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Original Articles

Outcomes of Prophylactic Indomethacin for Extremely Low Birth Weight Infants

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Abstract

Background: Prophylactic indomethacin (PI) administered to preterm infants has been shown to decrease severe intraventricular haemorrhage (IVH) and the need for surgical ligation of patent ductus arteriosus (PDA). The aim of this study was to compare the short-term and long-term outcomes of a PI-treated group (Indo group) with a recent retrospective, historical cohort (control group). ***Methods:*** We performed a retrospective review of 85 infants, 40 iodomethacin-treated and 45 untreated controls, born ≤28 weeks' gestation and weighing <1000 g. Short-term outcomes and neurodevelopmental outcomes at 24 months of corrected age were compared between the two groups. ***Results:*** Severe IVH was less in the Indo group (7.5%) than in the control group (13.3%), but this difference did not reach statistical difference (*P*=0.38). The occurrence of significant PDA was significantly lower in the Indo group (30%) compared to the control group (51%) (*P*=0.04). Patients who received PI experienced a decreased PDA surgical ligation rate (control group = 35.6%, Indo group = 12%; *P*=0.01). This statistical difference persisted even after logistic regression analysis (*P*=0.04). At 2 years, no significant differences were found between the groups in terms of Mental development index and the psychomotor development index scores <70, the incidence of cerebral palsy, neurodevelopmental impairment, or composite outcomes. ***Conclusion:*** PI decreased surgical PDA in preterm infants. However, PI did not cause an improvement in neurodevelopmental outcomes once these children reached 2 years. PDA may play a limited role in the multifactorial factors in the causation of neurodevelopmental impairment of preterm infants.

Key words Extremely low birth weight infant; Indomethacin prophylaxis; Intraventricular haemorrhage; Patent ductus arteriosus; Premature infant

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Introduction

Despite improvements in the survival for extremely low birth weight infants (ELBWI), intraventricular haemorrhage (IVH) and patent ductus arteriosus (PDA) remain common morbidities in this vulnerable population. The tendencies for developing both diseases are inversely related to gestational age (GA) and birth weight (BW) in preterm infants. The incidence of IVH has shown no further decline over the past decade.[1] Currently, IVH occurs in 20% to 25% of very low birth weight infants and it is found at an even higher prevalence in the ELBWI.[1] Preterm infants with severe IVH are at high risk of neurodevelopmental impairment and mortality.[1] For ductus arteriosus, although spontaneous closure occurs in approximately 34% of ELBWI,[2] 55-70% of these infants ultimately require pharmacological treatment or surgical ligation.[3-5] An untreated haemodynamically significant PDA is associated

with pulmonary haemorrhage, bronchopulmonary dysplasia (BPD), necrotising enterocolitis (NEC), IVH, and death.[6] Despite the significant morbidities associated with IVH and PDA, few safe and effective preventative therapies are available. This unmet need led to the use of pharmacologic and care-oriented prevention strategies to reduce complications associated with IVH and PDA in preterm infants.[7]

Indomethacin is a prostaglandin synthesis inhibitor that has long been used to treat haemodynamically significant PDA in preterm infants. Intravenous administration of indomethacin also has been used prophylactically to prevent IVH through the effects on cerebral blood flow and basement membrane maturation. A meta-analysis of 19 randomised controlled trials (RCTs) revealed that prophylactic indomethacin has a number of short-term benefits, including a reduction of severe IVH and the need for surgical ligation of a PDA.[8] However, almost all RCTs in the meta-analysis were conducted in the 1990s or earlier, these may not be entirely applicable to the clinical situation of the modern era. Furthermore, the long-term neurodevelopmental benefit of indomethacin treatment has been more controversial.[8] Therefore, the aim of this study was to analyse the neonatal outcomes of prophylactic indomethacin for ELBWI at our institution, comparing them with those obtained from a retrospective, historical cohort. To our knowledge, this was the first study of intravenous prophylactic indomethacin with long-term follow up for preterm infants in Chinese population.

