A Comparison of Early Ibuprofen and Indomethacin Administration to Prevent Intraventricular Hemorrhage Among Preterm Infants

Majid Kalani[1], Mamak Shariat[2], Nasrin Khalesi[3], Zahra Farahani[4], and Sahar Ahmadi[5]

[1] *Department of Pediatrics, Akbar-Abadi Hospital, Iran University of Medical Sciences, Tehran, Iran*

[2] *Department of Maternal and Child Health, Maternal, Fetal and Neonatal Research Center, Tehran University of Medical Sciences, Tehran, Iran*

[3] *Department of Pediatrics, Aliasghar Hospital, Iran University of Medical Sciences, Tehran, Iran*

[4] *Department of Physiology, Maternal, Fetal and Neonatal Research Center, Tehran University of Medical Sciences, Tehran, Iran*

[5] *Department of Pediatrics, School of Medicine, Iran University of Medical Sciences, Tehran, Iran*

Received: 13 Jul. 2016; Revised: 04 Sep. 2016, Accepted: 14 Sep. 2016

Abstract- Intraventricularhemorrhage (IVH) is one of thecommon morbidities among preterm neonates. In thepresentstudy, we set out to evaluate the efficacy of two prophylactic modalities (ibuprofen and indomethacin prophylaxis) for prevention of IVH in our local setting. A prospective study was carried out in Akbar-Abadi Hospital, Tehran-Iran (2013-2014). Ninety-six preterm neonates who cared in closed incubator entered the study**.** Neonates randomly assigned into 3 groups; control, oral indomethacin (0.2 mg/kg indomethacin daily for 3 days) and oral ibuprofen (10,5,5 mg/kg ibuprofen every 24 hours during 3) administration. For all subjects brain sonography examination was performed in 3rd day, first, 2nd week of life and when infants reached to 36 and 42 weeks of postmenstrual age. The IVH prevalence and the effectiveness of the drugs among groups were statistically assessed. Of all 93 subjects; 14 cases had IVH (15.1%). IVH was significantly more frequent in the controls than in other groups (P=0.049). Prophylactic treatment could significantly decrease the incidence of grade 3 or 4 IVH in experimental groups (P=0.008). There were no significant differences between the three experimental groups with respect to theincidence of GI bleeding, Oliguria, renal dysfunction or NEC (P>0.05). This study demonstrates that low-dose prophylactic indomethacin and ibuprofen are equally associated with a reduction of IVH without any significant side effects like renal dysfunction, GI bleeding or NEC.

Acta Med Iran, 2016;54(12):788-792.

Keywords: Intraventricular hemorrhage; Prophylaxis; Indomethacin; Ibuprofen

Introduction

Approximately 15 million preterm births occur each year, and intraventricular hemorrhage (IVH) is one of thecommon related morbidities. In the US the prevalence of IVH among preterm infants is reported about 12 000 annually (1-4).

Low dose Indomethacin prophylaxis as an effective modality in declining the incidence of severe grades of IVH has confirmed by theprevious meta-analysis of randomized control trials (5). Its efficacy with thelack of side effects for theclosure of patent ductus arteriosus (PDA) is also well established (6). Ment *et al*. has indicated the role of Indomethacinadministration in decreasing theincidence of IVH in preterm infants (7). Mirza *et al*., also showed Indomethacin prophylaxis at the first 6 hours of life in females but not males was correlated with less IVH. Indomethacin by inhibition of prostaglandin synthesis and promotion of microvessel maturation may prevent ischemia related impaired cerebral perfusion in preterm infants (4).

Despite some former studies of the role of Indomethacin prophylaxis, few studies have focused on the efficacy of Ibuprofenin declining the incidence of IVH (8-10). This non-steroidal anti-inflammatory drug enhances cerebral blood flow autoregulation and protects neurologic functions in animal model (10). Because of fewer side effects and less renal impairment, Ibuprofen as an alternative to indomethacin has been used for thetreatment of patent PDA worldwide (11).

