The Efficacy and Safety of Montelukast Sodium in the Prevention of BronchopulmonaryDysplasia

by

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Major in Medicine

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감사의 글

병원 생활 틈틈이 연구 데이터를 수집하기 위하여 미숙아 보호자를 만나고, 자료를 정리하고, 논문을 작성한 지난 2 년의 시간은. 저에게인고의 시간이기도 했지만, 미숙아 질환에 대한 기본적인 개념과 더불어, 전향적, 다기관 연구의 설계 및 진행 등 연구자로서 필수적으로 알아야 할 많은 부분을 체득한, 매우 값진 시간 이었습니다.

연구의 시작부터 끝까지, 부족한 제자를 위해물심양면으로 헌신하시고, 연구의 즐거움을 알게 해 주신 이장훈 교수님, 본 연구의 책임자로서 값진 연구에 참여할 기회를 주시고, 여러 기관의 중재자로서 궂은 일을 마다하지 않고 도와주신 박문성 교수님, 그리고 바쁘신 와중에 논문을 세심히 검토해 주시고 심사해 주신 박준은 교수님께 진심으로 존경과 감사를 드립니다. 그리고 연구 기간 동안 자료 정리에 도움을 주신 소아과학 교실원들과 약동학적 통계분석을 도와주신 연세대학교 박민수 교수님께도 감사의 인사를 드립니다.

마지막으로, 언제나 아낌없는 사랑과 기도로 힘이 되어 주시는 부모님, 가족들, 그리고 늘 지켜주시는 하나님께 깊은 감사의 마음을 전합니다.

2013 년 12 월 17 일

김상범 드림.

-Absctract-

The efficacy and safety of Montelukast sodium in the prevention of bronchopulmonary dysplasia

Objective: The objective of this study is to evaluate the efficacy and safety of Montelukast sodium in the prevention of bronchopulmonarydysplasia(BPD)

Methods: This study was designed as a multicenter, prospective, randomized, open labelled, parallel-group, intervention study. 66 infants were enrolled and allocated to Case group (n=30) and Control group (n=36) by random assignment stratified by gestational age (GA) (≥28 weeks, <28 weeks). Assigned to the Case group, infants were given Montelukast sodium (Singulair®) according to the body weight(BW). Day 0 was defined as the start time of the study.

Results: There was no difference in BW (case 1097g±327.3 vs. control 997g±235.3, p=0.153) and GA(case 27.6±1.4weeks vs. control 27.3±1.6weeks, p=0.374) between the two groups. The incidences of moderate to severe BPD were not remarkably different between the groups. (case 13/30 (43.3%) vs. control 19/36 (52.8%), p=0.912). The ventilaton index between the two groups were not significantly different at neither day 0 (Case 17.5±9.6 vs. control 23.7±8.8, p=0.141) nor day 28 (case 12.8 vs. control 28.5, p=not applicapable). The use of systemic steroid was not different either (case 7/30 (23.3%) vs. control 7/36 (19.4%), p=0.768). There was no serious adverse drug event, and no statistically significant difference (case 10/42 (23.8%) vs. control 6/48 (15.8%) p=0.414). Modeling reveals that the volume of distribution decreases as the serum creatinine concentration increseases, and the clearance decreases as the age increases

Conclusions: Montelukast was not effective in reducing the moderate or severe BPD.

Additionally, there was no significant increase of adverse drug event. associated with montelukast treatment. And we suggest pharmacokinetic study of Montelukast sodium.

Keyworld :broncopulmonary dysplasia, montelukast sodium, leukotriene receptor antagonist, preterm infants, pharmacokinetic modeling

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INTRODUCTION

Despite increasing survival rate, with recent advances in medical treatments; the use of antenatal steroids, surfactant therapy, and mechanical ventilation,bronchopulmonarydysplasia(BPD) is a major complication of preterm infants. (Jobe and Ikegami, 2001; Baveja and Christou, 2006). The incidence of BPD at 36weeks' postmentrual age (PMA) is reported 16~39% in preterm infants born at less than 32 weeks'gestation or very low birth weight infants.(Payne et al., 2006; Zeitlin et al., 2008; Choi et al., 2012)Especially, infants born at less than 28 weeks' gestation had 40~52% BPD at 36 weeks' PMA. (Laughon et al., 2009; Stoll et al., 2010) Thus, BPD remains a significant problem in preterm infants.

In 1975, Philip proposed that the etiology of BPD was multifactorial, mostly composed of external forces, like as exposure to oxygen and pressure.(Philip, 1975) Inflammation entered this paradigm, including external sources (chorioamnionitis, postnatal infections), iatrogenic sources (ventilation, oxygen), and the internal host response.(Speer, 2001)Even as, this paradigm was confirmed by experimental data, few innovative therapies have proven efficacious.(Wright and Kirpalani, 2011)Vitamin A, caffeine, postnatal corticosteroids, and stem cells from cord blood may help repairing the preterm lung. Specific anti-inflammatory treatments hold some promise, but developing drugs for infants is a most difficult task. (Jobe, 2012; Martin and Fanaroff, 2013)

Leukotrienes, a metabolite of arachidonic acid,have potent chemotactic activity for polymorphonuclear leukocytes. They play an important role in chronic pulmonary inflammation,(Beller et al., 2004) and are associated with hyperoxia induce inhibition of alveolarization.(Phillips et al., 1995) In accordance with this role, several studies between BPD and leukotriens had been conducted. Sheikh(2001) and Joung(2011) et al,theyreported that infants with established BPD have higher levels of urinary leukotriene E_4.(Sheikh et al., 2001; Joung et al., 2011)

Montelukast sodium is a selective cysteinyl leukotriene receptor antagonist that provides clinical benefit in the treatment of asthma and allergic rhinitis both in adults

and children (as young as 6 months of age for perennial allergic rhinitis in the United States and for asthma in Europe). But, the efficacy and safety for children younger than 6 months are not established. Kerns et al(2006,2008), reported pharmacokinetics and safety of montelukast in children 1 to 3months and 3 to 6 months of age, administration of a single dose of montelukast 4mg was generally well tolerated. (Knorr et al., 2006; Kearns et al., 2008)

Likewise, the relationship between BPD and cysteinyl leukotriene receptor antagonist was recognized the potential by the animal experiment and small clinical trial. But, there is no prospective, randomized trial of montelukast in BPD, the object of this study is to compare the efficacy and safety of montelukast sodium, prospectively.