Materials and Methods

This retrospective cohort study was performed at a single, regional referral level III neonatal intensive care unit of Hsinchu Mackay Memorial Hospital (Hsinchu, Taiwan), with approximately 25 ELBWI admissions each year. The medical charts of all ELBWI from January 2006 and December 2009 were retrospectively reviewed. ELBWI born between January 2006 and December 2007 who received prophylactic indomethacin formed the Indo-study group. The control group included infants born between January 1, 2008 and December 31, 2009 as a historical cohort since indomethacin was not imported into Taiwan during this period. We decided that in stock indomethacin was only used for treatment of haemodynamically significant PDA from 2008. We excluded infants with congenital anomalies, a cyanotic congenital heart lesion, or lack of at least one cranial ultrasound performed. Clinical nursing management, mode of ventilation, adjustment of ventilator settings, fluid administration, and nutrition policy were not altered during the different study periods. The study was approved by our institutional review board.

In the Indo group, infants received indomethacin (Indocid P.D.A., Merck Frosst, Kirkland, Que., Canada, and Merck, West Point, Pa.) 0.1 mg/kg/dose intravenously beginning at 6-24 hours of life once every 24 hours for a total of three doses without prior echographic confirmation of IVH or PDA. Neonates did not receive indomethacin if they had any contraindications including thrombocytopaenia (platelet count <50,000/mL), coagulopathy, and oliguria in the first 6 hours of life.

The following intrapartum and demographic variables were collected: mother's age and education level, antenatal steroids, chorioamnionitis, prolonged rupture of membranes (PROM), inborn, mode of delivery, multiple birth, GA, BW, gender, first- and fifth-min Apgar scores, and resuscitation in the delivery room (DR). In our institution, indomethacin was not used as a tocolytic agent.

Outcomes

Adverse events in the first 3 days of life associated with indomethacin use were collected including oliguria (urine output <1 cm^3/kg/hour), spontaneous intestinal perforation or NEC, hypernatraemia (>150 mEq/L), and hyperbilirubinemia requiring a blood exchange transfusion. NEC was diagnosed using Bell's criteria.[9] Major clinical outcomes such as mortality, IVH, symptomatic PDA requiring medical and/or surgical treatment, and pulmonary haemorrhage were analysed. In-hospital mortality was calculated for deaths before discharge. Routine cranial ultrasounds were performed, by a single pediatric neurologist, within the first 3 days of life, on days 7 and 28 of life, and between 34 and 36 weeks of postmenstrual age. IVH was graded according to Papile et al,[10] and grades III or IV IVH were defined as severe. Additional ultrasounds were obtained based on the clinical judgment of the attending physician. PDA was diagnosed by echocardiography and Doppler flow studies, which were requested based on the clinical suspicion of the condition by the attending physician. Left-to-right ductal shunting and ductal size had to be confirmed before any therapy decision was undertaken. A ductus was considered symptomatic if clinical signs (heart murmur, heart failure, bounding pulses with wide pulse pressure, worsening respiratory status attributable to PDA) persisted. A haemodynamically significant PDA was considered if

patients had the above symptoms with echocardiographic evidence of ductal size >1.5 mm/kg, left atrial/aortic root ratio >1.4, and left-to-right shunting. Fluid restriction to 100-120 ml/kg/d was performed on all patients with significant PDA. Indomethacin was the only rescue drug used for duct closure during the study period and was started at a dose of 0.2 mg/kg intravenously and repeated at 12 and 24 hours. The maximal course of rescue indomethacin for duct closure was one course in the Indo group and two courses in the control group. Surgical ligation was reserved for infants who had a significant PDA that failed pharmacologic therapy or under very limited circumstances (massive pulmonary haemorrhage or contraindication of indomethacin use). Pulmonary haemorrhage was diagnosed if a blood-tinged tracheal aspirate was noted.

