Permissive Hypotension in Extremely Low Birth Weight Infants (≤1000 gm)

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Purpose: We performed this study to evaluate the safety of permissive hypotension management in extremely low birth weight infants (ELBWIs). Materials and Methods: Medical records of all inborn ELBWIs admitted to Samsung Medical Center from January 2004 to December 2008 were reviewed retrospectively. Of a total of 261 ELBWIs, 47 (18%) required treatment for hypotension (group T), 110 (42%) remained normotensive (group N), and 104 (40%) experienced more than one episode of hypotension without treatment (group P) during the first 72 hours of life. Treatment of hypotension included inotropic support and/or fluid loading. Results: Birth weight and Apgar scores were significantly lower in the T group than the other two groups. In the N group, the rate of pathologically confirmed maternal chorioamnionitis was significantly higher than other two groups, and the rate was higher in the P group than the T group. After adjusting for covariate factors, no significant differences in mortality and major morbidities were found between the N and P groups. However, the mortality rate and the incidence of intraventricular hemorrhage (≥stage 3) and bronchopulmonary dysplasia (≥moderate) were significantly higher in the T group than the other two groups. Long term neurodevelopmental outcomes were not significantly different between the N and P groups. Conclusion: Close observation of hypotensive ELBWIs who showed good clinical perfusion signs without intervention allowed to avoid unnecessary medications and resulted in good neurological outcomes.

Key Words: Hypotension, prognosis, infant, extremely low birth weight

INTRODUCTION

Early hypotension during the initial 3 days of life is common in preterm infants and the incidence of early hypotension has been reported to range between 20-50% in very low birth weight infants.1-3 Many studies have reported that hypotension might be related to cerebral hemorrhage and ischemia, and have demonstrated that hypotension is associated strongly with intraventricular hemorrhage (IVH) and periventricular leukomalacia.4,5 Fanaroff, et al.6 showed that infants treated for hypotension have higher mortality and worse morbidities, including delayed motor development and hearing loss, than their non-hypotensive counterparts. However,
permissive hypotension group (P group; MAP < gestational age with signs of good perfusion and no intervention), and 3) a treated hypotension group (T group; MAP < gestational age and intervention including volume pushes, vasopressors or corticosteroids).

GA was defined as the time from the date of the last menstrual period to birth. Hypotension was defined as a blood pressure in mm Hg less than gestational age in weeks. We collected blood pressure (BP) data during the first 72 hours after birth at intervals of 6 hours and included the lowest blood pressure records, regardless of the interval during which they were taken. Peripheral blood pressure was measured using an oscillometric technique (M1866A, Philips Medical Systems, Inc., WA, USA) and invasive blood pressure was measured using a calibrated pressure transducer (42584, ICU Medical, Inc., UT, USA) connected to an umbilical arterial catheter, which was positioned between thoracic vertebrae 6 to 10 in the abdominal aorta. End organ perfusion status was assessed by skin color, capillary refill rate, urine output, blood lactate level, and acidosis.

We analyzed the following potentially confounding variables: gestational age, birth weight, gender, 1- and 5-minute Apgar scores, antenatal steroid use, mode of delivery, pregnancy-induced hypertension, pathologically confirmed choioamnionitis, small for gestational age (SGA), and respiratory distress syndrome (RDS). SGA was defined as a birth weight less than ten percentile. RDS was defined as respiratory difficulty requiring surfactant and mechanical ventilation with endotracheal intubation. In addition, we evaluated the following outcome measures: death before discharge, bronchopulmonary dysplasia (≥ moderate, need for oxygen or positive pressure support at 36 weeks postmenstrual age), IVH (≥ grade 3), periventricular leukomalacia, necrotizing enterocolitis (≥ Bell’s stage 2b), and retinopathy of prematurity requiring laser treatment.

Long-term, 2-year outcomes including hearing impairment and cerebral palsy were investigated. Cerebral palsy, as diagnosed by a pediatric rehabilitation specialist or a pediatric neurologist, was defined as a non-progressive neurological disorder characterized by an inability to control posture and movement and abnormal tone in the limbs. Hearing impairment was defined as the need for a hearing aid as recommended by an otolaryngologist. Finally, the Bayley Scales of Infant Development-II mental development index (MDI) and psychomotor development index (PDI) at a corrected age of 18 months were assessed.

The software package SPSS version 17 was used for all
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Statistical analyses. ANOVA was used for continuous variables with normal distributions. To compare nominal variables such as mortality and morbidity, chi-square tests with binary logistic regression analysis were performed. Data are expressed as mean±SEM; and p-values less than 0.05 were considered significant.

