Use of an online screening algorithm - Weight, Insulin-derived growth factor 1, Neonatal Retinopathy of Prematurity (WINROP) for predicting retinopathy of prematurity in Indian preterm babies

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Purpose: Inopathy of prematurity (WINROP) Weight, insulin-derived growth factor 1, neonatal ROP algorithm is an online tool that has been validated as a predictor of retinopathy of prematurity (ROP) in various countries. The current study was designed to evaluate the predictive ability of WINROP algorithm (http://winrop.com) using postnatal weight gain in detecting Type 1 ROP in Indian babies. **Methods:** Prospective single centre observational study of 153 consecutive preterm babies who were eligible for screening for ROP as per the standard guidelines. Sixteen babies were excluded from the study because of various reasons. Thirty-five babies had gestational age ≥32 weeks and were ineligible for WINROP algorithm. Online WINROP algorithm was used for 102 babies with gestation at birth less than 32 weeks. The alarms triggered by WINROP were documented. **Results:** Laser treatment was done in 30 babies who developed Type 1 ROP. Of these, WINROP alarm was signaled in 24 babies and 6 babies developed ROP without any WINROP alarm. These babies had associated comorbidities like respiratory distress syndrome, patent ductus arteriosus, bacterial sepsis, and ventilatory support. WINROP alarm was significantly associated with Type 1 ROP (*P* < 0.001). The sensitivity of WINROP was 80% and specificity was 80.6% with a positive predictive value of 63.2% and negative predictive value of 90.6% in detecting Type 1 ROP. In the present study, no baby who was ineligible for WINROP developed Type 1 ROP. **Conclusion:** WINROP provides a novel online monitoring screening tool for identifying babies at risk of developing Type 1 ROP. In our cohort, none of the babies whose period of gestation was more than or equal to 32 weeks developed sight threatening Type 1 ROP. WINROP algorithm may also be useful in Indian population.

Key words: Risk factors for ROP, Type 1 ROP, WINROP

India is home to 3.5 million preterm babies out of 15 million preterm births all over the world every year.[1] Retinopathy of prematurity (ROP) is recognized as a major health challenge in these babies and the Indian government has included ROP under the Rashtriya Bal Swasthya Karyakram.[2] The national screening guidelines recommend the screening of all preterm babies with a birth weight less than 2000 g, gestational age of less than 34 weeks, and gestational age between 34 and 36 weeks in the presence of risk factors.[3] This translates into a huge cohort of patients needing screening. Of the babies screened for ROP 10–50% develop ROP and of these, only 5–10% require treatment.[4-7] Keeping in mind the limited number of retina specialists trained for screening and treating these neonates for ROP, we need a simpler algorithm which can be applied by the health workers of primary health centers. The health workers can then make necessary referrals of babies to higher centers for treatment.

WINROP algorithm is one of the online surveillance systems [https://winrop.com, weekly body weight, insulin-derived growth factor 1 (IGF-1) measurement][8,9] that identify babies who will develop Type 1 ROP using the postnatal birthweight gain and insulin like growth factor (IGF) levels. The longitudinal weight change is suggested to be the surrogate marker for IGF-1 levels.[10] Nowadays, there have been trends to use a simplified WINROP algorithm that ignores IGF levels.[11,12] There is scarce data from India regarding the use of the WINROP algorithm.[13]

Objective

The present study was carried out to evaluate the predictive ability of "WINROP algorithm" (http://winrop.com) using postnatal weight gain alone in detecting Type 1 ROP in a cohort of preterm Indian babies.

Methods

The hospital-based prospective observational study was conducted in a tertiary care hospital of India over a period of 10 months from June 2017 to March 2018. The hospital has a 13-bed level III neonatal intensive care unit (NICU). The

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study was approved by the Institutional Ethics and Research Committee (IEC/2016, 0048) and written informed consent was taken from the parents.

A total of 153 consecutive inborn neonates with birth weight less than 2000 g and gestational age of less than 34 weeks were eligible for ROP screening.