Additional data collected include respiratory distress syndrome requiring surfactant therapy, pneumothorax, duration on ventilatory and oxygen support, BPD, NEC, post-haemorrhagic hydrocephalus, sepsis, severe retinopathy of prematurity (ROP), cystic periventricular leukomalacia (cPVL), and length of stay.

Long-term Outcomes

Neurological examination and developmental outcomes were assessed at a corrected age of 24 months, but the protocol allowed a window of 23 to 25 months. The Bayley Scales of Infant Development-Second Edition (BSID-II) was the only tool to assess developmental outcomes during the study period. The assessments were performed by a single trained psychologist. Mental development index (MDI) and the psychomotor development index (PDI) scores were collected. Neurodevelopmental impairment (NDI) was defined as the presence of any of the following: cerebral palsy (CP), hearing loss requiring amplification in both ears, blindness in both eyes, MDI or PDI lower than 70.[11] Hydrocephalus, requiring the placement of a shunt, and seizure disorder were also recorded. Composite outcomes of NDI and death were compared between groups.

Statistical Analysis

Categorical data were analysed using the standard χ^2 test and Fisher's exact test. Continuous data were analysed using the independent t-test and the nonparametric Wilcoxon rank sum test for between-group comparisons, where appropriate. Multivariate analyses were performed using the logistic regression model to identify the implication of indomethacin usage to the short- and long-term outcomes. Perinatal variables including BW, multiple births, PROM, chorioamnionitis, complete antenatal steroids, DR resuscitation, cesarean section, maternal education level, and sex, were included in the logistic regression models to identify the variables significantly associated with those outcomes. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were computed for all outcomes. The correlation between continuous variables and prophylactic indomethacin were analysed using linear regression models. All statistical analyses were performed using SAS 9.2. Statistical significance was defined as $P<0.05$. All P values in this analysis were of the two-sided type.

Results

During the 4-year study period, 90 infants meeting the GA and BW criteria were hospitalised in our unit. Five infants (2 in the Indo group and 3 in the control group) were excluded due to early death without any cranial ultrasound examination. Our study population consisted of 40 ELBWI who received indomethacin prophylaxis and 45 ELBWI who served as a control group. Infants in these two groups were comparable in intrapartum and demographic characteristics (Table 1). Prophylactic indomethacin was given at the mean age of 9.3±4.8 hours (range 6 hours to 20 hours) in the Indo group. All infants received 3 complete doses.

Neonatal Outcomes

Neonatal short-term outcomes are presented in Table 2. IVH of all grades did not differ between the two groups. Severe IVH was numerically lower in the Indo group (7.5%) than in the control group (13.3%) (P=0.38). Of the 9 neonates who developed severe IVH, 5 (56%) died; including 1 in the Indo group (1/3, 33%) and 4 in the control group (4/6, 67%).

Echocardiography was performed on 36/40 (90%) of the indomethacin-treated and 37/45 (82%) of the control neonates. Figure 1 illustrates the treatment of PDA. The incidence of PDA was significantly decreased in Indo group (30%) as compared to the control group (51%) (P=0.04). However, logistic regression analysis showed that after controlling for confounding variables, the significance disappeared (P=0.08). For those neonates with significant PDA, 11 in the Indo group and 17 in the control group received intravenous indomethacin for closure of PDA. This rescue indomethacin was administered at 7±6 and 8±7 postnatal days for the Indo and control group, respectively. The incidence and timing of the one required course of