METHOD

Study design This study was a multicenter, prospective, randomized, open labeled, parallel group, intervention study. All protocols were approved by the institutional review board at each site, and the studies were conducted in conformance with the Korea Food and Drug Administration (KFDA). A parent or guardian of every infant provided written informed consent.

Inclusion and exclusion criteria Inclusion criteria were preterm infants born at less than 32 weeks; birth 14 days after, oxygen or artificial ventilation who are using patient; more than 20cal/kg/d by enteral feeding; voluntarily agree to participate in clinical trials, with the consent of the parents who signed. Exclusion criteria were any of the following: with congenital anomaly, impossible to sample blood for pharmacokinetic study due to cardiovascular collapse, in addition, clinical trials were deemed difficult by the investigator.

Examinees who confirmed criteria for selection and exclusion, were registered in the trial and allocated to test and control group (1:1) by random assignment stratified by gestational age (>28 weeks, ≤28 weeks), using shuffled blocks of random numbers of Microsoft office Excel2007. Assigned to the test group, infants were given Montelukast sodium (Singulair®) according to body weight (<1000g : 0.5mg, 1000g~1500g: 1.0mg, 1500g~ 2000g : 1.5mg, ≥2000g : 2mg). Drug was given viaorogastrictube or oral administration, once a day, at a given time. Each infant was given drug until 36 weeks of gestational age or discharge, and was measured body weight every weeks to determine of dose.

All clinical assessments and data collections were performed prospectively by the local investigator, who are all trained pediatricians. The evaluation of data was progressed; 1) the efficacy of drug 2) the safety of drug 3) pharmacokinetic evaluation.

Efficacy The efficacy of the drug was evaluated by incidence and severity of

bronchopulmonary dysplasia (primary outcome). In secondary outcome, we evaluated ventilationindex (VI,R x (PIP-PEEP) x $PaCO_2$/1000), mean airway pressure(MAP, {R x It x PIP + (60- R x It x PEEP)} / 60). We also evaluated usage of mechanical ventilation,oxygen, systemic steroid and change of body weight. Serial tracheal aspirates were collected from each patient (before and after 2 weeks). 0.5ml of saline solution was instilled in the endotracheal tube, with 4 insufflated breaths followed by suctioning after each instillation. The tracheal secretions were collected in eppendorf tube, centrifuged at 3000g for 5 minutes to remove cellular debris, refrigerated at -70℃.

Tumor necrosis factor-a (TNF-α), Interleukin-2,6,8,10,12,Interferon-γ, Chemokine ligand 5(CCL5,RANTES), Chemokine ligand 11(CCL11,Eotaxin), Leukotriene C4(LTC4), Leukotriene D4(LTD4), Leukotriene E4(LTE4)were assayed (Bui et al., 1992).

Safety The safety of the drug was evaluated by the rate of adverse event and classified by SOC classification. Each adverse event was also classified with intensity, progress, complication, treatment, causal relation.

Pharmacokinetic study17 of 36 Montelukast groups who agree pharmacokinetics study, divided them into A, B by using shuffled blocks of random numbers. According to each center, they also divided according to sampling time, single dose study groups (A group : at 2, 6 hours after medication, B group : at 4, 24 hours after medication) and multiple dose study group (A group : at 2,6 hours in 7^{th} day after medication, B group : at 4,24 hours in 7^{th} day after medication). Pharmacokinetic sampling was analyzedatBioInfra®. Quantification of montelukast was done by Ultra performance liqid chromatography (UPLC)-MS/MS. The results were reported that $C= 1/x^2$ by linear regression using MassLynx V4.1 (Waters®) (C=concentration, x= Montelukast peak area / ISTD peak area) x ISTD concentration)(Kearns et al., 2008)

Each preterm infant was evaluated ventilating mode (mode, fiO2, MAP, OI), medication history, weight, associated disease (IVH,hemodynamically significant PDA, NEC, Pneumonia, sepsis), lab data (Hb, Hct, Plt, BUN, Creatinine, SGOT, SGPT,

blood culture), proinflamatory cytokine (intubated infant only) at enrolled time, and every week.(Proinflamatory cytokine was only evaluated in 2week after medication.) We set the end point of studies as 36 gestational age or discharge date.

Statistical Analysis

The result was described as mean and standard deviation for continuous variables, and frequency and percentage for categorical variables. The superiority test with R 2.14.1 was used forprimaryoutcome. The secondary efficacy rating variables between two groups are done by T-test and Fisher's exact test. T-test was used for ventilation index,mean airway pressure,Fisher's exact test was used for demographic data, usage of mechanical ventilation and steroid. Mann-whitneyutest was used for proinflammatory cytokine of tracheal aspirates.

The safety of the drug evaluation was performed by Fisher's exact test to compare between two groups that the incidence and severity of adverse reaction, causation with drugs. Vital sign, physical examinations, laboratory results is evaluated by descriptive statistic comparison between two groups.