We excluded 16 babies. This included babies who expired before the first ROP screening. Two babies were discharged early so longitudinal weight data was missing and these babies did not follow up for ROP screening. One infant expired after the first ROP screening, and therefore was excluded. In total, 137 babies were finally included and analyzed. Ophthalmic screening and follow-up examinations were done in all babies by an experienced ophthalmologist (SN) as per the national neonatology forum guidelines. The ophthalmologist was also blinded to the results of WINROP. The babies <32 weeks of gestational age were enrolled for online WINROP algorithm (http://winrop.com)[6] for daily weight gain.

The gestational age was the only criterion for enrolling of baby in WINROP algorithm as babies with higher birth weight are also affected with ROP in India[7] The babies who were >32 weeks of gestation were not enrolled in WINROP algorithm and were followed up as per the national screening guidelines without WINROP enrolment. Of the 137 babies, 35 neonates who had gestational age ≥ 32 weeks were ineligible for WINROP algorithm and the data of the remaining 102 infants was entered into the online WINROP algorithm (http://winrop. com)[8] for daily weight gain and to determine the accuracy and the diagnostic performance of WINROP alarm.

All the babies were followed up till the time of the first ROP screening or WINROP alarm or till the retina was fully vascularized, whichever was later.

A detailed history and review of neonatology records was done for date of birth, gender, gestational age, postconceptional age, and various risk factors of ROP including birth weight, growth status, maternal medical conditions, and obstetric problems. Neonatal morbidities such as oxygen requirement, ventilatory support, respiratory distress syndrome (RDS), transient tachypnoea of newborn, patent ductus arteriosus (PDA), and other congenital heart diseases, bacterial sepsis, cardiogenic shock, use of any inotropic drug, exchange transfusion, intraventricular hemorrhage (IVH), jaundice requiring treatment, days of mechanical ventilation, and days of oxygen support other than ventilation were also looked for. Following standard clinical routines, weight measurements were performed on all of the infants daily from the day of birth until discharge and then weekly till term gestation (40 weeks). The international classification for ROP (ICROP classification) was used for classifying ROP,[14] and the treatment indications were based on the early treatment for ROP criteria.[15]

Statistical analysis

All data was collected in an Excel database (Microsoft Office 2013; Microsoft Inc., Redmond, Washington). Data analysis was performed using Statistical Package for Social Sciences version 18 (SPSS, Inc., Chicago, IL, version 15.0 for Windows). The mean and median was calculated for all the qualitative variables and for the measures of dispersion, standard deviation, and standard errors were calculated. Sample size of 123 was calculated for this study keeping in mind that the expected prevalence of Type 1 ROP in the enrolled neonates was 10% and sensitivity and specificity of WINROP as 90 and 80%, respectively, and for achieving 5% precision of sensitivity and 5% alpha error. The independent factors predicting the development of WINROP alarm were determined using multivariate analysis. The sensitivity and specificity of the WINROP algorithm in the Indian setup were also determined. The system's positive predictive values and negative predictive values were also calculated. We calculated 95% confidence intervals for estimated binary proportions (sensitivity and specificity).

Results

One hundred and two infants met the WINROP criteria, and their data was entered into the website (https://winrop.com) including gestational age, birth weight, and daily weights until an alarm was signaled or until the time of the first ROP examination [Fig. 1].

Based on the alarm, infants were categorized into two groups: (1) Alarm group in whom the WINROP alarm for severe Type 1 ROP triggered (*n* = 38) and (2) no alarm group who were unlikely to develop ROP as per the WINROP algorithm (*n* = 64). The mean gestational age was 29.3 ± 1.4 and 30.4 ± 1.2 weeks in groups 1 and 2, respectively. The mean birth weight was 1104 ± 165 and 1545 ± 233 g in groups 1 and 2, respectively.

