Prophylactic Intravenous Ketorolac for Prevention of Intraventricular Hemorrhage in Preterm Infants ≤ 32 Weeks and < 1500 Grams: A Double-Blind, Randomized, Placebo-Controlled Trial

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ABSTRACT

Intraventricular hemorrhage (IVH) remains an important cause of morbidity and mortality in Very Low Birth Weight (VLBW) infants. Since 2004, Indomethacin, which is effective in preventing IVH, has been removed from the Philippine market. Ketorolac is a nonselective cyclooxygenase inhibitor which is structurally-related and of equal potency to Indomethacin.

Objective. This study aims to determine if prophylactic ketorolac compared to placebo will decrease IVH and its associated morbidities among preterm neonates.

Methods. We conducted a double-blind, randomized, placebo-controlled trial among neonates born in a tertiary government university hospital. Newborns with gestational age ≤32 weeks and birth weight <1500 g were eligible for inclusion. Participants were randomized to either ketorolac (0.5 mg/kg, at 6-12 hours of life, followed by 0.5 mg/kg after 24 and 48 hours) or placebo. Randomization concealment was maintained using sealed opaque envelopes. Cranial ultrasonography was performed on postnatal day 2 and 7, and at 36 to 40 weeks postconceptional age. IVH at postnatal day 7 was the outcome of interest. Adverse effects and complications were monitored and recorded.

Results. A total of 134 infants were included in the study. There was no difference in the proportion of infants who developed IVH between the ketorolac and placebo groups (46% vs. 45%). The mean serum creatinine levels were significantly higher in the ketorolac group (1.15 ± 0.69 vs. 0.79 ± 0.38; p = 0.002). The rates of death, sepsis, necrotizing enterocolitis, bleeding, platelet counts of <50,000/mm3, mean urine output and the lengths of hospital stay were similar in the two groups.

Conclusion. Prophylactic intravenous ketorolac was ineffective in preventing IVH among preterm infants. Ketorolac cannot be recommended for the prevention of IVH.

Key Words: intraventricular hemorrhage, ketorolac, preterm, infants

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Introduction

Despite advances in neonatal critical care, intraventricular hemorrhage (IVH) remains an important cause of morbidity and mortality in very low birth weight (VLBW) infants. The fragile blood vessels in the germinal matrix and the instability of blood flow are the main mechanisms behind IVH.[1] It occurs in 20 – 25% of VLBW preterm infants and is associated with significant short- and long-term sequelae.[2] Infants with IVH are at risk for both post-hemorrhagic hydrocephalus and periventricular leukomalacia, while those with parenchymal involvement may suffer significant neurodevelopmental disability at follow-up.[3] Due to its high prevalence and significant impact on function, several pharmacologic and care-oriented prevention strategies have been explored. These include muscle paralysis, phenobarbital, Vitamin E, indomethacin, ethamsylate and surfactant. Of these, investigations have shown that low dose indomethacin given at 6-12 postnatal hours and every 24 hours for two more doses decreases the incidence of all grades of IVH within the first 5 days of life.[4] This protective effect has been attributed to the ability of indomethacin to diminish carbon dioxide (CO_2) reactivity of cerebral blood vessels and decrease cerebral blood flow through its inhibition of cyclooxygenase.[4,5,6,7]

In the Philippines, IVH remains a significant cause of mortality and neurodevelopmental disability. In the University of the Philippines-Philippine General Hospital (UP-PGH), the incidence is 13% with a case fatality rate of 65% among very low birth weight (VLBW) infants. Since 2004, indomethacin has been removed from the Philippine market due to low demand. Ketorolac, a nonselective cyclooxygenase inhibitor structurally-related and of equal potency to indomethacin, has been explored in a study involving four healthy adults. Results suggest that a single administration of ketorolac causes a small but significant decrease in cerebral CO_2 reactivity.[8] Along with its low cost and availability, this makes ketorolac a potential alternative to indomethacin for the prevention of IVH.

This clinical trial aims to determine if prophylactic ketorolac compared to placebo will decrease IVH and its associated morbidities among preterm infants.

