The use of indomethacin for the prevention of intraventricular brain hemorrhage in high-risk neonates

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ABSTRACT

Objective: The objective of this study was to determine the effect of indomethacin on reducing the incidence of intraventricular hemorrhage in premature infants treated in our units at King Faisal Specialist Hospital and Research Centre.

Methods: This historical cohort study included 45 infants born with birth weights of 1250g or less and received indomethacin in the first 12 hours of life for intraventricular hemorrhage prevention. The treated infants were compared to 33 other infants with birth weights of 1250g or less who did not receive indomethacin for intraventricular hemorrhage prevention. Data collected included demographic, complications of prematurity, renal function and maternal data.

Results: Mean birth weight (grams) and gestational age (week) were 928.6±34, 1066.2±38.9, 27.2±0.37 and 29±0.42 for the treated and the control infants. Overall incidence of intraventricular hemorrhage decreased significantly in the treated infants in comparison to the controls (P=0.0169). There was no infant with Grade 3-4 intraventricular hemorrhage found in the treated group while 2 developed grade 3-4 intraventricular in the control group which was insignificant. There were no statistically significant differences between the groups in terms of the complications of prematurity, Apgar scores at 5 minutes, airleak syndrome and the use of umbilical catheters. The total fluid intake in the first 4 days after starting the treatment was comparable between the groups. There were no significant differences between the groups in urine output in day 1, 3 and 4. However the urine output decreased significantly in day 2 in the treated group (P = 0.0349). There were no statistically significant differences in serum urea and creatinine between the groups

Conclusion: Low dose indomethacin given in the first 12 hours of life was shown to be associated with a decrease in intraventricular hemorrhage in premature infants and it was not associated with significant adverse effect.

Keywords: Premature infants, intraventricular hemorrhage, indomethacin.

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Improvement of survival and prevention of brain injury is the main goal of the caregivers in the neonatal intensive care unit (NICU). Intraventricular hemorrhage (IVH) is one cause of brain injury that leads to neurodevelopmental handicaps.

Multiple pharmacological intervention trials to prevent IVH have been published with inconsistent results.[1] Such inconsistencies are expected in view of the multifactorial pathogenesis of IVH. Indomethacin, a cyclo-oxygenase inhibitor of prostaglandin synthesis, has been suggested as a single therapy for the prevention of IVH. Recently Ment et al[2,3] in a prospective, randomized, placebo-controlled trial, showed that a low-dose indomethacin significantly lowered the incidence and severity of IVH, particularly parenchymal involvement of

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Table 1 - Infants data.

	Indomethacin n=45	Controls n=33	p value
Birth weight (g)	928±34	1055±38	0.009
Gestational age (week)	27±0.3	29±0.4	0.001
Apgar score at 5 minutes	5.2±1	6.8±0.9	NS
Delivery: Vaginal	23	19	NS
Cesarean	22	14	NS

hemorrhage, in very low birth-weight (VLBW) infants with no evidence of IVH in the first 6 postnatal hours.

In the NICU at King Faisal Specialist Hospital and Research Centre, the use of low-dose indomethacin to prevent IVH in VLBW infants was started routinely in January 1996. This historical cohort study was carried out to review our practice whether or not low-dose indomethacin was effective in the prevention of IVH in premature infants.

Methods. The administration of indomethacin to prevent IVH in mechanically ventilated neonates with birth weights of less than 1250 gm was adopted in our NICU in January 1996. Indomethacin was given as 0.1 mg/kg over 20 minutes within the first 12 hours of life followed by the same dose every 24 hours for a total of 3 doses. Cranial ultrasounds were performed on the third day of life and then every week if the first one showed abnormal findings. If the ultrasound findings were normal then it was repeated prior to discharge to look for PVL. Indomethacin was discontinued if urine output was less than 0.5 ml/kg/hour and or if serum creatinine was 105 umolL or more.

Between January 1996 and January 1998, neonates with a birth weight of less than1250 gm who received indomethacin for IVH prevention and discharged from the hospital were identified. Similarly neonates born between 1994 and 1996 with a birth weight of less than 1250gm who did not receive indomethacin and discharged from the hospital were selected as controls. Ten neonates, 5 indomethacin-treated and another 5 controls, were reviewed and excluded from the study because either they did not complete the indomethacin course or died in the first 72 hours of life respectively. All indomethacin-treated group were inborn while 3 in the control group were out-born. Analysis was performed in 45 and 33 infants in the indomethacin-treated and control groups. Small for gestational age was diagnosed in 3 infants in the indomethacin-treated and 2 in the control groups. There were 5 and 4 sets of twins identified in the indomethacin-treated and the control groups. In addition there were 2 and 3 sets of triplets in the indomethacin-treated and the control groups.

Neonatal data collected was birth weight, gestation age, sex, Apgar score at 5 minutes and mode of delivery. Data about the complications of prematurity were obtained which included respiratory distress syndrome (RDS), chronic lung disease (CLD), IVH, periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP) patent ductus arteriosus (PDA) and airleak syndrome. Data about the use of umbilical catheters were also recorded. Urine output, urea and creatinine in the first 4 days of life were collected. Maternal history included pregnancy-induced hypertension (PIH), the use of antenatal steroids and the use of magnesium sulfate. All radiological images were performed and read by pediatric radiologists who were not aware of this study.

