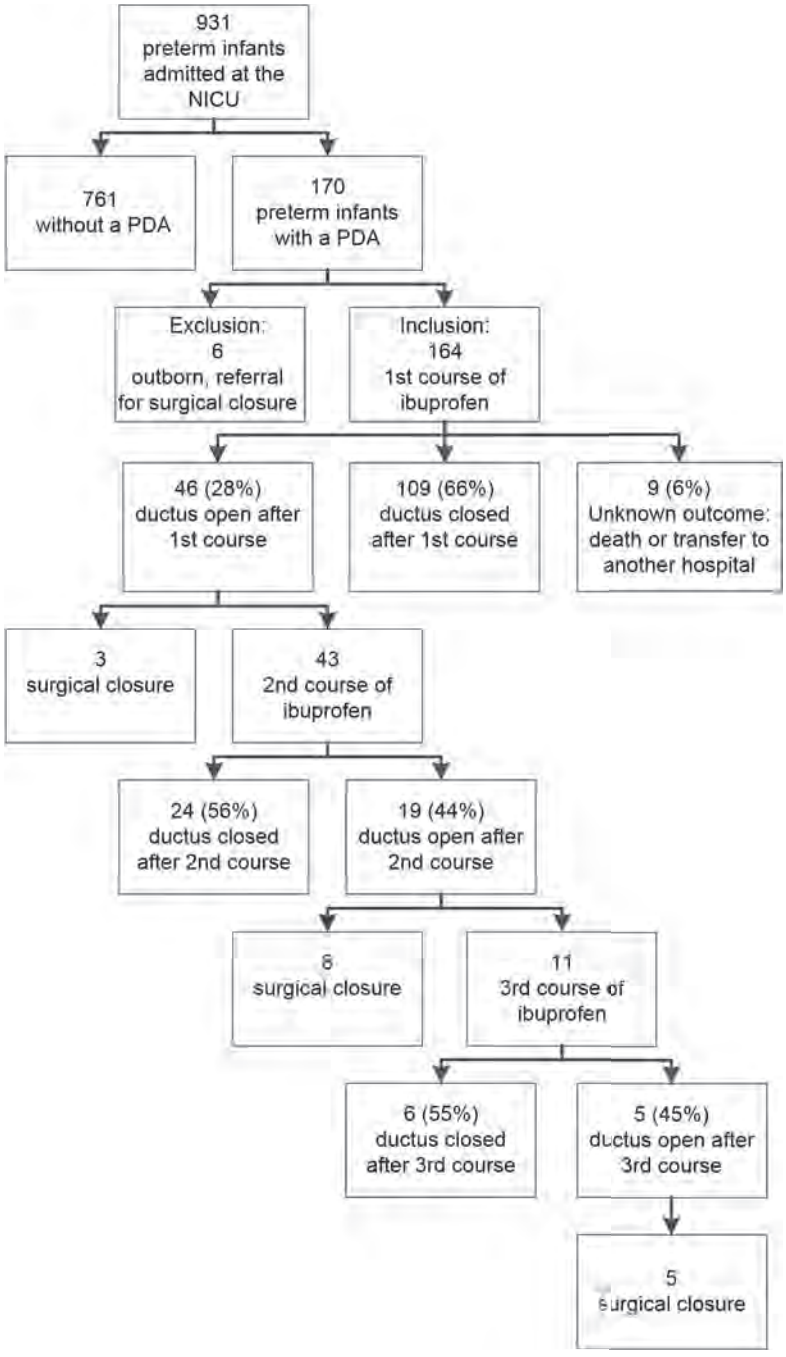

Figure 1. Flowchart of included infants.

Table 1. Characteristics of the studied population.

	N = 164
Gestational age at birth (weeks) [a]	27.0 (23-31)
Birth weight (grams) [a]	995 (525-2041)
Gender (male) – n (%)	81 (49)
Multiple gestation – n (%)	60 (37)
Chorioamnionitis – n (%)	6 (4)
Pre-eclampsia – n (%)	36 (22)
IUGR – n (%)	16 (10)
Respiratory distress syndrome – n (%)	125 (76)
Duration of mechanical ventilation (days) [a]	8 (0-36)
Postnatal steroids – n (%)	42 (26)
Bronchopulmonary dysplasia – n (%)	13 (8)
Hypotension – n (%)	64 (39)
Necrotizing enterocolitis – n (%)	12 (7)
Neonatal sepsis – n (%)	64 (39)
Periventricular leukomalacia (≥ grade 2) – n (%)	6 (4)
Intraventricular hemorrhage (≥ grade 3) – n (%)	15 (9)
Duration of admission (days) [a]	27 (3-138)
Mortality – n (%)	14 (9)

[a] Value given as median (range)

PDA closure rate was similar after the first (109/164), second (24/43) and third (6/11) course of ibuprofen ($X^2 = 2.1$, $p = 0.350$) (table 2).