The timing of the alarm was recorded. All included infants completed their final ROP screening follow-up. The high-risk alarm for the WINROP algorithm was triggered in
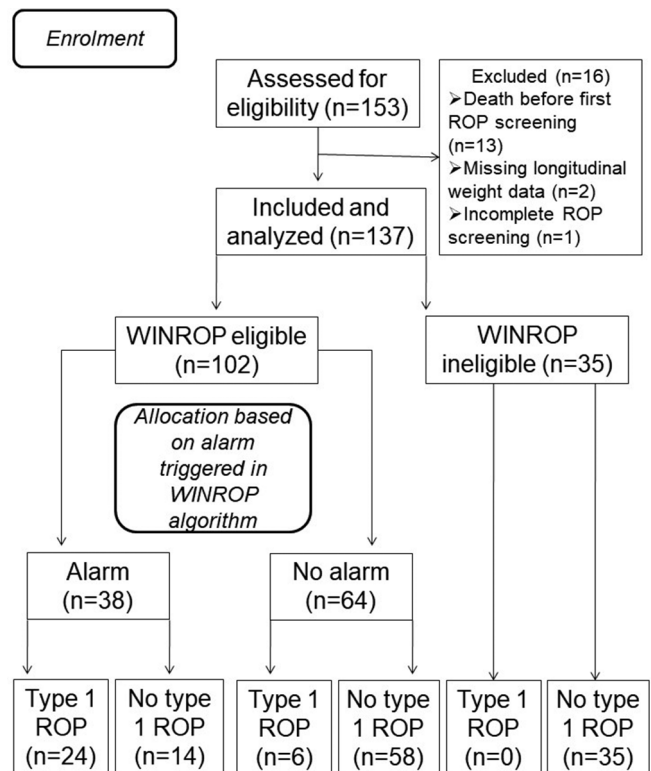

Figure 1: Flow chart of the study

Table 1: Neonatal characteristics of WINROP eligible infants in alarm vs no alarm group

Neonatal characters	Alarm (*n*=38)	No alarm (*n*=64)	*P*
Gender (Male)	18 (47.%)	26 (40.6)	0.506
Gestation at birth (weeks)*	29.3±1.4	30.4±1.2	0.001‡
Birth weight (grams)*	1104±165	1545±233	0.001‡
Small for gestation (SGA)	7 (18.4%)	2 (3.1%)	0.008‡
Apgar at 5 min	7.66±2.044	8.73±0.859	0.001‡
Respiratory distress syndrome (RDS)	25 (65.8%)	28 (43.8%)	0.031‡
Transient tachypnoea of new-born (TTNB)	2 (5.3%)	3 (4.7%)	0.896
Patent ductus arteriosus (PDA)	23 (60.5%)	12 (18.8%)	0.001‡
Proven early onset sepsis	5 (13.2%)	5 (7.8%)	0.380
Meningitis	3 (7.9%)	1 (1.6%)	0.111
Use of ionotropic drug	7 (18.4%)	3 (4.7%)	0.024‡
Intraventricular hemorrhage (IVH)	7 (18.4%)	3 (4.7%)	0.024‡
Jaundice requiring treatment	19 (50%)	32 (50%)	1
Exchange transfusion	1 (2.6%)	1 (1.6%)	0.707
Days of mechanical ventilation (invasive)*	3.42±4.785	1.20±2.476	0.003‡
Days of oxygen support other than ventilation*	1.79±2.549	1.50±3.152	0.632
Weight gain in the first week (grams)§	-60.0 (125, -19.0)	-85.0 (-149.5, -47.5)	0.21
Weight gain in the second week (grams)§	-60 (28.0 90.0)	45.0 (15.0, 77.0)	0.19
Weight gain in the third week (grams)§	72 (50.0, 110.0)	80.0 (6.0, 108.0)	0.73
Weight gain in the fourth week (grams)§	45 (10.5, 78.5	102 (50.0, 130.0)	0.062

*Values are expressed in mean±SD, †*n* (%), ‡*P*<0.05 significant, §IQR: Interquartile range

38 babies (27.7%) and not triggered in 64 babies (46.7%). The details of the "alarm group" and the "No alarm group" and the baseline variables are given in Table 1. The independent factors that predicted the alarm on multivariate analysis were gestation (OR for each week increase: 0.57, 95% CI: 0.38–0.85), small for gestational age (SGA) status (OR: 20.2; 95% CI: 2.1–195.7), and PDA (OR: 3.89; 95% CI: 1.33–11.3). Notably weight gain was not included in the multivariate model for statistical evaluation as no difference was found in the bivariate analysis.

