Efficacy of the Screening Algorithm WINROP in a Korean Population of Preterm Infants

Jung-Han Choi, MD; Chatarina Löfqvist, PhD; Ann Hellström, MD, PhD; Hwan Heo, MD

Objective: To investigate the efficacy of WINROP (https://winrop.com), an algorithm based on serial measurements of neonatal body weight to predict proliferative retinopathy of prematurity (ROP), in a Korean population of preterm infants.

Methods: The records of preterm infants with gestational age less than 32 weeks who were admitted to the neonatal intensive care unit at Chonnam National University Hospital, Gwangju, South Korea, from October 2006 to November 2010 were reviewed. The body weight of infants was measured weekly and entered into a computer-based surveillance system, WINROP, and the outcome was analyzed.

Results: A total of 314 preterm infants participated in the study. The mean gestational age was 29 weeks (range, 25-32 weeks). The mean body weight was 1263 g (range, 590-2260 g). For 166 of 314 infants (52.9%), a high-risk alarm was noted. In the high-risk alarm group, 36 infants developed type 1 ROP, according to the Early Treatment for Retinopathy of Prematurity criteria, and they were treated for ROP. The remaining 148 infants (47.1%) had a low-risk alarm. In the low-risk alarm group, 3 infants with bronchopulmonary dysplasia and intraventricular hemorrhage, a risk factor for ROP, and 1 infant without any risk factors for ROP developed type 1 ROP and were treated.

Conclusions: In a Korean population, the WINROP algorithm had a sensitivity of 90% for identifying infants with type 1 ROP. Although some limitations are present, adjustment to the WINROP algorithm for a specific population may improve the efficacy of predicting proliferative ROP and reduce the frequency of retinal examinations.

fants; the algorithm is based solely on weight development, and, to our knowledge, this is the first time it has been conducted in an Asian population.

METHODS

PATIENTS

The study group included all preterm infants born with a GA of less than 32 weeks in the Chonnam National University Hospital, Gwangju, South Korea, during October 2006 through December 2010. All preterm infants in the study group were admitted to the neonatal intensive care unit (NICU) and screened for ROP, and their body weight was measured daily. All infants survived from the initial ROP screening test to 45 weeks’ PMA. The Chonnam National University Hospital is a university-based tertiary hospital located in Gwangju, a city with approximately 1.5 million people in southwestern Korea. The participating infants were from an urban or rural population in the region surrounding Gwangju, the main city in the state of Jeollanam-do. The Chonnam National University Hospital NICU cares for about 130 preterm infants with very low BW (≤1500 g) every year. At the time of the study, the survival rate was 94.7% for preterm infants with very low BW. The serial body weight measurements were performed according to clinical routines in all participating infants daily from the day of birth until hospital discharge. The infants were weighed outside the incubator on a digital scale. The GA of participating infants was determined by the obstetricians and neonatologists according to clinical criteria, early obstetric ultrasonography, and last menstrual date of the infant’s mother.

ROP SCREENING AND TREATMENT

All participating infants received a ROP examination according to a routine protocol of the Chonnam National University Hospital NICU. The initial ophthalmologic examination was performed between the fourth and sixth weeks after birth and repeated every 2 weeks or more frequently according to the severity of ROP until full vascularization of the peripheral retina was observed or until 45 weeks’ PMA. Retinopathy of prematurity examinations consisted of binocular indirect ophthalmoscopy after pupillary dilatation with tropicamide, 0.5%, and phenylephrine, 0.5%, using a 20-diopter lens and an eye speculum. To better identify peripheral retinal findings, sclera depression was used. All ROP examinations were performed by the same experienced pediatric ophthalmologist (H.H.). Retinopathy of prematurity was classified according to the International Classification of Retinopathy of Prematurity (stages 1-5).18 The indications for treatment were based on the Early Treatment for Retinopathy of Prematurity study (ETROP) criteria.19 If the eyes of a participating infant reached type 1 ROP according to ETROP criteria, treatment was conducted.

WINROP SCREENING

In our study, the WINROP algorithm based on weight development alone was developed using the methods of online statistical surveillance.20-22 In short, the algorithm based on the data from preterm infants with no ROP or with stage 1 ROP calculated the expected safe weight for each individual infant. Then, the difference between the expected weight gain and the measured postnatal weight development at each point was calculated and accumulated. If the accumulated risk for proliferative ROP reached above a high-risk alarm limit, then a high-risk alarm was called.13

The body weight of participating infants was measured daily on a digital scale in the NICU. One weight measurement per week was entered into the online statistical surveillance system of the WINROP algorithm by a person unaware of the maximum ROP stage. The WINROP algorithm system calculated weekly the statistics of each participating infant to judge whether there was enough risk for severe ROP. After the WINROP analysis, all participating infants were divided into 2 groups, the high-risk alarm group and the low-risk alarm group. The results were correlated with the maximum ROP stage for each infant as extracted from the infants’ files.