Table 2. Closure rate of ductus arteriosus after ibuprofen or ligation.

	Courses of ibuprofen		
	1	2	3
Number of infants	164	43	11
Closed ductus after ibuprofen	109	24	6
Closed ductus after ligation	3	8	5
Unknown outcome	9		

We studied several general characteristics, postnatal characteristics and age at start of ibuprofen for possible associations with failure of closure (as potential risk factors or consequences). Analysis of each ibuprofen course separately, showed a positive

correlation between postnatal age at start of the first dose of ibuprofen and the need for a second course of ibuprofen: the older the neonate (in terms of postnatal age at start of ibuprofen), the lower the chance of definitive PDA closure after one course of ibuprofen. The median age at the start of the first course of ibuprofen in the group with successful closure after one course was 4 days (range 2-24), compared to 5 days (range 2-19) in the group with unsuccessful closure after one course. Closure rate after the first course of ibuprofen significantly increased if ibuprofen treatment was started prior to postnatal day 5: 64/84 when started before day 5 versus 43/71 when started on day 5 or later ($X^2 = 4.4$, $p = 0.036$).

Oliguria was observed in 10 infants (9 during the first, 1 during the second course of ibuprofen). One infant had an increased serum creatinine level >133 μmol/L during the first course of ibuprofen without oliguria. Four infants developed severe thrombocytopenia (platelet count < 50 x 10^9/L) during the first course of ibuprofen, without clinical signs of bleeding. All reported side effects were transient and resolved spontaneously. No relationship was found between adverse effects and the number of courses of ibuprofen.

Discussion

This study shows that the closure rate of PDA after a second or third course of ibuprofen was similar to the closure rate after the first course and that multiple courses of ibuprofen were not associated with an increase in adverse effects.

Recently, two small studies reported on the PDA closure rate in a population of premature infants receiving multiple courses of ibuprofen. In a study in 182 preterm infants, Kushnir et al found closure rates for the first, second and third course of 92% , 54% and 19%, respectively[10], whereas PDA closure rates in a study from Richards et al were 45%, 40% and 66%, respectively[13]. In comparison, the closure rates in our study cohort were 66%, 56% and 55%. The cumulative closure rate after all courses of ibuprofen was 71% (130/183) in the study by Kushnir et al[10] and 69% (110/160) in the study by Richards et al[13] versus 85% (139/164) in this study. Differences in closure rates between the studies are probably due to differences in study designs and methodology. The preterm infants in the study of Richards et al[13] had a lower mean gestational age and birth weight (25.6 weeks, 757 gram) than the infants included in our study. In the study of Kushnir et al[10] mean gestational age and birth weight were comparable (27.8 weeks, 1083 gram).

Kushnir et al[10] reported more adverse effects, i.e. an increase of serum creatinine levels and decrease of urine output in infants receiving more than one course of ibuprofen. We found no additional adverse effects during second and third courses of ibuprofen in our study, similar to the findings of Richards et al[13]. The most remarkable difference between the patient populations was the duration between the first and second course of ibuprofen (1 day in Kushnir et al, 6 days in Richards et al versus 3 days in our study population) and the second and third course of ibuprofen (1 day in Kushnir et al versus 5 days in our study).[10,13] The relatively short interval between the treatment courses in the Kushnir study might explain the increased risk of adverse effects.

The value of our study lies in the meticulous analysis of a large cohort, the focus on timely start of ibuprofen therapy and evaluation of current experience with repeated courses of COX-inhibitors versus surgical closure. The importance of this type of information is supported by the web-based questionnaire survey by Amin et al which evaluated the use of repeated courses of indomethacin in neonatal intensive care programs in the USA. Those centers using more than two courses of indomethacin, based their usage of a third course on local experience, because of lack of evidence on repeated courses in clinical literature.[24] The reported harmful effects of surgical ductal closure, such as chronic lung disease, retinopathy and neurodevelopmental impairment, warrant in depth investigation of a pharmacological alternative without major side effects.[14,15]

Several factors have been associated with a higher closure rate after pharmacological treatment, including earlier age and a large ductal diameter (>2 mm) at start of the first course of ibuprofen.[25] Our findings confirm the association between advanced postnatal age at the start of the first course and failure of ductal closure after the first course of ibuprofen. Closure rate after the first course of ibuprofen significantly increased if ibuprofen treatment was started prior to postnatal day 5. Similarly, in a study using indomethacin, re-opening of the ductus arteriosus with echographic luminal flow after the first course of indomethacin was more common in infants who received their indomethacin course at a higher postnatal age.[26] None of these studies showed a relationship between closure rate and starting age of the second and third course of ibuprofen or indomethacin.