More than two third of all preterm birth (85%) was reported from Asian and African countries, and the

Corresponding Author: N. Khalesi
Department of Pediatrics, Aliasghar Hospital, Iran University of Medical Sciences, Tehran, Iran
Tel: +98 912 4000379, Fax: +98 21 66581529, E-mail address: nasrinkhalessi@yahoo.com

increasing number of preterm neonates in tertiary centers is notable (12,13). IVH as a common related complication not only increases the long life neonatal morbidities but also imposes a great financial burden on the healthcare system. We, therefore, set out to evaluate the efficacy of two prophylactic modalities (ibuprofen and indomethacin prophylaxis) for prevention of IVH in our local setting.

Materials and Methods

Participants

A retrospective study was carried out in the neonatal intensive care unit (NICU) of Akbar-Abadi Hospital affiliated to Iran University of Medical Sciences (Tehran-Iran) in 2013-2014. Ninety-six preterm neonates in first 6-12 hours of life who cared in closed incubator entered the study. Inclusion criteria were preterm birth (<32 weeks), birth weight<1500 gram, no contraindication for administration of Ibuprofen or Indomethacin (Creatinine levels<1.2 mg/dl, platelet count>50000, no GI bleeding and necrotising enterocolitis) and parents' informed consents. Preterm infants with gestational age<26 weeks, severe birth asphyxia, chromosomal and congenital anomalies were excluded. Laboratory tests including CBC, BUN, and Creatinine levels were performed for all subjects. Participants' demographic data including sex, age, gestational age, weight, and first and five-minuteApgar scores were recorded in some checklists.

Intervention

Preterm infants who met the inclusion criteria entered the study. Neonates randomly (simple randomization) assigned into 3 groups; control, oral indomethacin and oral ibuprofen administration.

Participants in the control group received only standard care. Newborns in thesecond group received 0.2 mg/kg indomethacin daily for 3 days. Indomethacin suspension was prepared based on Ora-Base® و Ora-Sweet® (table 1).

Table 1. Preparation of indomethacin suspension

Ingredients	% (W/V)
○Avicel RC 591	0. 5%
○Citric acid anhydrous	0.35%
○Glycerin	5%
○Sorbitol solution 70%	5%
○Indomethacin	0.05%
○Tween 80	0.3%
○Sugar	45%
○DW	Up to 100%

Subjects in thethird group received 10,5,5 mg/kg ibuprofen every 24 hours during 3 consecutive days. Each group's intervention was started during in physiological stable state. All infants were monitored for potential drug side effects, and intervention was immediately stopped if any infant's complications such as thrombocytopenia, IVH (>grade 2), GI or pulmonary bleeding, Creatinine>1.2 mg/dl, Na<120 mEq/L, urinary output<0.5ml/hour happened.

IVH grades (1-4) were determined based on papile*et al*., classification (14). For all subjects brain sonography examination was performed in 3rd day, first, 2nd week of life and when infants reached to 36 and 42 weeks of postmenstrual age (PMA; gestational age plus the time elapsed after Birth). Blood test including CBC, urea, Creatinine; electrolytes was carried out daily in first 4 days. Urinary output was measured and recorded in thechart. All gathered data in both experimental and control groups were recorded in some checklists.

The primary outcome was IVH prevalence and the effectiveness of the drugs in 2 experimental groups. Secondary outcome included determination of prevalence necrotising enterocolitis, renal failure, hemorrhagic episodes and infant demise.

Statistical analysis

All recorded data were analyzed and compared in three groups statistically by software package SPSS version 18. Frequency was reported by mean+SD. ANOVA, Fisher exact test, *Chi*-square and student *t*-test were used to analyze the correlations between variables. The level of significance was considered as$P<0.05$. With the proposed sample size of 93, the study had a power of 70% and an alpha error of 0.05.