STATISTICAL ANALYSIS AND ETHICS

The WINROP system was evaluated using sensitivity (probability that a high-risk alarm would be called, given that the infant developed type 1 ROP) and specificity (probability that a high-risk alarm would not be called, given that the infant did not develop type 1 ROP). In addition, the positive predictive value (probability that the infant would develop type 1 ROP, given that a high-risk alarm was called) and negative predictive value (probability that the infant would not develop type 1 ROP, given that a low-risk alarm was called) were calculated using the sensitivity, specificity, and prevalence in the participating infants. We calculated 95% confidence intervals for estimated binary proportions (sensitivity and specificity). Our study protocol was approved by the institutional review board of Chonnam National University Hospital and conformed to the Declaration of Helsinki.

RESULTS

ROP OUTCOME

In our study, a total of 314 infants were screened for ROP and had daily body weight measurements in the Chonnam National University Hospital NICU. The mean (SD) GA of the participating infants at birth was 29.3 (1.7) weeks (range, 25-32 weeks), and the mean (SD) BW was 1263.73 (307.35) g (range, 590-2260 g). Infants with a GA greater than 32 weeks were excluded because WINROP was not developed for GA greater than 32 weeks. Of the 314 infants in the study, 40 infants developed type 1 ROP according to ETROP criteria, resulting in an incidence of 12.7%. Of the 40 infants who developed type 1 ROP, 34 infants were treated with laser retinal ablation alone, and the other 6 infants were treated with intravitreal injection of bevacizumab combined with laser retinal ablation to prevent progression. Total retinal detachment and progression of disease occurred in 1 infant treated with intravitreal injection of bevacizumab combined with laser retinal ablation. Six infants in the study developed type 2 ROP, and the disease subsequently resolved. Clinical characteristics of study groups are shown in Table 1.

WINROP OUTCOME

For all 314 infants, weekly body weight measurements were registered and entered into the online surveillance system. For 148 infants (47.1%), a low-risk alarm occurred, and the other 166 infants (52.9%) received a high-risk alarm. In the low-risk alarm group, 4 infants devel-
oped type 1 ROP according to ETROP criteria. Three of 4 infants who developed type 1 ROP in the low-risk group were treated with laser retinal ablation alone, and 1 infant was treated with intravitreal injection of bevacizumab combined with laser retinal ablation. Three of these infants had some complications of prematurity including mild intraventricular hemorrhage grade 1 or 2, periventricular leukomalacia, and bronchopulmonary dysplasia. The remaining infant had no complication of prematurity or risk factors for ROP. Characteristics of 4 infants who developed type 1 ROP in the low-risk group are shown in Table 2. In the high-risk alarm group, 36 infants developed type 1 ROP, and the median chronologic age at treatment was 36.4 weeks (range, 33-43 weeks). And the median time from the high-risk alarm to treatment was 7.4 weeks (range, 1-16 weeks). Thirty-one of 36 infants (86.1%) who developed type 1 ROP in the high-risk alarm group were treated with laser retinal ablation alone, and the other 5 infants were treated with intravitreal injection of bevacizumab combined with laser retinal ablation.

Under the present screening guidelines, preterm infants with GA of 32 weeks or less are examined repeatedly (at least every 2 weeks) by an ophthalmologist from PMA of 30 to 32 weeks. Infants screened in Chonnam National University Hospital received a mean (SD) of 5.38 (3.63) ophthalmologic examinations per infant during October 2006 through December 2010. On the basis of the results of this study, only preterm infants with a high-risk alarm would need an eye examination. With the surveillance system using weight only, 166 of 314 infants (52.9%) in the study would need ROP examinations, and the number of infants needing ROP examinations would be reduced by 34.6%.

### TEST CHARACTERISTICS

Using the WINROP algorithm to predict type 1 ROP that required aggressive treatment, the sensitivity of the WINROP algorithm was 90.0% (36 of 40), and the specificity was 52.6%. The negative and positive predictive values in the study group with a 12.7% incidence (40 of 314) of type 1 ROP were 97.3% and 21.7%, respectively (Table 3).