RESULTS

Demographic data
During the 4-year study period, 261 infants were born and admitted to the Samsung Medical Center NICU. Seven died within 72 hours of birth and had incomplete blood pressure data. We evaluated a total of 261 ELBWIs: 110 (42%) in the N group, 104 (40%) in the P group, and 47 (18%) in the T group. Table 1 lists the subjects’ demographic characteristics. Birth weight was significantly lower in the T group than the other two groups. The 1-minute and 5-minute Apgar scores were significantly lower in the T group than the other two groups. The incidence of pathologically confirmed chorioamnionitis was significantly higher in the N group than the P and T groups, and higher in the P group than the T group.

Mean blood pressure trends
Invasive blood pressure monitoring was performed in 56% (62/110) infants in the N group, 54% (56/104) infants in the P group, and 77% (36/47) infants in the T group. The T group depicted significantly higher rate of invasive BP monitoring (p-value: 0.02). The trend in mean blood pressures for all ELBWIs is shown in Fig. 1, while the trends in mean blood pressures of the N/P/T groups during the initial 72 hours of life are shown in Fig. 2. A spontaneous increase in mean arterial blood pressure was observed in the N and P groups, with a statistically significant difference in MAP between the N and P groups at every time point. In the T group, hypotension developed usually and was treated within 12 hrs from birth. Although the T group received treatment, in-

Table 1. Subject Demographics

|                  | N group (n=110) | P group (n=104) | T group (n=47) |
|------------------|----------------|----------------|---------------|
| Gestational age (wks) | 26±22          | 25±21          | 25±22         |
| Birth weight (gm)   | 781±138        | 764±147        | 672±152*†     |
| Gender (male)       | 55 (50%)       | 61 (59%)       | 25 (53%)      |
| One-minute Apgar score | 4.7±1.6      | 4.5±1.5        | 3.3±1.3*      |
| Five-minute Apgar score | 7.3±1.3      | 7.0±1.0        | 6.1±1.8*      |
| Cesarean delivery   | 77 (70%)       | 82 (79%)       | 37 (79%)      |
| Small for gestational age | 14 (13%)   | 24 (23%)       | 12 (26%)      |
| Antenatal steroids  | 22 (20%)       | 23 (22%)       | 13 (28%)      |
| Pathologically confirmed chorioamnionitis | 56 (51%) | 40 (39%)* | 10 (22%)* |
| Pregnancy-induced hypertension | 20 (18%) | 21 (20%) | 5 (11%) |

*p<0.05 versus N.
†p<0.05 versus P.

Fig. 1. Mean blood pressures of all infants (A) and infants in each of the three groups (B) during the first 72 hours of life. Data are expressed as mean±SD (A), mean±SEM (B). *p<0.05 versus N, †p<0.05 versus P. SD, standard deviation; SEM, standard error of the mean.
compared to the other two groups, and higher in the P group than the N group. In multivariate analyses, adjusted for confounding factors including birth weight, Apgar scores and pathologically confirmed chorioamnionitis, there was no significant difference in IVH rate between the N and P groups, but the rate of IVH in the T group was significantly higher than the other two groups.

Severe IVH infants in the P group

Even though the severe IVH rate in the P group was not significant after multivariate analysis, severe IVH was seen in more infants in the P group than in the N group. In T group infants, 87% (41/47) received volume expansion treatment (10 mL/kg of normal saline or bivon), 60% (28/47) dopamine, 30% (14/47) dobutamine, and 25% (12/4) intermittent epinephrine injections.

Adverse outcomes

The mortality rate and the incidence of moderate to severe bronchopulmonary dysplasia (BPD) were significantly higher in the T group than the other two groups even after adjusting for birth weight, Apgar score, and pathologically confirmed chorioamnionitis (Table 2 and 3). The incidence of severe IVH (≥grade 3) was the highest in the T group compared to the other two groups, and higher in the P group than the N group. In multivariate analyses, adjusted for confounding factors including birth weight, Apgar scores and pathologically confirmed chorioamnionitis, there was no significant difference in IVH rate between the N and P groups, but the rate of IVH in the T group was significantly higher than the other two groups.

Severe IVH infants in the P group

Even though the severe IVH rate in the P group was not significant after multivariate analysis, severe IVH was seen in more infants in the P group than in the N group. The gestational ages of 90% (18/20) of infants with severe IVH ranged from 23 to 26 weeks. To compare trends in the blood pressures of infants with and without severe IVH, the P group was divided into two subgroups: an IVH group and a non-IVH group. The data were analyzed according to gesta-
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Dience of cerebral palsy, hearing loss, or developmental delay, defined as Bayley score MDI or PDI <75 (Table 4). None of the infants developed blindness. Due to substantial proportion of missing data and follow-up loss, the long-term neurological outcomes of group T were not analyzed.