The higher closure rate after the first course of ibuprofen, if started at a lower postnatal age, maybe due to the pharmacokinetic characteristics of ibuprofen. Ibuprofen is metabolized by the cytochrome P450 complex, especially the CYP2C9 and CYP2C8 enzymes. Directly after birth these enzymes are absent in the serum, during the first week of life they increase to 33% of the adult serum level, independent of gestational

age. Therefore, the available concentration of ibuprofen decreases during the first week of life due to increased metabolism, resulting in less bio-availability for closure of the ductus.[27,28] The reason why the starting age of the second and third course of ibuprofen does not influence the closure rate is not clear. Hypothetically, it could be expected that the fast increase in serum level of the CYP enzymes during the first week of life will flatten to a stable level in the next weeks, without influencing closure rate anymore.

The results of this study may have important consequences for clinical practice, especially when a second course of ibuprofen fails to close the PDA. Our data suggest that a third course of ibuprofen may be an effective alternative to surgical closure, without additional risks for pharmacological side effects. As shown in this study, closure rates of a second and third course of ibuprofen are independent of postnatal age at the start of the consecutive course. Therefore, advanced postnatal age may not be an argument in favor of surgical ligation instead of a second or third course of ibuprofen.

For many years PDA closure was the main goal in ductal management. More recently, various studies have raised important questions concerning the optimal management of PDA and the potential benefits of ductal closure.[4,29,30] The management of PDA at our institution is to date still based on ductal closure. This will remain our standard of care unless new evidence is provided showing that ductal closure is associated with more disadvantages compared to conservative management.

Although our results add to the understanding of efficacy and safety of repeated courses of ibuprofen on PDA closure, we recognize there are several potential limitations. The retrospective design of this study is the first limiting factor. We tried to minimize possible bias by using strict definitions and cut-off values. A second limitation is the relatively small size of the study population receiving multiple ibuprofen courses. Nevertheless, retrospective and small studies are necessary to design future randomized controlled trials. Such a trial is urgently required to determine whether short and long-term outcome of pharmacological management of PDA with multiple courses of ibuprofen is better or worse than surgical closure. In addition, a larger prospective study using a third course of ibuprofen is needed to determine its pharmacological effects and side-effects.