Methods

We conducted a double-blind, randomized, placebo-controlled trial in the Neonatal Intensive Care Unit (NICU) of the UP-PGH, a tertiary government university hospital.

Study Population

We included neonates delivered at the PGH with gestational age ≤32 weeks and birth weight <1500 g. We excluded patients with fatal congenital malformations, unstable hemodynamics, platelet count of < 50,000 platelets/mm3, or tendency to bleed (blood in the endotracheal aspirate, gastric aspirate, urine or stools, or oozing from puncture sites). We recorded birth weight, gestational age, sex, antenatal administration of steroids, tocolysis, duration of ruptured amniotic membranes, Apgar scores, maternal age and risk factors, manner of delivery, and the presence of respiratory distress syndrome.

Study Procedure

After obtaining informed consent from the parents, we randomized patients into one of two treatment groups. Participants in the ketorolac group were given the study drug at a dose of 0.5 mg/kg, at 6-12 hours, followed by 0.5 mg/kg after 24 and 48 hours. The placebo group received an equivalent amount of normal saline as placebo. A neonatal nurse not directly involved with patient care prepared the study drugs. The randomization schedule was prepared by a third party who was not involved in the care of the patients. We concealed randomization assignments using sealed opaque envelopes.

The parents, care providers (physicians and nurses), investigators and outcome assessors were blinded to the participants' randomization assignment and treatment status.

Echoencephalographic Studies

All participants underwent serial cranial ultrasonography conducted by a neurologist blinded to the participants' treatment status. Ultrasonography was performed on postnatal day 2 and 7. Follow-up ultrasound was done as necessary among those who developed IVH. All participants underwent a follow-up cranial ultrasound between 36 to 40 weeks postconceptional age to evaluate for the presence of periventricular leukomalacia (PVL) and post-hemorrhagic hydrocephalus (PHH). The images were obtained in both coronal and sagittal projections through the anterior fontanel. The grading system for hemorrhage was adapted from that described by Papile as follows: grade 1, blood in the periventricular germinal matrix regions or germinal matrix hemorrhage; grade 2, blood within the lateral ventricular system without ventricular dilation; grade 3, blood acutely distending the lateral ventricles; grade 4, blood within the ventricular system and parenchyma.[9] Hemorrhage was considered to have extended if an intraventricular or parenchymal component developed from a germinal matrix hemorrhage or a second hemorrhage developed in the hemisphere contralateral to an existing hemorrhage. PVL was defined in this study as focal necrosis with subsequent cystic formation of white matter surrounding the cerebral ventricles. PHH was defined in this study as the progressive post-hemorrhagic ventricular dilatation.

Evaluation for Adverse Effects of Ketorolac

Fluid intake and urine output were monitored continuously during the first week. Serum creatinine level and platelet count were determined after the 7th postnatal day. Renal insufficiency was defined as oliguria (urine output <1 cc/kg/hr) and elevated serum creatinine level. We took note of active bleeding (e.g., hematuria, gastric bleeding, blood in the endotracheal aspirate and oozing from puncture sites). Participants were worked-up for suspected necrotizing enterocolitis (abdominal radiographs and fecal occult blood). Signs of feeding intolerance (number and volume of gastric residuals) were monitored.

Statistical Analysis

The outcome of interest was IVH at post-natal day 7. To detect a 15% difference in IVH between the placebo and treatment groups, adopting a type I error of 0.05 and a type 2 error of 0.20 (power of 0.80), a sample size of 67 in each group was needed.

Statistical analyses were performed using STATA 11.1. Chi-square test was used to determine if the difference in the proportion of those who developed IVH among the treatment groups was significant. The students T-test was used to determine if the difference in baseline continuous variables were statistically significant and the chi-square test was used to determine if the proportions of baseline categorical variables were statistically significant. A p-value of less than 0.05 was considered statistically significant.

Prior to data collection, the study protocol was reviewed and approved by the University of the Philippines Research Ethics Board.