Pharmacokinetic modeling Pharmacokinetic modeling was done with a single compartmental model. Because of insufficient information about the absorption period, the modeling of intravenous administration exclude absorption modeling was assumed. Based on this, covariate analysis like age, weight, and sex were added.The evaluation of developed model was done by three method. 1) relativestandard error (standard error/estimate value; RSE) : sensitivity of parameter estimate value, less than 50% is reliable. 2) visual inspection 1 : Comparison of similarity between longitudinal progress of predicted value and observed value. 3) visual inspection 2 : In group or individual, evaluate bias whether weighted residual is distributed around a line of zero. (weighted residual : residual / observed value)

RESULT

Study populationA total of 83 infants enrolled in 5 NICU, but only 77 infants constituted the study group; 1 infants were excluded for the lack of parental consent, 1 infants for exclusion criteria, 1 infants for exceed of number, and 3 for medication violation of unassgned group. Among the 77 infants, 37 enrolled in the Case group and 40 in the control group. 7 infants of the case group were terminated early ; 3 infants were excluded for onset of comorbidity, 1 infants for using of phenobarbital, 1 infants for the lack of parental consent, 1 infants for protocol violation, 1 infants for researcher's opinion. 4 infants of the control group were terminated early ;2 infants for medication of montelukast, and 2 infants for protocol violation. (figure 1)

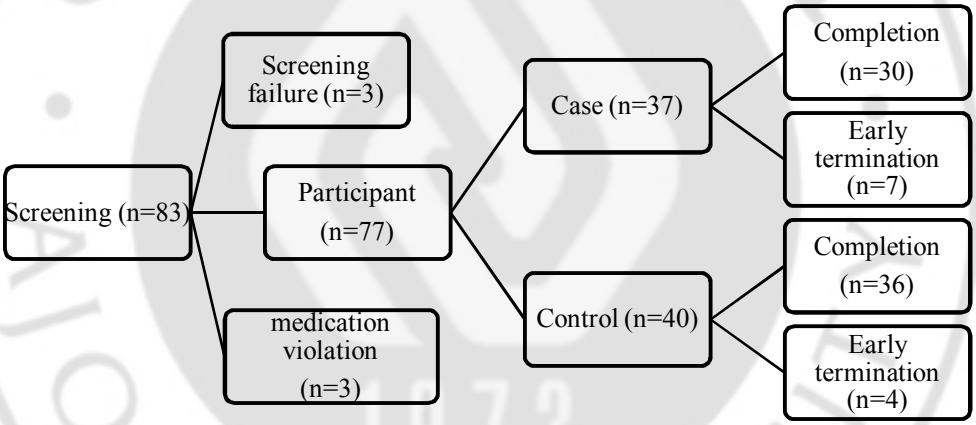

Fig. 1. Participant flow By referring to the comparison of regimens of vitamin A (Ambalavanan et al. (2003)), superiority limit was set to 10%.(Ambalavanan et al., 2003)Dani et al.(2006) confirmed 40%, the combination of death and BPD (BPD/Death) between NO and control groups, and the proportion of the BPD / Death of control group is 90%. (Dani et al., 2006) So, we supposed that the difference of morbidity and mortality of BPD between two groups is 40%, and the rate of morbidity and mortality of BPD is 90%.And then, Statistical power 80%, type I error 0.025 were set. As a result, the number of 60 patients was calculated (PASS 2008), considering exclusion rate (20%), we designed 72 patients.

The characteristics of the patients in the 2 groups were shown. (table 1).There was no difference in birth weight (Case 1097g±327.3 vs. Control 997g±235.3, p=0.153) and gestational age (case 27.6±1.4weeks vs. control 27.3±1.6weeks, p=0.374) at birth between the two groups. Also, there were not demonstrate significant differencesin other characteristics (Apgar scores, usage of antenatal steroid, the incidence of necrotizing enterocolitis and intraventricular hemorrhage).

Table 1.Comparisons of demographic data of studygroups.

	Case croup	Control group	p-value
Gestational age at birth (week)*	27.6± 1.6	27.3 ± 1.6	0.374
Gestational age at 0 week (week)*	31.3 ± 1.3	30.6 ± 1.6	0.205
Weight at birth (g)*	1097 ± 327	997 ± 235	0.153
Weight at 0 week (g)*	1328 ± 305	1199 ± 328	0.107
Apgar score 1 min at screening†	3 [2-5]	3 [2-5]	0.440
Apgar score 5 min at screening†	5 [4-7]	5 [4-7]	0.426
Antenatal steroid (n)	11/30 (36.7%)	17/36 (47.2%)	0.458
NEC (stage ≥II) (n)	2/30 (6.7%)	2/36 (5.6%)	1.000
IVH (stage ≥III) (n)	0/30 (0%)	3/36 (8.3%)	0.245

*expressed as mean±SD; †expressed as median[25%-75%];NEC, necrotizing enterocolitis, IVH, intraventricular hemorrhage

Efficacy The incidence of moderate to severe BPD was not different between the groups. (Case 43.3% vs Control 52.8%, p=0.912) (primary outcome, table 2).There were no significant differences in FiO_2 at 2 weeks after treatment (Case 0.28±0.07 vsControl 0.29±0.08, p=0.472), MAP (Case 6.33±2.25vs Control 8.63±1.92 p=0.062), ventilation index (Case 23.1±13.8vs Control 18.5±9.6, p=0.507), need of invasive ventilator{Case 7 (24.10 %)vs Control 7 (19.40 %), p=0.131}, use of systemic steroid {Case 7/30 (23.3%)vs Control 7/36 (19.4%) p=0.768}(secondary outcome, table 3).The level of pro-inflammatory cytokines in tracheal aspirate was not different between the groups(table 4). And the change of values from baseline was not different, also. (data not shown)

Table 2.Incidence & Severity of BPD.(primary outcome) no (%)