Table 1 Characteristics of study population

	Indo group No./total no. (%)	Control group No./total no. (%)	*P* value
Mother's age	29.7±4.3	29.2±5.8	0.70
Maternal education (≥college)	27/40 (67.5)	31/45 (68.9)	0.89
Antenatal steroids	35/40 (87.5)	45/45 (86.7)	0.89
Clinical chorioamnionitis	1/40 (2.5)	3/45 (6.7)	0.62
PROM >18 hours	10/40 (25.0)	10/45 (22.2)	0.76
Inborn	34/40 (85.0)	39/45 (86.7)	0.83
Cesarean section	23/40 (57.5)	22/45 (48.9)	0.43
Singleton birth	33/40 (82.5)	37/45 (82.2)	0.18
GA, week (mean±SD)	26.3±1.4	25.9±1.6	0.26
BW, gm (mean±SD)	861±134	848±128	0.65
BW <10th percentile for GA	1/40 (2.5)	2/45 (4.4)	1.00
Male	21/40 (52.5)	23/45 (51.1)	0.90
Apgar score at 1 minute, <7	29/40 (72.5)	34/45 (75.6)	0.99
Apgar score at 5 minutes, <7	9/40 (22.5)	10/45 (22.2)	0.90
DR resuscitation	5/40 (12.5)	4/45 (8.9)	0.73

BW, birth weight; DR, delivery room; GA, gestational age; PROM, prolonged rupture of membranes.

Antenatal steroids was defined as any doses of betamethasone given before delivery. Clinical chorioamnionitis was diagnosed if the mother had fever, uterine fundal tenderness, and foul amniotic fluid. DR resuscitation was defined as chest compressions plus or minus medications.

Table 2 Short-term outcomes of the two study groups

	Indo group	Control group	Adjusted for BW stratum		Adjusted for other factors†	
	No./total no. (%)	No./total no. (%)	OR (95% CI)	*P* value	OR (95% CI)	*P* value
All IVH	8/40 (20)	15/45 (33.3)	0.45 (0.17-1.20)	0.11	0.53 (0.15-1.85)	0.32
Severe IVH (≥Gr 3)	3/40 (7.5)	6/45 (13.3)	0.52 (0.12-2.25)	0.38	0.51 (0.07-3.84)	0.51
Significant PDA	12/40 (30)	23/45 (51.1)	0.40 (0.16-0.98)	0.04	0.40 (0.14-1.11)	0.08
PDA need medical treatment	11/40 (27.5)	17/45 (37.8)	0.62 (0.24-1.55)	0.30	0.69 (0.24-1.97)	0.49
PDA ligation	5/40 (12.5)	16/45 (35.6)	0.24 (0.07- 0.74)	0.01	0.28 (0.08- 0.99)	0.04
Pulmonary haemorrhage	5/40 (12.5)	12/45 (26.7)	0.41 (0.13-1.29)	0.13	0.56 (0.16-2.03)	0.38
Mortality	8/40 (20)	12/45 (26.7)	0.77 (0.25-2.33)	0.64	0.97 (0.21- 4.42)	0.97
RDS need surfactant	33/40 (82.5)	39/45 (86.7)	0.75 (0.23-2.47)	0.63	0.72 (0.19-2.67)	0.62
Pneumothorax	3/40 (7.5)	5/45 (11.1)	0.71 (0.15-3.29)	0.66	1.19 (0.19-7.26)	0.85
Oxygen at 36 weeks*	19/32 (56.3)	24/35 (65.7)	0.50 (0.16-1.52)	0.22	0.53 (0.11-2.51)	0.42
Post-haemorrhagic hydrocephalus	1/40 (2.5)	3/45 (6.7)	0.32 (0.03-3.28)	0.34	2.00 (0-78.0)	1.00
NEC ≥stage 2	1/40 (2.5)	2/45 (4.4)	0.57 (0.05-6.59)	0.65	0.48 (0-6.14)	0.57
Sepsis	8/40 (20)	11/45 (24.5)	0.84 (0.29-2.42)	0.74	0.85 (0.26-2.78)	0.79
ROP ≥stage 3*	5/32 (6.3)	6/35 (14.3)	0.26 (0.06-1.09)	0.07	0.25 (0.05-1.24)	0.09
cPVL*	6/32 (15.6)	3/35 (5.7)	2.36 (0.53-10.57)	0.26	2.27 (0.27-19.48)	0.45

CI, confidence interval; cPVL, cystic periventricular leukomalacia; IVH, intraventricular haemorrhage; NEC, necrotizing enterocolitis; OR, Odds Ratio; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity.