DISCUSSION

In this retrospective study, we characterized blood pressure trends during the initial 72 hours from birth and compared the mortality and morbidities between normotensive and permissive hypotension infants. The mortality rate and incidence of severe IVH and moderate to severe BPD were high-

Table 2. Mortality and Major Morbidities of Extremely Low Birth Weight Infants

|                     | N group (n=110) | P group (n=104) | T group (n=47) | p value |
|---------------------|----------------|----------------|---------------|---------|
| PDA                 | 86/110 (78%)   | 89/103 (86%)   | 38/43 (88%)   | 0.13    |
| BPD (≥moderate)     | 30/101 (30%)   | 33/90 (37%)    | 18/26 (69%)*  | 0.001   |
| NEC (≥stage 2)      | 7/109 (6%)     | 10/99 (10%)    | 6/34 (18%)    | 0.15    |
| ROP requiring laser surgery | 23/104 (22%) | 26/97 (27%)   | 13/33 (39%)   | 0.15    |
| IVH (≥stage 3)      | 9/110 (8%)     | 18/104 (17%)*  | 18/40 (45%)*  | 0.001   |
| PVL                 | 8/106 (8%)     | 8/88 (9%)      | 2/34 (6%)     | 0.83    |
| Mortality           | 13/110 (12%)   | 17/104 (16%)   | 24/47 (51%)*  | 0.001   |

PDA, patent ductus arteriosus; BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia.

* p<0.05 versus N.
† p<0.05 versus P.

Table 3. Odds Ratios for Mortality and Major Morbidities after Adjusting Birth Weight, Apgar Scores and Pathologically Confirmed Chorioamnionitis

|                     | p value | Odds ratio (95% CI) | p value | Odds ratio (95% CI) |
|---------------------|---------|---------------------|---------|---------------------|
| PDA                 | 0.30    | 1.5 (0.7-3.2)       | 0.72    | 1.2 (0.4-3.9)       |
| BPD (≥moderate)     | 0.51    | 1.2 (0.7-2.3)       | 0.02    | 3.6 (1.3-10.3)      |
| NEC (≥stage 2)      | 0.38    | 1.5 (0.6-4.4)       | 0.11    | 2.9 (0.8-10.8)      |
| ROP requiring laser operation | 0.79    | 1.1 (0.5-2.2)       | 0.79    | 1.1 (0.4-3.0)       |
| IVH (≥stage 3)      | 0.07    | 2.4 (1.0-5.9)       | 0.01    | 7.4 (2.6-21.5)      |
| PVL                 | 0.73    | 1.2 (0.4-3.4)       | 0.66    | 0.7 (0.1-3.8)       |
| Mortality           | 0.92    | 1.0 (0.5-2.4)       | 0.01    | 3.3 (1.3-8.5)       |

N, normotensive group; P, permissive hypotension group; T, treated hypotension group; PDA, patent ductus arteriosus; BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia.

* p<0.05 versus N.
† p<0.05 versus P.

Table 4. Long-Term Neurodevelopmental Outcomes

|                     | N group (n=110) | P group (n=104) | p value |
|---------------------|----------------|----------------|---------|
| Delayed mental function, Bayley score, MDI <75 | 3/30 (10%) | 3/36 (8%) | 0.82  |
| Delayed motor function, Bayley score, PDI <75 | 4/30 (13%) | 5/36 (14%) | 0.61  |
| Hearing abnormalities | 1/102 (1%) | 1/90 (1%) | 0.49  |
| Cerebral palsy       | 14/89 (16%) | 15/83 (18%) | 0.28  |

MDI, mental development index; PDI, psychomotor development index.

Long-term outcomes

A total of 97/110 (88%), 87/104 (84%), and 23/47 (49%) ELBWIs from the N, P, and T groups, respectively, were discharged successfully. Of these, 89 (92%), 83 (95%), and 20 (87%) were followed-up for 2 years, and Bayley testing was performed in 28 (29%), 33 (38%), and 8 (17%) patients from the N, P, and T groups, respectively. There was no significant differences between groups N and P in inci-
er in treated hypotension infants than in permissive hypoten-
sion or normotensive infants. There were no differences
in mortality or morbidities, including neurodevelopment
outcomes, between normotensive and permissive hypoten-
sion infants. The results of this study support the proposal
that a permissive hypotension approach does not result in
poor outcomes.