Results

A total of 277 patients was considered for inclusion in this trial. One hundred forty-three were excluded and 134 infants were randomized (Figure 1). Sixty-seven infants were randomized to both the ketorolac and placebo groups. Both groups had comparable baseline maternal and obstetric factors (Table 1). Both groups likewise had comparable baseline clinical characteristics (Table 1).

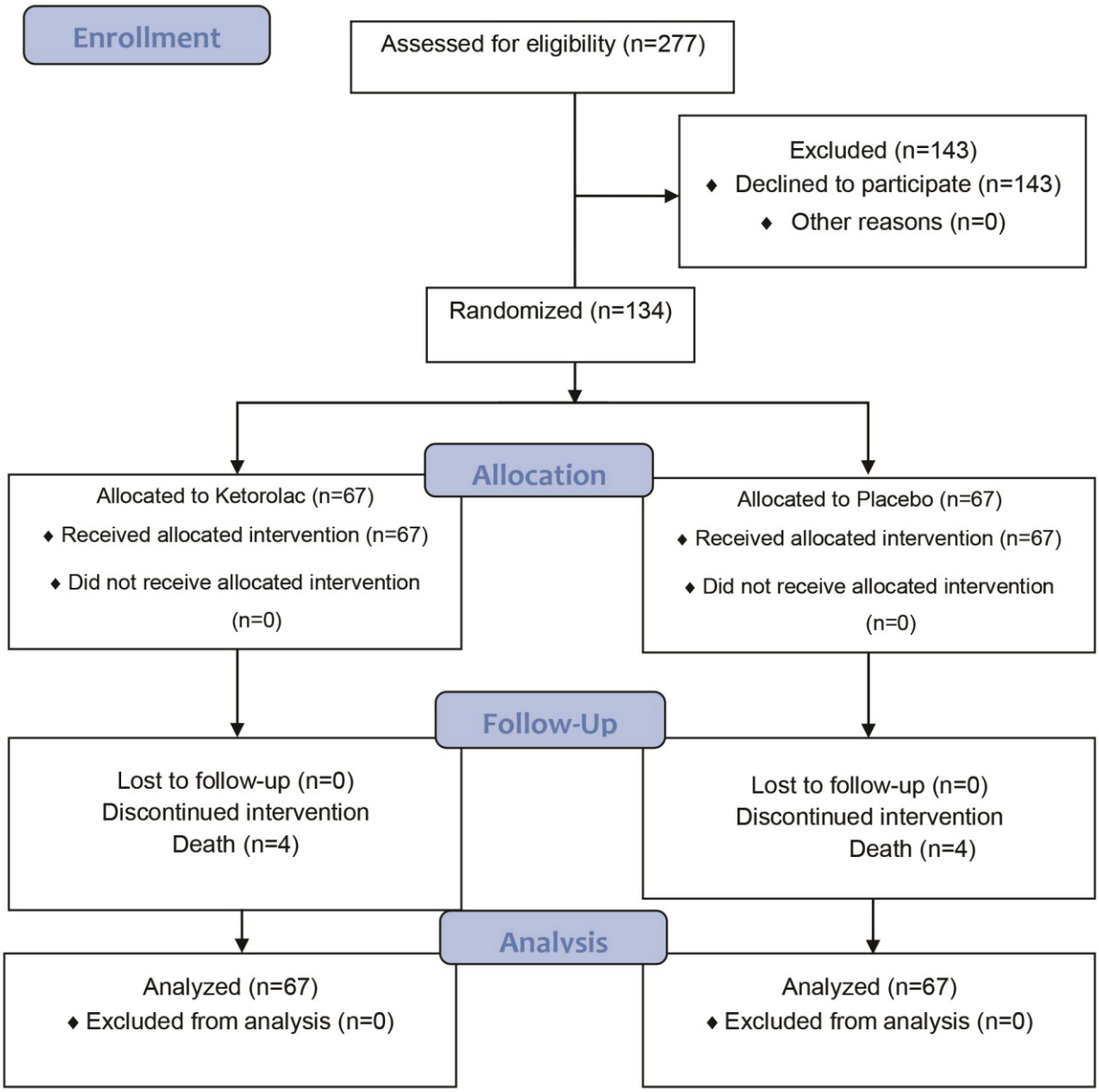

Figure 1. Study flow diagram.