For the purpose of this study, the gestational age was determined by antenatal ultrasound performed between 14 and 24 weeks, and date of last menstrual period. Respiratory distress syndrome was defined as a clinical respiratory distress with compatible radiological findings. Chronic lung disease was defined as an oxygen requirement beyond 36 weeks' corrected age with compatible radiological findings. The grading system used for intraventricular hemorrhage was: grade 1, blood in the periventricular germinal matrix regions; grade 2, blood within the lateral ventricular system without ventricular dilatation; grade 3, blood within and distending the lateral ventricles; and grade 4, blood within the ventricular system with parenchymal involvement. PVL was defined by identification of periventricular

Table 2 - Complications of prematurity.

	Indomethacin n=45	Controls n=33	p value
IVH (all grades)	8	14	0.022
PVL	1	3	0.330
ROP	18	9	0.209
PDA	9	11	0.185
RDS	44	29	0.079
CLD	23	8	0.018
NEC	11	7	0.791
Sepsis	32	18	0.147

cysts on serial ultrasound. ROP was defined by the clinical grading. The diagnosis of airleak was made if the infant experienced pneumothorax, pulmonary interstitial emphysema, pneumopericardium, or pneumomediastinum. Necrotizing enterocolitis was diagnosed when there was evidence of feeding intolerance, abdominal distention or positive blood in the stool with radiographic findings of pneumatosis intestinalis. Patent ductus arteriosus was diagnosed clinically and confirmed by echocardiogram. Sepsis was defined when blood culture was positive for bacteria in clinically ill infant.

Statistical methods used were Chi-square or Fishers exact for categorical data and t-test or Wilcoxon/Kruskal-Wallis test for continuous data, and P value less than 0.05 was considered significant. This study was approved by the Pediatric Research Committee at King Faisal Specialist Hospital and Research Centre.

Results. In Table 1, the birth weight and the gestational age was lower in the indomethacin-treated neonates in comparison to their controls and the differences were statistically significant (P=0.009, P=0.001). There was no statistically significant differences in Apgar score at 5 minutes between the 2 groups.

The overall incidence of IVH was lower in the indomethacin-treated neonates when compared to their controls (P=0.022), Table 2. There was one neonate who was diagnosed to have PVL in the control group. All neonates who were diagnosed to have RDS received surfactant therapy (Exosurf (Neonatal, The Wellcome Foundation Ltd, London, UK).

There were no statistically significant differences between the 2 groups in the incidence of RDS, PVL, NEC, ROP, PDA, sepsis, airleak syndrome and the rate of using umbilical catheters.

The incidence of CLD in the indomethacin-treated neonates was more than their controls and this was statistically significant (P=0.018). There were no statistically significant differences between the indomethacin-treated neonates and their controls in the rate of PIH (11 verses 21, P=0.226), and the use of antenatal steroids (22 verses 12, P=0.268) and magnesium sulfate (7 verses 2, P=0.959). There were also no statistically significant differences in the incidence of urine output between the groups in day 1, 3 and 4, however, urine output decreased significantly in day 2 in the indomethacin-treated group (P=0.034). There were no statistically significant differences in urea and creatinine between the 2 groups.

Discussion. Indomethacin is a synthetic indole derivative which may prevent IVH by several mechanisms. These mechanisms include inhibition of prostaglandin H synthase,[4] and prostacyclin receptor-mediated vasodilatation[5] inhibition of oxygen-free radical generation,[6] and promotion of germinal matrix microvessel maturation.[7]

Indomethacin, in this study, lowered the overall incidence of IVH in the indomethacin-treated neonates when compared to their controls who did not receive indomethacin for IVH prophylaxis.

The indomethacin-treated neonates were not matched exactly to their controls thus incidentally they were lower in weight and gestational age, which may pose them even at higher risk for IVH. In spite of the statistically significant difference in weight and gestational age, indomethacin appeared to be effective in the prevention of IVH. This low birth weight and low gestation in the indomethacin-treated neonates may explain the high incidence of CLD in this group.

Our results which show that indomethacin is effective in lowering the incidence of IVH are in agreement with previously reported studies. Ment et al[2] showed that 12% of indomethacin-treated neonates and 18% of placebo-treated neonates developed IVH (P=0.03).

More importantly severe IVH, such as grade 4, was nearly eliminated in the indomethacin-treated neonates.

The successful closure of PDA with indomethacin offers advantage to its use for the prevention of IVH.[8] In this study we found no statistically significant differences in terms of the incidence of PDA in the 2 groups.

The adverse side effects of indomethacin are the major concerns, which may limit its use in a routine basis in order to prevent IVH. These acute effects include renal insufficiency, decreased mesenteric blood flow, decreased cerebral blood flow and cerebral intracellular oxygenation, and impaired platelet aggregation.[9] Fowlie[10] demonstrates that prophylactic indomethacin reduces the incidence of grade 3 and 4 IVH, at the expense of 5 infants with renal complications and perhaps an increased number with necrotizing enterocolitis. In this study there was a significant decrease in urine output in day 2 in the indomethacin-treated group that was not accompanied by a change in urea and creatinine. Furthermore there was a concern that indomethacin may reduce cerebral blood flow and this may increase the risk for neurodevelopmental handicaps. Ment et al[11] showed that low dose indomethacin given for IVH prophylaxis in VLBW infants was not associated with adverse cognitive and motor outcome at 36 months' corrected age.

This study had limitations concerning the small number of recruited neonates and the design of the study which was a historical cohort.

The question arises that should indomethacin be given routinely to all neonates with a birth weight of 1250 gm or less? It is not adequate to use the birth

weight as the only risk factor for developing IVH to give prophylactic indomethacin. Although it was not an objective of this study, the use of indomethacin for IVH prophylaxis may be limited only for appropriate for gestational age neonates with a birth weight of less than 1250 gm who require mechanical ventilation.

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