The WINROP trigger was significantly associated with sight-threatening Type 1 ROP (*P* < 0.001) requiring treatment in 24 out of 38 babies in group 1; however, it missed six babies with Type 1 ROP in group 2. One baby developed Type 2 ROP. The six babies who developed Type 1 ROP despite no alarm had comorbidities like RDS, septic shock, PDA, IVH, jaundice requiring treatment, and bronchopulmonary dysplasia; the details of which are given in Table 2. Of the 102 babies, 30 babies developed Type 1 ROP requiring treatment giving the disease prevalence as 29.4% with accuracy of 80.39% (CI 71.35–87.59). The details of the zone and stage of ROP with and without WINROP alarm are given in Table 3. There was no correlation of the alarm with the zone or stage of ROP. WINROP alarm was significantly associated with APROP (*P* = 0.006).

Of the 24 babies in the alarm group, who developed sight threatening type 1 ROP, the alarm was triggered at birth in two infants. The median post conceptual age for alarm in babies who developed Type 1 ROP was 31 weeks (interquartile range: 29–31 weeks). The median time from alarm to development of Type 1 ROP was 4.2 weeks. The retina was fully vascularized at a mean conceptual age of 43.9 ± 1 and 42.3 ± 1.2 weeks in Group 1 and Group 2, respectively. The

Table 2: Neonatal comorbidities in infants who developed ROP without signaling WINROP alarm

RDS*	†PDA	IVH‡	JT§	BPD‖	SS¶
Yes	Yes	Yes	No	No	Yes
Yes	No	No	No	No	No
No	No	No	Yes	No	No
Yes	Yes	No	Yes	No	No
Yes	Yes	No	Yes	No	No
Yes	No	No	No	Yes	No
83.33%	50%	16.67%	50%	16.67%	16.67%

RDS*: Respiratory distress syndrome, †PDA: Patent ductusarteriosus; ‡IVH: Intraventricular hemorrhage; JT§: Jaundice requiring treatment; BPD‖: Bronchopulmonary dysplasia; SS¶: Septic shock

Table 3: WINROP alarm with location and stage of ROP

	Total *n*	WINROP alarm	No alarm	Fisher's exact *P*
No ROP	65	8	57	1.000
Z-I	5	5	0	
Z-II	32	25	7	
Z-III	0			
No ROP	65	8	57	1.000
S-1	1	1	0	
S-2	29	22	7	
S-3	2	2	0	
APROP	5	5	0	0.006

There was no correlation of the alarm with the zone or stage of ROP. Z*: Zone, †S: Stage; ‡APROP: Aggressive posterior retinopathy of prematurity

Table 4: Diagnostic performance of WINROP alarm

	Alarm Status		Sensitivity	Specificity	Predictive value	
	Yes	No	Percentages (95% CI‡)		PPV*	NPV†
Type 1 ROP	24	6	80	80.6	63.2	90.6
Type 2 ROP	6	1	85.7	66.3	15.8	98.4
No ROP	8	57	81.1	87.7	78.9	89.1

*PPV: Positive predictive value; †NPV: Negative predictive value; ‡CI: Confidence interval

age of complete vascularization was significantly higher in alarm group ($P < 0.001$). No baby who was ineligible for WINROP ($n = 35$) due to higher gestational age of ≥32 weeks developed Type 1 ROP.

Diagnostic performance of WINROP

WINROP online database sensitivity was found to be 80% (95%CI: 61.43–92.29) and specificity was found to be 80.6% (95%CI: 69.53–88.94). The positive predictive value was 63.2% (95%CI: 50.90–73.92), and the negative predictive value was 90.6% (95%CI: 82.41–95.23). The disease prevalence was found to be 29.4% (95%CI: 20.80–39.25), and the accuracy was 80.4% (95%CI: 71.35–87.59) [Table 4].