There was no difference in the proportion of infants who developed IVH between the treatment groups (46% vs 45%). The incidences of grade 1, grade 2, grade 3, and grade 4 IVH were similar in the ketorolac and placebo groups (Table 2). There was a higher incidence of IVH grades 1-3 at 48 hours of life in the placebo group but this was not statistically significant (0.06% vs 0.13%, p=0.6) (Table 3).

The infant survival rates were similar in the two groups (Table 4). The most frequent cause of death was sepsis (54%). The rates of death, sepsis, necrotizing enterocolitis, and the lengths of hospital stay were similar in the ketorolac and placebo groups (Table 4). There were no findings of PVL and PHH among participants screened at 36-40 weeks post-conception age. The incidence of serum creatinine levels of >1.5 mg/dL and mean serum creatinine levels were higher in the ketorolac group (Table 4). Mean urine output, bleeding tendency, and platelet counts of <50,000/mm3 did not differ between the ketorolac and placebo groups (Table 4).

Table 1. Comparison between Ketorolac and Placebo Groups in obstetric and maternal and infant characteristics.

Parameter	Ketorolac (n= 67)	Placebo (n= 67)	p-value
Obstetric and Maternal Characteristics			
Cesarean delivery, rate (%)	43.28	58.21	0.067
Prenatal steroids, rate (%)	64.2	73.1	0.264
No. of cycles of antenatal steroids, mean	1.3 ± 1.5	1.8 ± 1.9	0.104
Preeclampsia, rate (%)	14.9	32.8	0.198
Preterm premature rupture of membranes, rate (%)	16.4	13.4	0.198
Gestational diabetes mellitus, rate (%)	2.99	2.99	0.198
Abruptio placentae, rate	1.49	1.49	0.198
Infant Factors			
Birth weight, g, mean	1073 ± 278	1101 ± 239	0.528
Gestational age, wk, mean	30 ± 1.7	30 ± 1.7	0.683
Percentage male, %	50.8	49.3	0.863
Apgar score, median			
1 min	7	7	0.300
5 min	8	8	0.630
Respiratory diseases			
Rate (%)	85.07	92.53	0.077
RDS rate (%)	52.24	52.24	
Transient tachypnea of the newborn, rate (%)	22.39	14.93	
Pneumonia (%)	10.45	25.37	
Oxygen therapy			
Rate (%)	91.04	97.01	0.145
Duration, day, mean	6.6±6.2	9.4 ± 12.4	0.109
Mechanical ventilation			
CMV, rate (%)	70.2	60.7	0.850
HFOV, rate (%)	0	0	
Duration, h, mean	3.8±5.3	4.2±6.0	0.700
Surfactant			
Rate (%)	10.5	6.0	0.345
Total or partial parenteral nutrition, rate (%)	55.2	46.3	0.300
Vasoactive drugs			
Dopamine, rate (%)	64.2	53.7	0.219
Dobutamine, rate (%)	70.2	62.7	0.360
Epinephrine, rate (%)	32.84	22.39	0.176
PRBCs transfused during week 1, rate (%)	23.9	21	0.670
Plasma transfused during week 1, rate (%)	20.9	11.94	0.162

Table 2. Comparison of rates and risks of IVH at 7 days of life

	Rate (%)		p-value	RR (95% CI)
	Ketorolac (n= 67)	Placebo (n= 67)		
No IVH	36 (53.7)	37 (55.2)	0.862	
Grade 1	6 (8.96)	7 (10.5)	0.770	0.857 (0.304,2.417)
Grade 2	2 (2.99)	2 (2.99)	0.690	1.0 (0.137,7.315)
Grade 3	0 (0.0)	0 (0.0)	NE	NE
Grade 4	2 (2.99)	2 (2.99)	0.690	1.0 (0.137,7.315)
Total IVH	10 (15.0)	11 (16.4)	0.812	0.909 (0.414,1.996)