	Case group (n)	Control group (n)	p-value
mild BPD	17/30 (56.7%)	17/36 (47.2%)	0.912
Mod/severe BPD	13/30 (43.3%)	19/36 (52.8%)	

Table 3.Comparison of secondary outcome parameters. Mean ± SD, no (%)

		Case group	Control group	P-value
FiO_2 at 2 weeks after Treatment (%)		0.28±0.07	0.29±0.08	0.472
MAP at 2 weeks after Treatment (mmHg)		6.33±2.25	8.63±1.92	0.062
Ventilation indexat 2 weeks after Treatment		23.1±13.8	18.5±9.6	0.507
Need of Ventilator at2 weeks	Invasive (n)	7 (24.10 %)	7 (19.40 %)	0.131
	Noninvasive (n)	17 (58.60 %)	25 (69.40 %)	
	None (n)	17 (56.70 %)	15 (41.70 %)	
Use of systemic steroid (n)		7/30 (23.3%)	7/36 (19.4%)	0.768

MAP : mean airway pressure, {R x It x PIP + (60- R x It x PEEP)} / 60,
Ventilation index :R x (PIP-PEEP) x $PaCO_2$/1000

Table 4.Pro-inflammatory cytokines in tracheal aspirate. Mean ± SD

		Case group (n=7,3)	Control group (n=9,5)	P-value
Screening	IL-6 (pg/ml)	115.2±88.8	532.2±751.5	0.606
	IL-8 (pg/ml)	1671.0±2249.7	2291.1±2624.4	0.758
	IFN-γ (pg/ml)	2.8±4.9	3.6±7.2	1.000
	TNF-α (pg/ml)	3.3±3.6	6.9±7.8	0.529
2 week	IL-6 (pg/ml)	594.3±737	463±505.7	0.786
	IL-8 (pg/ml)	2917.3±2867.9	2506.3±2275.6	0.786
	IFN-γ (pg/ml)	5.6±4.9	9.2±16.3	0.821
	TNF-α (pg/ml)	15.2±9.5	12.7±21.3	0.339

IL,interleukin ; IFN-γ, interferon–γ; TNF-α, tumor necrosis factor-α

Safety The rate of adverse event did not differ between the groups. {case group 10/42 (23.8%) vs control group 6/32 (15.8%) p=0.414}. There was no serious adverse drug event. According to SOC classification, the most common adverse event is infection(Case 8 vs Control 3, total 11).There were included staphylococcal bacteremia, other sepsis, candida infection, and septic shock.The following is gastrointestinal disorders(abdominal distension, necrotizing enterocolitis, ileus), investigation(elevation of liver enzyme) and blood and lymphatic system disorders(thrombocytopenia, anemia)(table 5). Intensity ofadverse event was more severe in case group (case 11 vs 0, p=0.023). But, most of them were evaluated unlikely to causal relation.(data not shown)In laboratory findings, the number of clinically significant(CS) abnormal platelet count was increased significantly in case group (Case 6 vsControl 1, P= .043). But it was not clinically significant, because, the number of non clinicallysignificant(NCS) abnormal platelet count was increased in the control group rather than case group. Otherwise,there were no significant differences in laboratory findings (table 6). There were no significant differences in CS rate {CS/ (normal + NCS)} of hemoglobin (Case 0.01 vs Control 0.00, p=0.621), platelet (Case 0.02 vs Control 0.00, p=0.066), blood culture (Case 0.05 vs Control 0.03, p=0.489) and other laboratory findings(data not shown).

Table 5.SOC classification of adverse event.

SOC	Case group (n)	Control group (n)	Total (n)
Blood and lymphatic system disorders	2	1	3
Cardiac disorders	1	0	1
Gastrointestinal disorders	5	1	6
General disorders and administration site conditions	2	1	3
Hepatobiliary disorders	1	0	1
Infections and infestations	8	3	11
Investigations	4	6	10
Pregnancy, puerperium and perinatal conditions	1	0	1
Renal and urinary disorders	2	0	2
Respiratory, thoracic and mediastinal disorders	1	1	2
Vascular disorders	1	0	1
Total (n)	28	13	41

Table 6.Summation of laboratory finding.no (%)

	Case group (n)		Control group (n)		P-value
	NCS	CS	NCS	CS	
Blood culture	7	5	2	3	0.140
BUN (3-25 mg/dl)	157	2	173	0	0.212
Creatinine (0.3-1.2 mg/dl)	119	2	120	0	0.514
Hb (11.5-22.5 g/dl)	201	2	197	1	0.506
Hct (28-69 %)	176	2	173	1	0.620
Platelet (84000-478000 x 10^3/ul)	108	6	131	1	0.043
AST (10-140 U/L)	15	3	30	5	0.062
ALT (3-54 U/L)	28	5	23	5	0.642
WBC (5000-34000 x10^3/ul)	75	3	81	1	0.617
total	886	30	930	17	0.126

NCS, Non clinically significant ; CS, Clinically significant ; BUN,blood urea nitrogen ; Hb, hemoglobin ; Hct, hematocrit ;AST, aspartate transaminase ; ALT, alanine transaminase ; WBC, white blood cell

Pharmacokinetic study17 infants in 3 NICU enrolled to the pharmacokinetic study. Among 17 infants, 9 enrolled in the single dose group and 8 in the multiple dosegroup.Using of the modeling of intravenous administration exclude absorption modeling, covariate analysis like age, weight, and sex were resulted like this.

$$TVV = \theta_1 \bullet (CR/CR_{MED})^{\theta 2}$$
$$V = TVV \bullet EXP(\eta)$$
$$TVCL = \theta_3 \bullet (AGE/AGE_{MED})^{\theta 4}$$
$$CL = TVCL$$
$$Y = PRED \bullet (1+\varepsilon)$$

TVV is a typical value of volume of distribution, TVCL is a typical value of clearance, V and CL are each individual value, CR_{med} and AGE_{med} are median value of CR and AGE(CR_{med}=0.6 mg/dl, AGE_{med}=27.0 days). ηis a random variable of inter-individual disfference, but CL is not significant, a typical value of group reveals individual value. Y is an observed value, PRED is a predicted value, ε is a random variable related residual error or intra-individual difference.