Discussion

The present study was undertaken to evaluate the predictive ability of the online WINROP model for the detection of Type 1 ROP in our setup. The WINROP algorithm surveillance software for predicting the likelihood of development of sight-threatening severe ROP requiring treatment has been validated in different countries in various cohorts.[16-24] We used only postnatal weight gain as a predictor of ROP in the present case series. It has been seen that postnatal weight gain can be regarded as a surrogate marker for IGF. There are simplified WINROP algorithms based on the postnatal weight gain as a predictor of ROP. Simplified WINROP algorithm without IGF has also been evaluated in various studies.[10,17,25,26]

The validation studies of the WINROP algorithm in various cohorts revealed varying sensitivity across all studies. In addition to the varying sensitivity, there is also a large variation in the reported specificity of the WINROP algorithm across all studies.[25,26] The discrepancies in the results could be owing to differences in underlying preterm study populations as well as difference in study design and inclusion criteria. The highest sensitivity was reported in cohorts from Sweden and North America.[10,21] The lower sensitivities seen in other populations have been largely attributed to the differences in the phenotype of ROP owing to different standards for neonatal care and requirements for oxygen saturation.[24,25] There is wide variation in the screening criteria of ROP owing to the differences in phenotype. In our setup, higher birth weight babies have been seen to have ROP[7,26] so the use of WINROP algorithm has been considered to be inappropriate for India. Notably, in the present cohort from level III nursery, none of the babies who were not evaluated by WINROP developed treatable ROP.

In a study from India by Sanghi *et al*.[13], the sensitivity of WINROP algorithm in detecting Type 1 ROP was 90.32% and specificity was 38.46%. This study had certain shortcomings. The sample size was small and the longitudinal weight data

was not available for a significant proportion of infants. The observer was not masked to the outcome of WINROP alarm which could have introduced bias in the observations. Further the overall specificity of WINROP alarm was low. This could be explained by the heterogeneous data from different levels of nurseries from the three different setups. The present study was a hospital-based single center study involving consecutive neonates fulfilling the inclusion criteria. The sample size was also adequate taking into account the expected prevalence of the disease. The sensitivity of 80% and specificity of 80.56% is comparable to that from other countries with ROP affecting higher birth weight babies.[18,19,20,24]

What distinguishes our study is that in our cohort, in addition to postnatal weight gain, we studied the postnatal comorbidities like blood transfusion, exchange transfusion, and ventilator and oxygen support to the neonates and their association with the alarm and the development of Type 1 ROP. Type 1 ROP showed a significant association with gestational age, SGA babies, and babies with PDA.

WINROP algorithm provides a novel online monitoring screening tool for identifying babies at a risk of severe ROP in the absence of any comorbidity. However, this does not appear to be sensitive in the presence of neonatal comorbidities or when ventilatory or oxygen support is required. The negative predictive value was fairly good at 90.6%. In our cohort, none of the babies, who did not fulfill the criteria for WINROP and therefore could not be entered into WINROP, developed sight threatening Type 1 ROP.

The limitation of our study was that we studied only a simplified WINROP algorithm. However, it is a simplified version that may be used to evaluate high-risk infants for closed monitoring in centers that do not have access to ophthalmic screening.

A large prospective multicentric study should be done from India to further validate WINROP and to subsequently redefine the screening criteria for ROP in India. The results of the present study show a negative predictive value of WINROP. Notably, all the babies who developed Type 1 ROP despite no alarm had comorbidities. The referral to higher centers for screening and treatment of ROP by special care neonatal units (SNCUs) in preterm babies without any comorbidities may be made based on the alarm, which is triggered using the WINROP algorithm.

Conclusion

In conclusion, WINROP algorithm is an effective and useful online tool for stratification of preterm babies for prediction of Type 1 ROP in level III NICU and may also be useful in the Indian population.

Ethical approval

Ethical clearance IEC/2016/0048.

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Conflicts of interest

There are no conflicts of interest.

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