*In survivors examined.

†Co-variates included in the logistic regression included BW, multiple birth, PROM, chorioamnionitis, complete antenatal steroids, DR resuscitation, cesarean section, and sex.

RDS was diagnosed as the radiographic findings and surfactant was delivered if ventilatory oxygen requirements were greater than 40%. Post-haemorrhagic hydrocephalus was diagnosed with evidence of ventricular dilatation. cPVL was defined as parenchymal cystic changes around the ventricles. Sepsis was confirmed by a positive blood culture with clinical symptoms of infection.

indomethacin for ductal closure did not differ between two groups. In the control group, 8 infants need repeated course of indomethacin. Four patients in the Indo group and 11 patients (5 after one course indomethacin, 6 after two courses indomethacin) in the control group failed on the indomethacin treatment regimen and required subsequent surgical ligation. Successful responses to indomethacin treatment were observed in 64% (7/11) of patients in the Indo group and 35% (6/17) of those in the control group. Owing to bleeding tendency and/or massive pulmonary haemorrhage, 1 (8.3%) infant from the Indo group and 5 (10%) from the control group underwent surgical ligation of PDA directly without indomethacin treatment. One patient in the control group with significant PDA died before any treatment was offered. The infants received surgery, on average, at 15±10 and 17±10 postnatal days for Indo and control groups, respectively. The overall surgical ligation rate was 12% (5/40) for the Indo group vs. 35.6% (16/45) for the control group (P=0.01). This statistical difference persisted even after logistic regression analysis, which controlled for confounders (P=0.04).

Seventy-seven of all 95 neonates survived during the first 28 days. There were no differences in the causes of death between the two groups (20% (8/40) for the Indo group vs. 22.2% (10/45) for the control group). Late deaths attributed to BPD complicated with cor pulmonale occurred in 2 infants in the control group. Neonatal deaths prior to hospital discharge occurred in 21% (20/95) of all study infants. Clinical characteristics such as respiratory distress syndrome, pneumothorax, BPD, sepsis, the total days of oxygen therapy and mechanical ventilation, and the length of intensive care unit stay, and hospital stay did not differ between groups. Cranial ultrasound studies and indirect ophthalmoscopy for retinopathy were available at 36-40 weeks post-menstrual age for 32 neonates in the Indo group and 35 neonates in the control group. A numerically higher incidence of cPVL was noted among infants the Indo group (15.6%), but this difference did not reach statistical significant when compared to the incidence in the control group (5.7%). In terms of adverse drug events, the rates of NEC, spontaneous intestinal perforation, thrombocytopaenia, and hypernatraemia were similar between both groups. Oliguria had a numerically higher incidence in the Indo group (37.5%) than in the control group (22.2%), but this difference did not reach statistical difference (P=0.09). No patient had hyperbilirubinemia requiring a blood exchange transfusion during the study period.