Table 3. Comparison of rates of IVH at 48 hours, 7 days of life

	Ketorolac N=67	Placebo N=67	p-value
No IVH			
48 hours	58 (86.6)	52 (77.6)	0.176
7 days	36 (53.7)	37 (55.2)	0.862
Grade 1			
48 hours	3 (4.5)	6 (9.0)	0.246
7 days	6 (9.0)	7 (10.5)	0.770
Grade 2			
48 hours	0 (0.0)	1 (1.5)	0.500
7 days	2 (3.0)	2 (3.0)	0.690
Grade 3			
48 hours	1 (1.5)	2 (3.0)	0.500
7 days	0 (0.0)	0 (0.0)	NE
Grade 4			
48 hours	0 (0.0)	0 (0.0)	NE
7 days	2 (3.0)	2 (3.0)	0.690
IVH or death at < 7 days	31 (46.3)	30 (44.8)	0.862
Total IVH			
48 hours	4 (6.0)	9 (13.0)	0.144
7 days	10 (15.0)	11 (16.4)	0.812

Table 4. Parameters of potential adverse effects and complications in the ibuprofen and placebo groups

Parameter	Ketorolac (n= 67)	Placebo (n= 67)	p-value
Post treatment serum creatinine level of >1.5 mg/dL, rate (%)	13.4	3.0	0.090
Post treatment serum creatinine level, mg/dl, mean ± SD	1.15 ± 0.69	0.79±0.38	0.002
Urine output, mL/kg per h, mean			
DOL 1	2.2 ± 0.99	2.1 ± 1.0	0.622
DOL 2	3.4 ± 1.2	3.4 ± 1.6	0.756
DOL 3	4.0 ± 1.5	4.1 ± 1.3	0.971
DOL 4	4.1 ± 1.6	4.2 ± 1.5	0.809
DOL 5	4.3 ± 1.2	4.2 ± 1.5	0.524
DOL 6	4.3 ± 1.4	4.3 ± 1.2	0.892
DOL 7	4.7 ± 1.8	4.1 ± 1.7	0.141
Bleeding tendency, rate (%)	49.3	47.8	0.863
Post-treatment Platelet counts of <50 000/mm3, rate (%)	22.4	17.9	0.803
Necrotizing enterocolitis, rate (%)	86.6	89.6	0.454
PVL, rate (%)	0	0	
Post-hemorrhagic hydrocephalus, rate (%)	0	0	
Death, rate (%)	64.2	59.7	0.594
Stay in hospital, d, mean	23.62+23.6	25.3+25.9	0.703
Early onset sepsis, rate (%)	7.5	11.9	0.529
Late onset sepsis, rate (%)	71.6	76.1	0.488

(DOL-days of life, PVL-postventricular leukomalacia)

Our study is the first clinical trial to investigate the use of ketorolac for the prevention IVH. The results showed that ketorolac was ineffective in preventing IVH among preterm infants ≤ 32 weeks and < 1500 g. Although not statistically significant, cranial ultrasound done at the 48th hour showed a lower incidence of IVH in the ketorolac group. Based on the difference in creatinine levels, it is assumed that ketorolac at the given dose managed to exert its pharmacologic effects. It is apparent, however, that it did not influence cerebral blood flow enough to impact on the prevention of IVH. It is not suggested to increase the dose or duration of ketorolac therapy as long-term use of ketorolac has been associated with gastrointestinal bleeding, impaired renal function and compromised hemostasis.[9] In this study, we noted that the mean serum creatinine levels, albeit within normal range, were significantly higher in the ketorolac group. There were no differences in the risk of bleeding, thrombocytopenia, NEC, or death among the treatment groups.

Conclusion

This study showed that prophylactic intravenous ketorolac was ineffective in preventing intraventricular hemorrhage among preterm infants, therefore, its use for this purpose cannot be recommended. We cannot recommend further investigations on the use of ketorolac for prevention of IVH in preterm infants.

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