Our study was taken from the medical student thesis with ID 1058 and approved by the institutional review board of Iran University of Medical Sciences according to Helsinki declaration. Participants' parents gave informed consent before entering the study. Our gathered data were confidential, and no extra cost was constrained on our participants

Results

Ninety-three neonates; 31 in each group entered the study. Mean age and weight were 30.27±1.7 weeks and 1448.4±331.7 gram. Forty-five cases were female. Mean hospitalization period was 23.1±17days. Of 93 subjects; IVH and NEC were seen in 14 (15.1%) and 8 (8.6%) neonates, respectively. Nine cases (6.5%) had GI bleeding, and five neonates died during hospitalization.

Seventy-five infants (80.6%) had received betamethasone administration prior birth. Demographic data of 3 groups are shown in table 2.

Table 2. Neonatal demographic data

variables	Control	indomethacin	ibuprofen	*P*-value
Mean age (weeks)	1.8±30.1	8.6±30.3	1.7±30.3	0.06
Mean birth weight (gram)	325±1342.9	287±1459	257±1542	0.83
Sex (female)	54.8(%17)	54.8 (%17)	45.2 (%14)	0.67
IVH (n %)	10(32.3)	2(6.5%)	2(6.5%)	0.005

Statistical analysis showed that IVH was significantly more frequent in the controls than in other groups (10 Vs. 2 and 2; *P*=.049). Prophylactic treatment could significantly decrease the incidence of grade 3 or 4 IVH in experimental groups (*P*=.008); of 7 cases with grade 3 and 4 IVH, 6 newborns were in control and one in indomethacin group. Results did not depict any significant differences between indomethacin and ibuprofen administration regarding the incidence of IVH. There were no significant correlations between incidence of IVH and the demographic variables including gestational age, birth weight, mortality rate, low first and five-minuteApgar scores, betamethasone administration prior birth and hospitalization period (*P*>.05). There were no significant differences between the three experimental groups with respect to theincidence of GI bleeding or NEC (*P*.value>.05). Oliguria or renal dysfunction was not observed in our population study. Details are shown in table 3.

Table 3. Incidence of complications according to treatment group

IVH	Grade	Control (N=31)	Indomethacin (N=31)	Ibuprofen (N=31)	*P*-value
In first three days	4	3(/9.7)	1)(/3.2)	--	0.226
	1	--	1)(/3.2)	--	
In first week	4	1(/3.2)	1)(/3.2)	--	0.65
	3	1(/3.2)	--	--	
	1	1(/3.2)	1(/3.2)	--	
In second week	4	4(/12.9)	1(/3.2)	--	0.116
	3	1(/3.2)	--	--	
	2	--	1(/3.2)	--	
	1	3(/9.7)	--	2(/6.5)	
Age (week)	26-28	5(/16.1)	5(/16.1)	4(/12.9)	0.52
	28-30	14(/45.2)	7(/22.6)	15(/28.7)	
	30-32	11(/35.5)	18(/58.1)	15(/48.4)	
	>32	1(/3.2)	1(/3.2)	--	
Birth weight (gr)	500-1000	5(/16.1)	2(/6.5)	2(/6.5)	.0.52
	1000-1500	16(/51.6)	15(/48.4)	14(/45.2)	
	1500-2000	10(/32.3)	14(/45.2)	15(/48.4)	
PDA		11(/35.5)	8(/25.8)	8(/25.8)	0.62
NEC		2(/6.5)	3(/9.7)	3(/9.7)	0.87
GI bleeding		1(/3.2)	4(/12.9)	1(/3.2)	0.20
mortality		2(/6.5)	1(/3.2)	2(/6.5)	0.80
Hospitalization (day)		25.3±13.9	21.9±17.9	32.1±18.1	0.69

Of 8 cases with NEC, 2 cases underwent surgery, 5 received medical treatment, and a neonate died. No significant differences were observed among 3 groups regarding to surgical or medical treatment (Table 4).