The concentration of montelukast according to the time was shown (figure 2), and the characteristics of the patients in 2 groups did not demonstrate significant differences. From the table 7, each typical value of distribution volume and clearance is 918 ml and 5.12 ml/hr. According to covariate analysis, the volume of distribution decreases as the serum creatinine concentration increases, and the clearance decreases as the age increases. ($p< 0.0005$). The relative standard error of estimated parameters is 7.2% to 34.6%, less than 50%,themodeling result can be reliable.(table 7)The 1mg group with the highest number of participants, predicted value(line) passes close to the center of observed values (dots), therefore, it means that modeling was appropriate. (figure3)

Table 7. Pharmacokinetic parameters

Parameter	Typical value	CV	P-value
V (ml)	Θ_1 =918 (18.7) Θ_2 = -1.63 (18.7)	66.3 (34.6)	P< 0.0005
CL (ml/hr)	Θ_3 =5.12 (16.3) Θ_4 =-3.17 (7.2)	- -	P< 0.0005
Weighted residual	47.7 (23.5)		

* ( ) = RSE (%) (relative standard error)* CV (%) : coefficient of variation

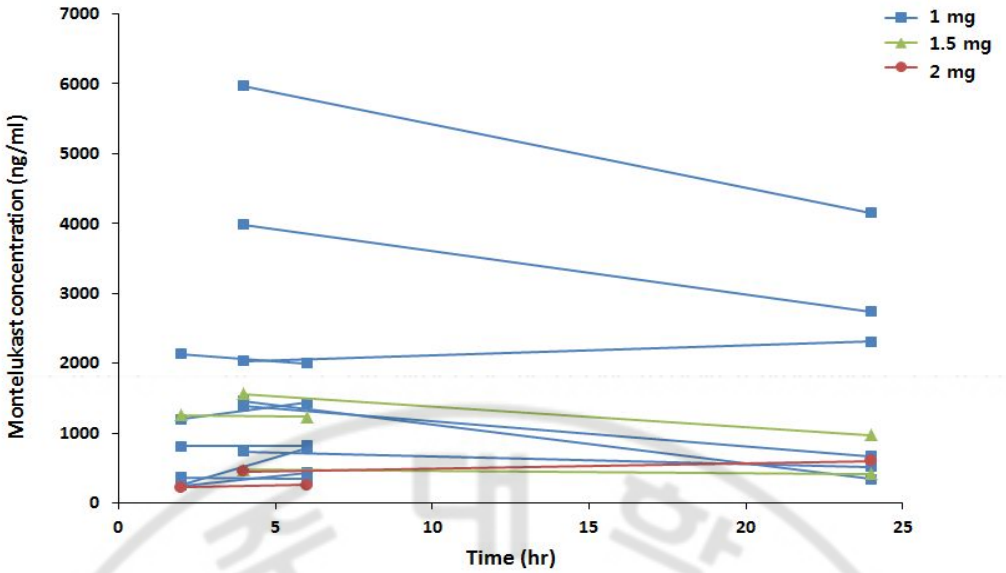

Fig.2. Concentration of montelukast over time. 17 infants in 3 NICU enrolled to the pharmacokinetic study. According to each center, they also divided according to sampling time, 9 enrolled in the single dose study groups (A group : at 2, 6 hours after medication, B group : at 4, 24 hours after medication) and 8 enrolled in the multiple dose study group (A group : at 2,6 hours in 7^{th} day after medication, B group : at 4,24 hours in 7^{th} day after medication). The concentration of montelukast according to the time was shown.

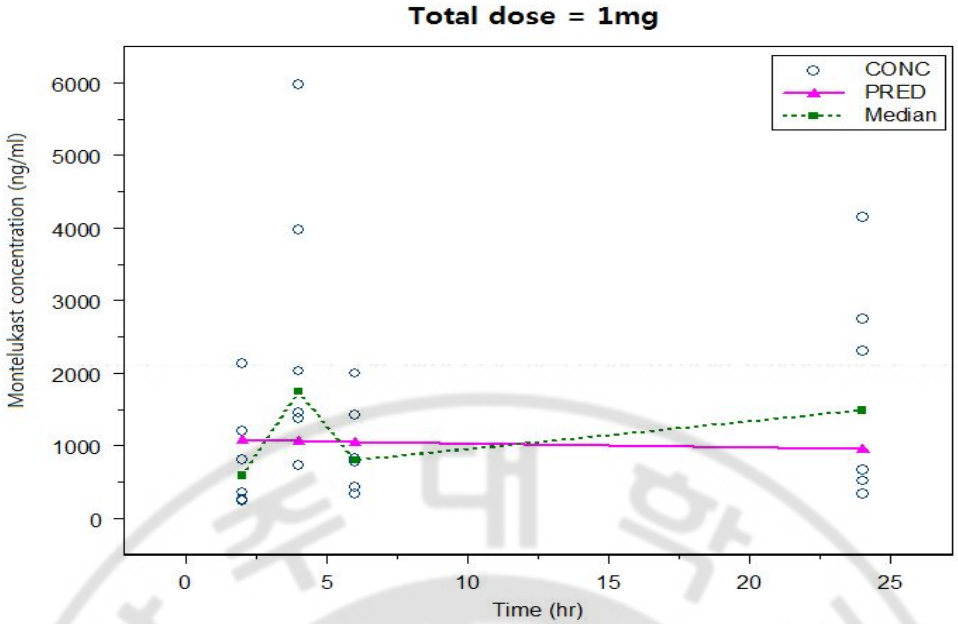

Fig.3. Predicted (line) and observed values (dots) over time The1mg group with the highest number of participants, predicted value(line) passes close to the center of observed values (dots), therefore, it means that modeling was appropriate.