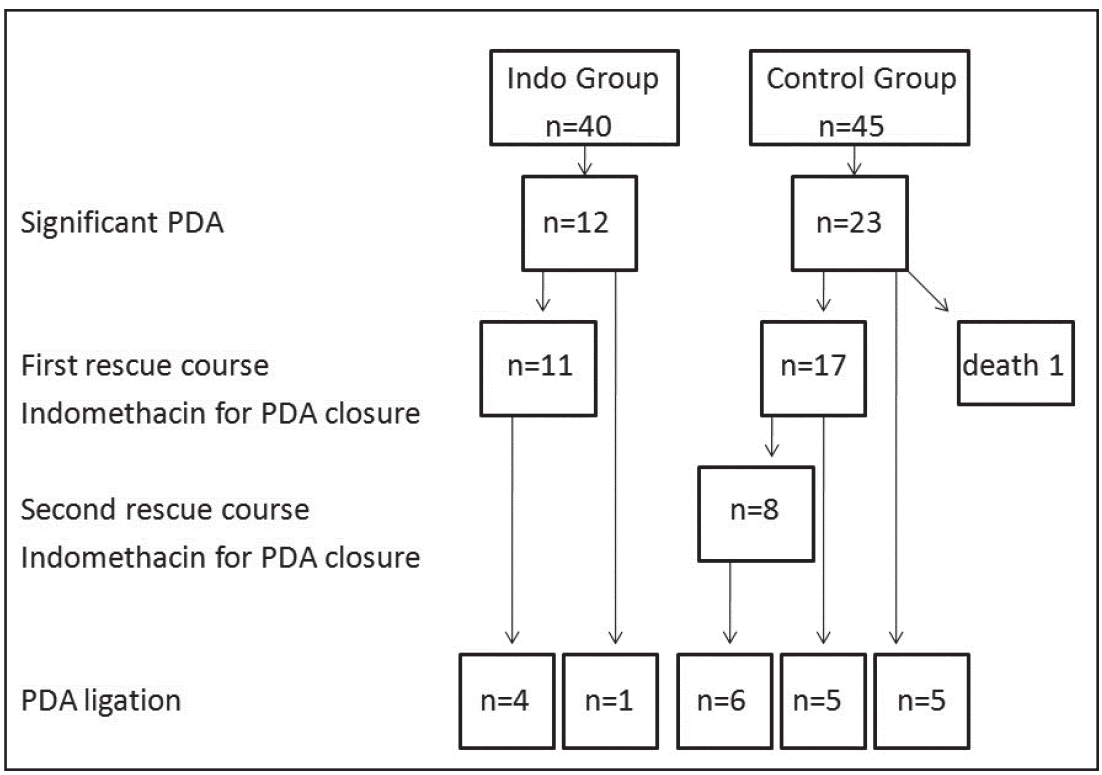

Figure 1 Patent ductus arteriosus treatment in indomethacin-treated and control groups.

Outcome at a Corrected Age of 24 Months

Thirty-two infants from the Indo group and 33 infants from the control group survived to a corrected age of 24 months. Four infants in each group were lost to follow up. The follow-up rate was 87.5% (28/32) in the Indo group and 87.9% (29/33) in the control group. The infants were assessed at a mean age of 23.4±1.3 months of corrected age. Indomethacin prophylaxis did not alter the rates of any of the neurosensory outcomes evaluated (Table 3). The mean MDI score was 92±18 in the Indo group and 87±16 in the control group. The mean PDI score was 83±16 in the Indo group and 84±15 in the control group. No significant differences were found between the groups in terms of mean MDI or PDI scores (P>0.05). Adjustments for important base-line characteristics all yielded insignificant P values in the long-term outcomes.

Discussion

The fragile cerebral vasculature of the ELBWI is at risk for rupture. One half to three quarters of infants who have severe IVH develop CP in childhood.[12] Indomethacin remains the most common pharmacologic intervention for prevention of IVH and has been used for decades. However, its mechanism of action on the cerebral vasculature is not completely understood. The use of indomethacin prophylaxis in the National Institute of Child Health and Human Development (NICHD) network increased after the multicentre randomised trial in 1994 by Ment et al, which reported a significant decrease in all forms of IVH.[13,14] A systematic review of RCTs also showed that prophylactic indomethacin significantly reduced the incidence of serious IVH by 35%.[8] The failure to detect a significant difference in our study may be explained by the small sample size, which indicated that the study might have been inadequately powered to detect small differences between the study groups. No improvement of IVH has been observed in other previous indomethacin prophylaxis studies.[15-17]

Although there was strong evidence to show a decreased incidence of severe IVH in infants treated with indomethacin prophylaxis in other RCTs, this positive effect did not translate into an improvement of the long-term outcomes.[18,19] The use of indomethacin prophylaxis in the