Table 4. ECN treatment among groups

	Control	Indomethacin	Ibuprofen
No NEC treatment	0 0.00%	1 33.30%	0 0.00%
Surgery	0 0.00%	1 33.30%	1 33.30%
Medical	2 100.00%	1 33.30%	2 66.70%

Discussion

There are many publications that provide valuable statistic data for management ofIVH in Iran (15-17), but to our knowledge, this study is the first investigation which assessed the effectiveness of indomethacin and ibuprofen in IVH prophylaxis.

Based on the results prophylactic indomethacin or ibuprofen administered at first 6-12 hours of life was significantly related with alower incidence of IVH. In consistentwith our result, Ment *et al*. showed the positive role of Indomethacinadministration on theincidence of IVH in preterm infants (7). Garner *et al*., demonstrated a lower IVH incidence with 9% increase in fractional cerebral oxygen extraction withindomethacinprophylaxis in 27 VLBW neonates (18). However, the best time for prophylactic administration has not been established. Mirza *et al*., in 2 different studies in 2008 and 2016 showed that in contrast indomethacin administration before 6 hours, prophylaxis at 6-12 hours of age significantly reduced the incidence of grade 3-4 IVH in preterm infants (4,19). On the other hand,Schmidt indicated that receiving indomethacin immediately after birth caused asignificant decline in the frequency of severe peri-intraventricular hemorrhage (odds ratio, 0.6; *P*=0.02) (20).

The incidence of grade 3 and 4 IVH in experimental groups was significantly lower than thecontrol group (3.2 Vs 19.4%) (*P*=.008). In accordance with our results Schmidt *et al*. revealed that the use of indomethacin prophylaxis had declined the incidence of severe peri and intraventricular hemorrhage in extremely-low-birth-weight neonates (20).

We could not depict any significant differences between indomethacin and ibuprofen groups with regard to the incidence of IVH. In contrary to our result Aranda *et al*., showed despite theefficacy of ibuprofen on theclosure of patent ductus arteriosus, it was not effective as indomethacin with respect to IVH prevention (8).

The results did not demonstrate any significant differences between two experimental groups with respect to adverse effects such as GI bleeding, NEC, Oliguria or renal dysfunction. On the other hand Johnston *et al*., pointed to greater side effects (spontaneous intestinal perforation, NEC, oliguria, and renal failure) with indomethacin than ibuprofen that may relate to themode of administration, dosage, prolonged versus short course and continuous infusion versus intermittent bolus (21).

Our study had some limitation; the main limitation was the small sample size. Moreover, we did not consider the different dosage, timing of administration or other prevention trials such as Activated factor VII, Phenobarbital that absolutely may provide more beneficial data.

In treatment for IVH with multifactorial etiology, responses to interventions should be considered (22). This study demonstrates that low-dose prophylactic indomethacin and ibuprofen are equally associated with a reduction of IVH without any significant side effects like renal dysfunction, GI bleeding or NEC.

Acknowledgement

The authors would like to express our gratitude to Akbar-Abadi Hospital NICU faculties and staff for their kindly collaboration**.**

References

1. Ryan JG, Dogbey E. Preterm Births: A Global Health Problem. MCN Am J Matern Child Nurs 2015;40:278-3.
2. Basten M, Jaekel J, Johnson S, Gilmore C, Wolke D. Preterm Birth and Adult Wealth: Mathematics Skills Count. Psychol Sci 2015;26:1608-19.
3. Iyer KK, Roberts JA, Hellström-Westas L, Wikström S, Hansen Pupp I, Ley D, Breakspear M, et al. Early Detection of Preterm Intraventricular Hemorrhage From Clinical Electroencephalography 2015;43:2219-27.
4. Mirza H, Oh W, Laptook A, Vohr B, Tucker R, Stonestreet BS. Indomethacin prophylaxis to prevent intraventricular hemorrhage: association between incidence and timing of drug administration. J Pediatr