DISCUSSION

Bronchopulmonary dysplasia (BPD) was originally described by Northway in 1967, the clinical, radiologic and pathologic changes seen in infants who had severe respiratory distress syndrome or prolonged mechanical ventilation and high inspiratory oxygen levels. (Northway et al., 1967). They were included inflammation, airway fibrosis and smooth muscle hypertrophy, alveolar collapse and hyperinflation and interstitial fibrosis of all tissues of the lung in the pathologic process.(Bonikos et al., 1976)Despite increased survival, with recent advances in medical treatment; the use of antenatal steroids, surfactant therapy, novel ventilator strategies,etc, BPD is a major complication of preterm infant. (Jobe and Ikegami, 2001; Baveja and Christou, 2006) Therefore, new category of BPD was suggested that have minimal or absent signs of RDS but who subsequently develop oxygen dependency and ventilatory needs within the first two weeks of life.These "new BPD" were compatible with an arrest in lung development than with a mechanical injury. There were larger and fewer alveoli with preserved airway structure and homogeneous lung inflation, as well as poorly formed secondary crests, indicating interference with septation.(Husain et al., 1998; Coalson, 2003)Accordingly, the definition of BPD was changed. In 2000, a workshop organized by the National Institute of Child Health and Human development, the National Heart, Lung and Blood Institute, and the Office of Rare Diseases defined diagnostic criteria for BPD based on gestational age (<32 weeks versus ≥32 week) and severity (mild, moderate, or severe based on oxygen supplementation at 28 days of age and 36 weeks postmenstrual age)(Jobe and Bancalari, 2001)Inflammation entered this paradigm, included external sources (chorioamnionitis, postnatal infections), iatrogenic sources (ventilation, oxygen), and the internal host response.(Speer, 2001) Even as this paradigm was confirmed by experimental data, few innovative therapies have proven efficacious.(Wright and Kirpalani, 2011) Vitamin A, caffeine, postnatal corticosteroids, stem cells from cord blood may help repair the preterm lung. Kim HM et al, (2009) reported montelukast as an add-on therapy in BPD. To 15 preterm infants with

established BPD, montelukast (1mg/kg/day) was given for a mean period of 12 weeks. Ventilation index was significantly improved after 2 weeks in montelukast group, and there were no differences in the incidence of adverse reaction between the 2 groups. (Kim et al., 2009) But, specific anti-inflammatory treatments hold some promise, but developing drugs for infants is a most difficult task. (Jobe, 2012; Martin and Fanaroff, 2013)

In our study, there were no differences in variables about efficacy such as incidence and severity of BPD, FiO_2 at 4 weeks after treatment, MAP, ventilation index, the need of ventilator, use of systemic steroid. Leukotrienes as mediators of hyperoxia induced aberrant alveolarization has been reported in many studies.(Phillips et al., 1995; Manji et al., 2001; Rogers et al., 2009)They suggested that the mechanisms involved in aberration of alveolarization may require more subtle alterations in the signal transduction pathways of growth factors and receptors involved in the alveolarization process other than simple inflammatory processes. Based on the drug mechanisms of action, the protective effects of the drug must involve the inhibition of leukotriene production, but not be attributed solely to anti-inflammatory mechanisms.(Park et al., 2011)According to this mechanism, instead of leukotriene receptor antagonist, leukotriene synthesis inhibitors like 5-lipoxygenase inhibitor (eg, Zileuton) or 5-lipoxygenase-activating protein (FLAP) inhibitor (eg, MK-0591, not approved to FDA) are considered as alternatives.

In addition, considering multifactorial etiology of BPD, this result cannot be generalized. Charafeddine et al.(1999) sub-classified BPD into two groups according to the criteria; ‘classic’ and ‘atypical’ BPD. ‘Atypical BPD’ was diagnosed in BPD cases without respiratory distress syndrome (RDS) or in BPD cases that were preceded by initial RDS that resolved within 10 days and required no oxygen supplementation for at least 72 hours, in addition to the 28-day oxygen requirement(Charafeddine et al., 1999). Joung et al. reported that although there was no significant difference between the no/mild and the moderate/severe BPD groups, when they compared ‘classic’ and ‘atypical’ BPD groups, there was a significant increase in urinary LTE_4levels on day 7 in the ‘atypical’ BPD group(Joung et al., 2011).This means that the possibility of two

kinds.The evaluation of incidence and severity of all BPD can mask that of 'atypical BPD'. Second, the evaluation of all period of treatment can mask that of early period related to inflammatory insult. Besides, the differences (40%) shown in previous studies(Dani et al., 2006) which were used to calculatepopulation might be exaggerated. If population increases by participating of more unit, the differences can decrease.

Several pediatric studies of montelukastshows that oral montelukast is generally well tolerated. (Storms et al., 2001; Bjermer, 2005; Nayak and Langdon, 2007). Bisgaard et al.(2009) reported the safety and tolerability of montelukast in placebo-controlled and open-labelled. The most common clinical adverse experiences were upper respiratory infection, worsening pulmonologic problem, and fever. And there were no clinically meaningful differences in laboratory safety parameters(Bisgaard et al., 2009). In addition, Sarkar et al. (2009) reported prospective study about infant outcomes for using montelukast during pregnancy. According to them, montelukastdose not appear to increase the baseline rate of major malformations, and was resulted lower birth weight but, is was most likely associated with the severity of the maternal condition. (Sarkar et al., 2009)In our study, there was no serious adverse drug event, and known adverse event (described above) did not differ between the groups.