Table 3 Long-term outcomes of the two study groups in survivors

	Indo group No./total no. (%)	Control group No./total no. (%)	Adjusted for BW stratum Odds ratio (95% CI)	*P* value	Adjusted for other factors[§] Odds ratio (95% CI)	*P* value
Seizure disorder	1/28 (3.6)	2/29 (6.9)	0.42 (0.04-4.99)	0.49	--*	--*
Hydrocephalus need shunt	1/28 (3.6)	1/29 (3.4)	0.89 (0.05-14.96)	0.93	-- *	--*
BSID-II MDI <70	2/28 (7.1)	4/29 (13.8)	0.40 (0.07-2.41)	0.32	0.71 (0.08-6.12)	0.89
BSID-II PDI <70	8/28 (28.6)	9/29 (27.6)	1.10 (0.33-3.61)	0.88	1.05 (0.25-4.41)	0.95
Bilateral blindness	1/28 (3.6)	0/29 (0)	0.89 (0.02-35)	1.00	-- *	-- *
Severe hearing impairment	0/28 (0)	1/29 (3.4)	0.89 (0.00-34.67)	0.94	-- *	-- *
Moderate to severe cerebral palsy	6/28 (21.4)	4/29 (13.8)	1.43 (0.30-5.83)	0.62	1.18 (0.18-7.60)	0.86
NDI[†]	9/28 (32.1)	8/29 (27.6)	1.29 (0.40-4.18)	0.67	1.03 (0.25-4.31)	0.97
Death or NDI[‡]	17/36 (47.2)	20/41 (48.8)	1.20 (0.46-3.13)	0.71	1.34 (0.44-4.08)	0.61

BSID-II, Bayley Scales of Infant Development-Second Edition; OR, Odds Ratio; CI, confidence interval; MDI, mental development index; NDI, neurodevelopment impairment; PDI, psychomotor development index.

*Data for this outcome was unable to adjust because there were too few events.

[†]NDI defined as any of MDI <70, PDI <70, blindness, hearing impairment, or cerebral palsy

[‡]Data for this outcome exclude infants who were lost to follow-up

[§]Co-variates included in the logistic regression included BW, multiple birth, PROM, chorioamnionitis, complete antenatal steroids, maternal education level, DR resuscitation, and sex.

Moderate to severe cerebral palsy was diagnosed when the child had nonprogressive motor impairment characterized by abnormal muscle tone and abnormal control of movement or posture. Audiometry was performed to determine the presence or absence of hearing loss. Blindness was defined as a corrected visual acuity of <20/200.

NICHD network significantly decreased since the Trial of Indomethacin Prophylaxis in Preterm Infants (TIPP) study showed no difference at 18 months in mortality or severe neurosensory impairment.[13,19,20] Our study also confirms indomethacin prophylaxis did not affect neurodevelopment and composite outcomes at 2 years' corrected age. There are some possible reasons why prophylactic indomethacin did not improve long-term outcomes. First, the etiology neurodevelopment impairment is multifactorial. Severe IVH is only one of these factors but its causal role in long-term impairment is not clear. Second, gene expression may alter the efficacy of prophylactic indomethacin. The COX-2 C765 allele in preterm infants has been associated with their decreased cognitive performance at ages 2 and 5.5 years when compared with their G-allele peers.[21] The existence of this gene in our population is still unknown. Furthermore, gender should be considered when evaluating whether to use prophylactic indomethacin in ELBWI. Ment and colleagues found the rate of IVH was significantly reduced in male neonates treated with indomethacin as compared to females.[22] In addition, boys treated with indomethacin performed significantly better on the verbal scores at 3 to 8 years' corrected age when compared with boys treated with placebo.[22] However, using multiple regression analysis, our data did not reveal the association of the effect of indomethacin with gender.