2013;163:706-10.e1.
5. Fowlie PW. Prophylactic indomethacin; systematic review and meta-analysis. Arch Dis Child 1996;74:F81-7.
6. Kumar Nair PA, Pai MG, Gazal HA, Da Costa DE, A Khusaiby SM. Indomethacin prophylaxis for intraventricular hemorrhage in very low birth weight babies. Indian Pediatr 2004;41:551-8.
7. Ment LR, Vohr BR, Makuch RW, Westerveld M, Katz KH, Schneider KC, et al. Prevention of intraventricular hemorrhage by indomethacin in male preterm infants. J Pediatr 2004;145:832-4.
8. Aranda JV, Thomas R. Systematic review: intravenous Ibuprofen in preterm newborns. Semin Perinatol 2006;30:114.
9. McCrea HJ, Ment LR. The Diagnosis, Management and Postnatal Prevention of Intraventricular Hemorrhage in the Preterm Neonate. Clin Perinatol 2008;35:777–vii.
10. Dani C, Bertini G, Pezzati M, Poggi C, Guerrini P, Martano C, Rubaltelli FF. Prophylactic ibuprofen for the prevention of intraventricular hemorrhage among preterm infants: a multicenter, randomized study. Pediatrics 2005;115:1529-35.
11. NM Chan, Law CW, Kwan KF. Ibuprofen versus indomethacin treatment of patent ductus arteriosus: comparative effectiveness and complications Hong Kong Med J 2014;20:205-12
12. Shah R, Mullany LC, Darmstadt GL, Mannan I, Rahman SM, Talukder RR. Incidence and risk factors of preterm birth in a rural Bangladeshi cohort. BMC Pediatr 2014;24:112.
13. Khoshnood M, Karimi Z, Rezaienejad M, Basiri A, Torkestani F, Saleh Gargari S. Perinatal complications associated with preterm deliveries at 24 to 33 weeks and 6 days gestation (2011-2012): A hospital-based retrospective study. Iran J Reprod Med 2015;13:697-702.
14. 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 1500 grams. J Pediatr 1978;92:529-34.
15. Khalessi N, Farahani Z, Shariat M, Rezaeizadeh G. Risk factors of intracranial hemorrhage in premature neonates. Acta Med Iran 2014;52:687-9.
16. Pishva N, Parsa G, Saki F, Saki M, Saki MR. Intraventricular hemorrhage in premature infants and its association with pneumothorax. Acta Med Iran 2012;50:473-6.
17. Jodeiry B, Heidarzadeh M, Sahmani-Asl S, Hoseini M, Javaherizadeh H, Eliasi S, et al. Study of intraventricular hemorrhage in VLBW neonates admitted in Al-Zahra Hospital, Tabriz, Iran. Niger J Med 2012;21:92-7.
18. Garner RS, Miller C, Burchfield DJ. Prophylactic indomethacin infusion increases fractional cerebral oxygen extraction in ELBW neonates. J Perinatol 2012;32:695-8.
19. Mirza H, Laptook AR2, Oh W, Vohr BR, Stoll BJ, Kandefer S, et al. Effects of indomethacin prophylaxis timing on intraventricular haemorrhage and patent ductus arteriosus in extremely low birth weight infants. Arch Dis Child Fetal Neonatal Ed 2016;101:F418-22.
20. Schmidt B, Davis P, Moddemann D, Ohlsson A, Roberts RS, Saigal S, et al. Trial of indomethacin prophylaxis in preterms investigators: long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants.N Engl J Med 2001;344:1966-72.
21. Johnston PG, Gillam-Krakauer M, Fuller MP, Reese J. Evidence-based use of indomethacin and ibuprofen in the neonatal intensive care unit. Clin Perinatol 2012;39:111-36.
22. Khalessi N, Farahani Z, Shariat M, Rezaeizadeh G. Risk factors of intracranial hemorrhage in premature neonates. Acta Med Iran 2014;52:687-9.