Pharmacokinetic study is a modeling using data that sampling blood twice in each infant.Final modeling reveals that the volume of distribution decreases as the serum creatinine concentration increeases, and the clearance decreases as the age increases. Comparing with weighted residual, residuals showed no tendency and distributed in standard normal distribution,predicted value was appropriate for observed value. (data not shown)Half-life of montelukast in 1 to 3 months of age reported to 1.2 hour, (Kearns et al., 2008) but, the first sampling was done late (after 2 or 4 hrs). As a result, because of insufficient information about the absorption period, the modeling of intravenous administration exclude absorption modeling was assumed. And then, parameter could be predicted.Therefore, for an accurate assessment, research reflecting absorption period might be needed.

CONCLUSION

In conclusion, montelukast was not effective in reducing the moderate or severe BPD. Additionally, there was no significant increase of adverse drug event associated with montelukast treatment. And we suggest pharmacokinetic study of montelukast sodium.

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References

1. Ambalavanan N, Wu TJ, Tyson JE, Kennedy KA, Roane C, Carlo WA: A comparison of three vitamin A dosing regimens in extremely-low-birth-weight infants. *J Pediatr* 142: 656-661, 2003
2. Baveja R, Christou H: Pharmacological strategies in the prevention and management of bronchopulmonary dysplasia. *Semin Perinatol* 30: 209-218, 2006
3. Beller TC, Friend DS, Maekawa A, Lam BK, Austen KF, Kanaoka Y: Cysteinyl leukotriene 1 receptor controls the severity of chronic pulmonary inflammation and fibrosis. *Proc Natl Acad Sci U S A* 101: 3047-3052, 2004
4. Bisgaard H, Skoner D, Boza ML, Tozzi CA, Newcomb K, Reiss TF, Knorr B, Noonan G: Safety and tolerability of montelukast in placebo-controlled pediatric studies and their open-label extensions. *Pediatr Pulmonol* 44: 568-579, 2009
5. Bjermer L: Montelukast in the treatment of asthma as a systemic disease. *Expert Rev Clin Immunol* 1: 325-336, 2005
6. Bonikos DS, Bensch KG, Northway WH, Jr., Edwards DK: Bronchopulmonary dysplasia: the pulmonary pathologic sequel of necrotizing bronchiolitis and pulmonary fibrosis. *Hum Pathol* 7: 643-666, 1976
7. Bui KC, Walther FJ, David-Cu R, Garg M, Warburton D: Phospholipid and surfactant protein A concentrations in tracheal aspirates from infants requiring extracorporeal membrane oxygenation. *J Pediatr* 121: 271-274, 1992
8. Charafeddine L, D'Angio CT, Phelps DL: Atypical chronic lung disease patterns in neonates. *Pediatrics* 103: 759-765, 1999
9. Choi CW, Kim BI, Kim EK, Song ES, Lee JJ: Incidence of bronchopulmonary dysplasia in Korea. *J Korean Med Sci* 27: 914-921, 2012
10. Coalson JJ: Pathology of new bronchopulmonary dysplasia. *Semin Neonatol* 8: 73-81, 2003
11. Dani C, Bertini G, Pezzati M, Filippi L, Cecchi A, Rubaltelli FF: Inhaled nitric oxide in very preterm infants with severe respiratory distress syndrome. *Acta*

Paediatr 95: 1116-1123, 2006

12. Husain AN, Siddiqui NH, Stocker JT: Pathology of arrested acinar development in postsurfactant bronchopulmonary dysplasia. *Hum Pathol* 29: 710-717, 1998
13. Jobe AH: What is BPD in 2012 and what will BPD become? *Early Hum Dev* 88 Suppl 2: S27-28, 2012
14. Jobe AH, Bancalari E: Bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 163: 1723-1729, 2001
15. Jobe AH, Ikegami M: Prevention of bronchopulmonary dysplasia. *Curr Opin Pediatr* 13: 124-129, 2001
16. Joung KE, Kim HS, Lee J, Shim GH, Choi CW, Kim EK, Kim BI, Choi JH: Correlation of urinary inflammatory and oxidative stress markers in very low birth weight infants with subsequent development of bronchopulmonary dysplasia. *Free Radic Res* 45: 1024-1032, 2011
17. Kearns GL, Lu S, Maganti L, Li XS, Migoya E, Ahmed T, Knorr B, Reiss TF: Pharmacokinetics and safety of montelukast oral granules in children 1 to 3 months of age with bronchiolitis. *J Clin Pharmacol* 48: 502-511, 2008
18. Kim HM, Song JE, Lee SM, Park MS, Park KI, Namgung R, Lee C: Montelukast as an add-on therapy in bronchopulmonary dysplasia. *Korean J Pediatr* 52: 181-186, 2009
19. Knorr B, Maganti L, Ramakrishnan R, Tozzi CA, Migoya E, Kearns G: Pharmacokinetics and safety of montelukast in children aged 3 to 6 months. *J Clin Pharmacol* 46: 620-627, 2006
20. Laughon M, Allred EN, Bose C, O'Shea TM, Van Marter LJ, Ehrenkranz RA, Leviton A, Investigators ES: Patterns of respiratory disease during the first 2 postnatal weeks in extremely premature infants. *Pediatrics* 123: 1124-1131, 2009
21. Manji JS, O'Kelly CJ, Leung WI, Olson DM: Timing of hyperoxic exposure during alveolarization influences damage mediated by leukotrienes. *Am J Physiol Lung Cell Mol Physiol* 281: L799-806, 2001
22. Martin RJ, Fanaroff AA: The preterm lung and airway: past, present, and future. *Pediatr Neonatol* 54: 228-234, 2013
23. Nayak A, Langdon RB: Montelukast in the treatment of allergic rhinitis: an