Prophylactic indomethacin for IVH co-evolved with efforts to effectively treat PDA.[8] The present study reconfirmed that early indomethacin prophylaxis reduces both the incidence of clinical significant PDA and the need for surgical ligation. The incidence of PDA ligation observed in the current study (total 22%, 21/95) is relative high, especially in the control group (36%). It is known that the incidence of surgical PDA varies widely between different institutions. However, in this study, the decision of surgical ligation during both study periods was made by the same attending physicians using the same criteria. Otherwise, the higher incidence of PDA ligation in our study might be due to the low success rate from the rescue indomethacin treatment, which was 64% of Indo group and 35% of control infants. The reported response rate to indomethacin treatment for symptomatic PDA is 60% to 80% in premature infants of GA 24-32 weeks.[23] The decreasing efficacy and higher recurrence rates are found in the most immature infants, especially in infants less than GA 26 weeks.[3,24] The low indomethacin response rate in our study (total 46%, 13/28) has also been observed in other investigators for infants with similar GA.[16] Surgical ligation of PDA is not only associated with significant morbidities, most importantly, it is linked with risk for poor developmental outcomes as reported in a recent TIPP study.[25] Therefore, surgical ligation should be considered as a last option in infants that do not respond to pharmacologic therapy.

Intravenous indomethacin therapy in preterm infants has caused concern due to increases in the incidence of NEC, spontaneous intestinal perforation, and ROP. In the present study, these diseases occurred with a low frequency in both groups. The cerebral vasoconstriction effects of indomethacin and the possible risk of brain ischemia are frequent concerns of neonatologists.[26,27] Some groups have proposed that indomethacin may be neuropathologic because it blocks COX activity with a resulting inhibition in production of the neuroprotective prostaglandin E_2.[21] Our study revealed an increased incidence of cPVL in the indomethacin-treated group. However, an association between indomethacin use and decreased white matter lesions has been found in magnetic resonance imaging studies.[28,29] Systematic review of the literature also did not find indomethacin prophylaxis to cause an increase in the incidence of cPVL.[8] The relationship of indomethacin prophylaxis and brain ischemia still needs to be clarified. No other adverse effects and long term brain damage are found more often in patients who received prophylactic indomethacin versus control in our study. Generally, prophylactic indomethacin is safe and without clinically significant adverse effects for ELBWI.

Our study is limited by its relative small sample size. The data also should be interpreted with caution due to the retrospective nature of the study. Although we attempted to eliminate potential confounding variables, several limitations still existed. First, we did not perform cranial ultrasound routinely before giving prophylactic indomethacin. Therefore, infants with preexisting IVH at the time of treatment were not identified. Second, since IVH develops most frequently during the first few hours of life, giving the drug as early as possible may be more effective than giving it in later life. Our initial dose of indomethacin was administered at 6-24 hours of life as recommendation in most RCTs. A recent study also reported that prophylactic indomethacin administered before 6 hours of life was not associated with lower incidence of IVH.[30] Chorioamnionitis has been reported as a risk factor for poor pulmonary and neurosensory outcomes in ELBWI. Our diagnosis of chorioamnionitis was based on chart documentation without histological studies. Clinical diagnosis chorioamnionitis in this fashion is somewhat insensitive and may have contributed to its low

incidence in our study. Otherwise, herbal mixtures are frequently consumed by pregnant mothers in Chinese population. Many herbal mixtures may contain some Western medicines such as asprin. How these herbal mixtures might affect the outcomes of preterm infants is still unknown. Furthermore, longer follow up may be needed in these infants since favourable neurodevelopmental outcomes have been reported in 4- and 8-year-old children who were treated with indomethacin prophylaxis at birth.[22,31]

In summary, the present study described a clinical experience during a recent period in Taiwan. We have shown a significant association between indomethacin prophylaxis and decreasing symptomatic and surgical PDA and we have further identified the safety of this treatment. In addition, indomethacin prophylaxis has not been shown to affect the neurodevelopment outcomes at a corrected age of 2 years in our experience. Given our findings, we suggest indomethacin prophylaxis is only indicated in units where the incidence of significant PDA and surgical PDA are very high. Our findings also suggest PDA may play only a limited role in the multifactorial causation of NDI in current practices. More research is needed to determine which factors are independently related to the risk of neurodevelopmental deficit and how to improve long-term outcomes in ELBWI.

Conflict of Interest Statement

We declare that we have no conflict of interests.

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