Dempsey, et al.\textsuperscript{7} reported that careful observation without
intervention in ELBWIs with hypotension (defined as
BP<GA) and good perfusion signs resulted in outcomes as
good as those of normotensive infants. In this earlier report,
the most important factor informing the decision whether
or not to treat hypotension was clinical assessment of end
organ perfusion. By careful observation of peripheral perfu-
sion, Dempsey, et al. were able to reduce the number of in-
fants who received intervention. Although they reported
only short-term outcomes, we herein evaluated long-term
outcomes, as assessed by the 18 month corrected age Bay-
ley DMI and DPI scores, cerebral palsy, and hearing abnor-
malities. Consistent with the previous short-term study, we
found that the long-term outcomes of permissive hypoten-
sion infants were as good as those of normotensive infants.

The brain of preterm infants is known to be quite vulner-
able to hypoperfusion of cerebral blood flow.\textsuperscript{1} Several stud-
ies reported that hypotension infants who received dopa-
mine showed increased cerebral blood flow with increased
blood pressure.\textsuperscript{18,19} Dopamine is regarded as the first choice
and the most commonly used inotropic agent in hypoten-
sion of premature infants. The hypotension in ELBWIs
might be related with myocardial dysfunction induced by
umbilical cord clamping, therefore, the removal of placenta
increases systemic vascular resistance. In such cases, dobu-
tamine may be more helpful by decreasing afterload and
improving cardiac contractility. However, vasopressor ad-
ministration may induce sudden increase of blood pressure
which is uncontrollable and possibly related with IVH or
periventricular white matter injury.\textsuperscript{20} Fanaroff, et al.\textsuperscript{6} sug-
gested that hearing and delayed motor development are re-
lated to treatment of symptomatic hypotension,\textsuperscript{21} and an-
other study suggested that anti-hypotensive treatment is
related to IVH, periventricular leukomalacia and major de-
velopmental impairments. Dopamine possibly induces
worse outcomes than hypotension itself by rapidly chang-
ing cerebral hemodynamics.\textsuperscript{1,22}

In these earlier studies, however, no clear therapeutic cri-
teria or treatment protocols for hypotension treatment were
used, thus making it hard to determine whether the treated
hypotension was symptomatic or not and whether these ad-
verse outcomes resulted from symptomatic hypotension it-
self or the side-effects of treatments such as fluid replace-
ment and vasopressor agents.

Pellicer, et al.\textsuperscript{20} therefore performed a cohort case-control
study to determine the impacts of hypotension treatment on
morbidity and neurodevelopmental outcomes in low birth
weight infants, however, found no differences in the rates
of neurodevelopmental outcomes. These authors suggested
that cautious use of cardiotonics in early systemic hypoten-
sion appears to be safe. However, Pellicer, et al. defined hy-
potension based on numerical blood pressure value alone
without considering organ perfusion or overall clinical con-
dition, therefore, they might have included healthy infants
with transient hypotension in their analyses who were treated
for hypotension.

At the Samsung Medical Center NICU, hypotension in
infants is managed only when infants exhibit hemodynamically
unstable status including unstable vital signs, and im-
paired perfusion signs such as delayed capillary refill, lack
of a pinkish skin color, or decreased urine output. Non-
symptomatic hypotension infants are treated by using a per-
missive hypotension approach. We found in the present
study that treatment of hypotension in ELBWIs was related
to IVH, BPD and mortality. However, the treated hypoten-
sion infants were relatively more immature, and thus more
likely to require intervention for hypotension. Although
birth weight, Apgar score and pathologically confirmed
chorioamnionitis were adjusted in comparison of morbid-
ties and mortality, it was difficult to ascertain that worse
outcomes in the T group were not related with their higher
vulnerability.

Nonetheless, infants in the P group in the present study
could avoid unnecessary treatment for hypotension, and the
P group showed as good outcomes as the N group.

Limitations of this study include the fact that it was a ret-
rospective study, and 18 (38%) of 47 treated hypotension
patients did not survive more than 7 days because of severe
illness. Furthermore, only 69 (26%) of 261 infants were
evaluated using Bayley tests, therefore, larger data would
be needed for more reliable and constant conclusion.

In the present study, invasive BP monitoring rate was sig-
ificantly higher in the T group, and this result could be re-
lated to the fact that the T group consisted of smaller babies
who need central lines including umbilical arterial line
more than others. However, between the N and P groups,
no significant difference was observed in the ratio of inva-
sive to non-invasive BP measuring method, indicating that this factor hardly affects the BP level and outcomes, at least between N group and P group.

In summary, a numerical blood pressure value lower than gestational age should not be used as the only indicator for treating early period hypotension in ELBWIs. Unnecessary treatment can be avoided by careful monitoring of ELBWIs with hypotension but good perfusion signs, and these infants have outcomes as good as those of normotensive infants. In contrast, hypotensive infants who showed unstable vital signs and received supportive treatment had higher mortality rate, and greater incidence of severe IVH (≥stage 3) and BPD (≥moderate) than normotensive and permissive hypotension infants.

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