### COMMENT

Retinopathy of prematurity should be detected and treated appropriately on time because if detected before progression, retinal detachment may be prevented. Thus, the sensitivity of ROP screening tests has been considered to be more valuable than the specificity. The present screening guidelines of ROP were developed based on GA at birth and BW after many international studies about the epidemiology of ROP. All preterm infants with low GA and

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Table 1. Characteristics of the Participating Preterm Infants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Infant</th>
<th>No ROP</th>
<th>ROP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Type 1</td>
</tr>
<tr>
<td>Total</td>
<td>314</td>
<td>228</td>
<td>40</td>
</tr>
<tr>
<td>Sex, no.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>168</td>
<td>120</td>
<td>24</td>
</tr>
<tr>
<td>Female</td>
<td>146</td>
<td>108</td>
<td>16</td>
</tr>
<tr>
<td>Gestational age, mean (range), wk</td>
<td>29.3 (25-32)</td>
<td>29.8 (25-32)</td>
<td>27.9 (25-31)</td>
</tr>
<tr>
<td>Birth weight, mean (range), g</td>
<td>1263 (590-2260)</td>
<td>1335 (680-2100)</td>
<td>1040 (640-1630)</td>
</tr>
<tr>
<td>Twin</td>
<td>69 (22.0)</td>
<td>47 (20.6)</td>
<td>9 (22.5)</td>
</tr>
<tr>
<td>NEC</td>
<td>27 (8.6)</td>
<td>15 (6.6)</td>
<td>6 (15.0)</td>
</tr>
<tr>
<td>BPD</td>
<td>172 (54.8)</td>
<td>116 (50.9)</td>
<td>27 (67.5)</td>
</tr>
<tr>
<td>IVH</td>
<td>143 (45.5)</td>
<td>97 (42.5)</td>
<td>20 (50.0)</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>18 (8.6)</td>
<td>10 (4.4)</td>
<td>3 (7.5)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>40 (12.7)</td>
<td>23 (10.1)</td>
<td>6 (15.0)</td>
</tr>
</tbody>
</table>

**Abbreviations:** BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity.

Table 2. Characteristics of 4 Infants who Developed Type 1 ROP in the Low-Risk Alarm Group

<table>
<thead>
<tr>
<th>Infant No./Sex</th>
<th>GA, wk + d</th>
<th>BW, g</th>
<th>BPD</th>
<th>IVH</th>
<th>NEC</th>
<th>Hydrocephalus</th>
<th>Sepsis</th>
<th>CA at Treatment, wk + d</th>
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<tr>
<td>1/Male</td>
<td>28 + 2</td>
<td>1570</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>33 + 1</td>
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<tr>
<td>2/Male</td>
<td>30 + 1</td>
<td>1470</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>34 + 5</td>
</tr>
<tr>
<td>3/Male</td>
<td>31 + 0</td>
<td>1630</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>36 + 0</td>
</tr>
<tr>
<td>4/Male</td>
<td>26 + 5</td>
<td>1090</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>36 + 5</td>
</tr>
</tbody>
</table>

**Abbreviations:** BPD, bronchopulmonary dysplasia; BW, birth weight; CA, chronologic age; GA, gestational age; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity.
BW should be screened by eye examinations to prevent blindness after progression of ROP. However, the ROP screening test with eye examination is time consuming, expensive, and stressful for preterm infants. The physical manipulation of the eye results in changes of cardiac pulse, respiratory rate, and oxygen saturation. In one study, a series of actions in the eye examination, which included instillation of eye drops, insertion of an eyelid speculum, and indentation of the globe, produced an oculocardiac reflex that induced change of heart beat and blood pressure in the patients. In this eye examination, the manipulation of the eye was a very stressful action for infants. However, only less than 10% of screened preterm infants need treatment to prevent retinal detachment.

Although ROP screening guidelines differ between countries, the present ROP screening guidelines exclude postnatal clinical measurements and other complications of prematurity considered to relate to the development of ROP. The WINROP algorithm is a new algorithm based on changes in the body weight development of infants to improve early prediction of severe ROP. There have been several studies to investigate and validate the WINROP algorithm. In the first study performed in Sweden, the WINROP algorithm was based on the postnatal factors of weight, insulinlike growth factor I, and insulinlike growth factor binding protein-3 level. All of the infants treated for ROP were identified at least 5 weeks before laser therapy was required according to ETROP criteria.