References

1. Hamrick SE, Hansmann G. Patent ductus arteriosus of the preterm infant. Pediatrics 2010;125:1020-1030.
2. Tauzin L, Joubert C, Noel AC, Bouissou A, Moulies ME. Effect of persistent patent ductus arteriosus on mortality and morbidity in very low-birthweight infants. *Acta Paediatr* 2012;101:419-423.
3. Bose CL, Laughon MM. Patent ductus arteriosus: lack of evidence for common treatments. *Arch Dis Child Fetal Neonatal Ed* 2007;92:F498-F502.
4. Clyman RI, Chorne N. Patent ductus arteriosus: evidence for and against treatment. *J Pediatr* 2007;150:216-219.
5. Dollberg S, Lusky A, Reichman B. Patent ductus arteriosus, indomethacin and necrotizing enterocolitis in very low birth weight infants: a population-based study. *J Pediatr Gastroenterol Nutr* 2005;40:184-188.
6. Marshall DD, Kotelchuck M, Young TE, Bose CL, Kruyer L, O'Shea TM. Risk factors for chronic lung disease in the surfactant era: a North Carolina population-based study of very low birth weight infants. North Carolina Neonatologists Association. *Pediatrics* 1999;104:1345-1350.
7. Ohlsson A, Shah SS. Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants. *Cochrane Database Syst Rev* 2011;CD004213.
8. Lago P, Bettiol T, Salvadori S, Pitassi I, Vianello A, Chiandetti L, Saia OS. Safety and efficacy of ibuprofen versus indomethacin in preterm infants treated for patent ductus arteriosus: a randomised controlled trial. *Eur J Pediatr* 2002;161:202-207.
9. Overmeire van B., Smets K, Lecoutere D, Broek van der H, Weyler J, Degroote K, Langhendries JP. A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus. *N Engl J Med* 2000;343:674-681.
10. Kushnir A, Pinheiro JM. Comparison of renal effects of ibuprofen versus indomethacin during treatment of patent ductus arteriosus in contiguous historical cohorts. *BMC Clin Pharmacol* 2011;11:8.
11. Keller RL, Clyman RI. Persistent Doppler flow predicts lack of response to multiple courses of indomethacin in premature infants with recurrent patent ductus arteriosus. *Pediatrics* 2003;112:583-587.
12. Quinn D, Cooper B, Clyman RI. Factors associated with permanent closure of the ductus arteriosus: a role for prolonged indomethacin therapy. *Pediatrics* 2002;110:e10.
13. Richards J, Johnson A, Fox G, Campbell M. A second course of ibuprofen is effective in the closure of a clinically significant PDA in ELBW infants. *Pediatrics* 2009;124:287-293.
14. Kabra NS, Schmidt B, Roberts RS, Doyle LW, Papile L, Fanaroff A. Neurosensory impairment after surgical closure of patent ductus arteriosus in extremely low birth weight infants: results from the Trial of Indomethacin Prophylaxis in Preterms. *J Pediatr* 2007;150:229-234.
15. Chorne N, Leonard C, Piecuch R, Clyman RI. Patent ductus arteriosus and its treatment as risk factors for neonatal and neurodevelopmental morbidity. *Pediatrics* 2007;119:1165-1174.
16. Sangem M, Asthana S, Amin S. Multiple courses of indomethacin and neonatal outcomes in premature infants. *Pediatr Cardiol* 2008;29:878-884.
17. Giedion A, Haefliger H, Dangel P. Acute pulmonary X-ray changes in hyaline membrane disease treated with artificial ventilation and positive end-expiratory pressure (PEP). *Pediatr Radiol* 1973;1:145-152.
18. Martin, R. J., Fanaroff, A. A., and Walsh, M. C. Fanaroff and Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant. 8 ed. Philadelphia: Elsevier; 2005. 1156-1157.
19. Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. *Pediatr Clin North Am* 1986;33:179-201.
20. de Vries LS, Eken P, Dubowitz LM. The spectrum of leukomalacia using cranial ultrasound. *Behav Brain Res* 1992;49:1-6.
21. 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;92:529-534.
22. Volpe, J. J. Neurology of the Newborn. 5 ed. Philadelphia: Saunders; 2008.
23. Stapleton FB, Jones DP, Green RS. Acute renal failure in neonates: incidence, etiology and outcome. *Pediatr Nephrol* 1987;1:314-320.

24. Amin SB, Handley C, Carter-Pokras O. Indomethacin use for the management of patent ductus arteriosus in preterms: a web-based survey of practice attitudes among neonatal fellowship program directors in the United States. *Pediatr Cardiol* 2007;28:193-200.

25. Desandes R, Jellimann JM, Rouabah M, Haddad F, Desandes E, Boubred F, Semama D, Vieux R, Hascoet JM. Echocardiography as a guide for patent ductus arteriosus ibuprofen treatment and efficacy prediction. *Pediatr Crit Care Med* 2011.

26. Weiss H, Cooper B, Brook M, Schlueter M, Clyman R. Factors determining reopening of the ductus arteriosus after successful clinical closure with indomethacin. *J Pediatr* 1995;127:466-471.

27. Dani C, Vangi V, Bertini G, Pratesi S, Lori I, Favelli F, Ciuti R, Bandinelli A, Martano C, Murru P, Messner H, Schena F, Mosca F. High-dose Ibuprofen for patent ductus arteriosus in extremely preterm infants: a randomized controlled study. *Clin Pharmacol Ther* 2012;91:590-596.

28. Hirt D, Van OB, Treluyer JM, Langhendries JP, Marguglio A, Eisinger MJ, Schepens P, Urien S. An optimized ibuprofen dosing scheme for preterm neonates with patent ductus arteriosus, based on a population pharmacokinetic and pharmacodynamic study. *Br J Clin Pharmacol* 2008;65:629-636.

29. Benitz WE. Patent ductus arteriosus: to treat or not to treat? *Arch Dis Child Fetal Neonatal Ed* 2012;97:F80-F82.

30. Vanhaesebrouck S, Zonnenberg I, Vandervoort P, Bruneel E, Van Hoestenberghe MR, Theyskens C. Conservative treatment for patent ductus arteriosus in the preterm. *Arch Dis Child Fetal Neonatal Ed* 2007;92:F244-F247.