evidence-based review. *Drugs* 67: 887-901, 2007

24. Northway WH, Jr., Rosan RC, Porter DY: Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. *N Engl J Med* 276: 357-368, 1967
25. Park MS, Sohn MH, Kim KE, Park MS, Namgung R, Lee C: 5-Lipoxygenase-activating protein (FLAP) inhibitor MK-0591 prevents aberrant alveolarization in newborn mice exposed to 85% oxygen in a dose- and time-dependent manner. *Lung* 189: 43-50, 2011
26. Payne NR, LaCorte M, Karna P, Chen S, Finkelstein M, Goldsmith JP, Carpenter JH, Breathsavers Group VONNICQIC: Reduction of bronchopulmonary dysplasia after participation in the Breathsavers Group of the Vermont Oxford Network Neonatal Intensive Care Quality Improvement Collaborative. *Pediatrics* 118 Suppl 2: S73-77, 2006
27. Philip AG: Oxygen plus pressure plus time: the etiology of bronchopulmonary dysplasia. *Pediatrics* 55: 44-50, 1975
28. Phillips GJ, Mohammed W, Kelly FJ: Oxygen-induced lung injury in the pre-term guinea pig: the role of leukotriene B4. *Respir Med* 89: 607-613, 1995
29. Rogers LK, Tipple TE, Nelin LD, Welty SE: Differential responses in the lungs of newborn mouse pups exposed to 85% or >95% oxygen. *Pediatr Res* 65: 33-38, 2009
30. Sarkar M, Koren G, Kalra S, Ying A, Smorlesi C, Santis M, Diav-Citrin O, Avgil M, Voyer Lavigne S, Berkovich M, Einarson A: Montelukast use during pregnancy: a multicentre, prospective, comparative study of infant outcomes. *European Journal of Clinical Pharmacology* 65: 1259-1264, 2009
31. Sheikh S, Null D, Gentile D, Bimle C, Skoner D, McCoy K, Guthrie R: Urinary leukotriene E(4) excretion during the first month of life and subsequent bronchopulmonary dysplasia in premature infants. *Chest* 119: 1749-1754, 2001
32. Speer CP: New insights into the pathogenesis of pulmonary inflammation in preterm infants. *Biol Neonate* 79: 205-209, 2001
33. Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, Hale EC, Newman NS, Schibler K, Carlo WA, Kennedy KA, Poindexter BB, Finer NN, Ehrenkranz RA, Duara S, Sanchez PJ, O'Shea TM, Goldberg RN, Van Meurs KP,

Faix RG, Phelps DL, Frantz ID, 3rd, Watterberg KL, Saha S, Das A, Higgins RD, Eunice Kennedy Shriver National Institute of Child H, Human Development Neonatal Research N: Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. *Pediatrics* 126: 443-456, 2010

34. Storms W, Michele TM, Knorr B, Noonan G, Shapiro G, Zhang J, Shingo S, Reiss TF: Clinical safety and tolerability of montelukast, a leukotriene receptor antagonist, in controlled clinical trials in patients aged > or = 6 years. *Clin Exp Allergy* 31: 77-87, 2001
35. Wright CJ, Kirpalani H: Targeting inflammation to prevent bronchopulmonary dysplasia: can new insights be translated into therapies? *Pediatrics* 128: 111-126, 2011
36. Zeitlin J, Draper ES, Kollee L, Milligan D, Boerch K, Agostino R, Gortner L, Van Reempts P, Chabernaud JL, Gadzinowski J, Breart G, Papiernik E, group Mr: Differences in rates and short-term outcome of live births before 32 weeks of gestation in Europe in 2003: results from the MOSAIC cohort. *Pediatrics* 121: e936-944, 2008

- 국문요약 -

기관지폐이형성증예방에대한 몬테루카스트의유효성및안전성평가연구

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목적 :이연구의목적은미숙아의기관지폐이형성증을예방에있어서몬테루카스트의유효성과안전성을평가하기위함이다.

방법 :이연구는다기관, 전향적, 무작위, 오픈라벨, 수평적, 개입연구이다. 66명의환아가등록되었고, 시험군(n=30)과대조군(n=36) 으로제태주수에따라무작위배정되었다. 시험군은체중에따라몬테루카스트를복용하였다. 0일을 study의시작일로정의한다.

결과 :인구학적평가상체중(시험군 1097g±327.3 vs대조군 997g±235.3, p=0.153), 제태주수(시험군 27.6±1.4주vs대조군 27.3±1.6주) 등에서두그룹간의유의한차이는없었다. 유효성평가에있어서, 중등도이상의기관지폐이형성증의유병률은두그룹간의차이를보이지않았다. (시험군13/30 (43.3%) vs대조군 19/36 (52.8%),p=0.912) 0일과 28일에평가한두그룹간의환기지수(ventilation index)도유의한차이를보이지않았다. 전신적스테로이드사용율도통계학적차이는없었다. 안전성평가에서보고된위중한부작용은없었으며, 두그룹간의이상반응의통계학적유의성은없었다. 약동학적모델링을시행한결과, 분포용적은혈중크레아티닌농도가증가할수록, 청소율은투약시연령이증가할수록모두유의하게감소하는것으로나타났다.

결론 :몬테루카스트는중등도이상의 BPD를감소시키는데있어서는유효성을확인하지못했다. 하지만, 몬테루카스트치료와관련된위중한부작용은보고되지않았다. 또한, 우리는몬테루카스트의약동학적연구를제시할수있었음에그의의를가진다.

핵심어 :기관지폐이형성증, 몬테루카스트, 루코트리엔수용체길항제, 미숙아, 약동학적모델링