The following studies that used the WINROP algorithm based only on serial neonatal measurements of body weight were performed in Sweden and the United States and showed that 100% of infants in the study group who developed stage 3 ROP were detected, and the number of ROP screening tests could be reduced by about 76% and 75%, respectively. A recent study of preterm infants in Brazil showed that 90.5% of infants who developed stage 3 ROP in the study were identified. And the latest multicenter study in a US and Canada population of preterm infants showed that 98.6% of infants who developed type 1 ROP in the study were identified.

In our present study, type 1 ROP according to ETROP criteria was the clinically appropriate indication for treatments of ROP. The sensitivity and specificity of the WINROP screening were thus based on type 1 ROP rather than stage 3 according to the International Classification of Retinopathy of Prematurity. The WINROP algorithm, which used only serial measurements of weight development, correctly identified 36 of 40 infants (90.0%) who had developed type 1 ROP that required treatment by ETROP criteria.

The WINROP algorithm was developed based on data from preterm infants with no or stage 1 ROP at a single NICU in Sweden, a developed country. In addition, a previous study in the developing country of Brazil demonstrated that the WINROP algorithm based on data from the Swedish population had a sensitivity of 90.5% and specificity of 55.0%. The somewhat lower sensitivity was explained by the fact that GA as well as dates of weight measurements were determined and registered more exactly in the Swedish and American studies using full gestational weeks plus days, while in the Brazilian study, an approximation to full weeks was performed. One study showed that more mature and larger infants who developed severe ROP needed treatment in less-developed countries. Korea is a developed, industrialized country, ranked 12th in 2010 by the United Nations Development Programme on the basis of its Human Development Index. However, the participating infants were from a population in the region surrounding Gwangju, which has the characteristics of a developing country. Gwangju and its surrounding region are less industrialized and developed than other regions in Korea. In our study, infants were not identified by the WINROP algorithm based only on weight development. These results suggested that WINROP screening criteria based only on body weight development have to include the country’s characteristics, especially for developing countries.

Several studies have shown that some complications of prematurity, including intraventricular hemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia, sepsis, and necrotizing enterocolitis, are related to the occurrence of ROP. In a previous study of a Brazil population, 2 infants who were not identified by the WINROP algorithm had sepsis, which could induce unexpected excessive weight gain after intensive nutritional supplements. However, in our study, 3 of 4 infants who were not identified by the WINROP algorithm had some complications of prematurity, including intraventricular hemorrhage, periventricular leukomalacia.
lac, and bronchopulmonary dysplasia, and the remaining infant had no risk factor for ROP or complication of prematurity that could induce excessive weight gain such as hydrocephalus and sepsis. Because ROP is a treatable disease if detected on time, sensitivity that is able to identify positive disease is very important. Thus, we applied additional risk factors for ROP to improve the sensitivity of the WINROP algorithm. These additional risk factors included intraventricular hemorrhage, bronchopulmonary dysplasia, necrotizing enterocolitis, sepsis, and hydrocephalus. In the low-risk alarm group, all infants with additional risk factors received a ROP examination. The sensitivity of the modified algorithm that included additional risk factors was 97.5% (39 of 40), and the specificity was 17.2%. The negative and positive predictive values of type 1 ROP were 97.9% and 14.7%, respectively, and the frequency of ROP examinations could be reduced by 10.0%. The number of ROP examinations using the modified algorithm increased compared with using the WINROP algorithm based only on weight development.

The WINROP algorithm provides a method to identify the preterm infants at risk for severe ROP. Although it has to be modified to optimally increase efficacy in countries where more mature infants develop ROP, it can be useful because it is entirely based on weight measurements that are already performed as part of clinical practice all over the world. The previous studies to validate the WINROP algorithm based only on serial weight measurements of body weight were performed in Swedish, American, and Brazilian populations of preterm infants.

This study validated the WINROP algorithm in a Korean population of preterm infants; it is the first such study conducted in an Asian population. We believe that more study in Asian countries will improve the efficacy of the WINROP algorithm for Asian populations, and subsequent improvements and modifications of the algorithm will help reduce the incidence and excessive performance of ROP examinations.

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Correspondence: Hwan Heo, MD, Department of Ophthalmology, Chonnam National University Medical School and Hospital, 8 Hak-Dong, Dong-Gu, Gwangju, 501-757, South Korea (opheye@hanmail.net).

Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

Conflict of Interest Disclosures: Drs Löfqvist and Hellström own shares in PremaCure AB, which owns the rights to WINROP.

REFERENCES


