Original Article

WINROP algorithm for prediction of sight threatening retinopathy of prematurity: Initial experience in Indian preterm infants

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Purpose: To determine the efficacy of the online monitoring tool, WINROP (https://winrop.com/) in detecting sight-threatening type 1 retinopathy of prematurity (ROP) in Indian preterm infants. **Methods:** Birth weight, gestational age, and weekly weight measurements of seventy preterm infants (<32 weeks gestation) born between June 2014 and August 2016 were entered into WINROP algorithm. Based on weekly weight gain, WINROP algorithm signaled an alarm to indicate that the infant is at risk for sight-threatening Type 1 ROP. ROP screening was done according to standard guidelines. The negative and positive predictive values were calculated using the sensitivity, specificity, and prevalence of ROP type 1 for the study group. 95% confidence interval (CI) was calculated. **Results:** Of the seventy infants enrolled in the study, 31 (44.28%) developed Type 1 ROP. WINROP alarm was signaled in 74.28% (52/70) of all infants and 90.32% (28/31) of infants treated for Type 1 ROP. The specificity was 38.46% (15/39). The positive predictive value was 53.84% (95% CI: 39.59–67.53) and negative predictive value was 83.3% (95% CI: 57.73–95.59). **Conclusion:** This is the first study from India using a weight gain-based algorithm for prediction of ROP. Overall sensitivity of WINROP algorithm in detecting Type 1 ROP was 90.32%. The overall specificity was 38.46%. Population-specific tweaking of algorithm may improve the result and practical utility for ophthalmologists and neonatologists.

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Retinopathy of prematurity (ROP) is a potentially blinding disorder affecting the developing retina of premature infants.[1] The major risk factors for developing ROP are low gestational age, low birth weight, and oxygen supplementation.[1,2] In 2010, an estimated 14·9 million babies (uncertainty range: 12·3–18·1 million) were born preterm.[3] This amounts to 11.1% of all live births worldwide. The screening guidelines formulated by the National Neonatology Forum suggest that infants born before 34 weeks of gestation or below 1750 g birth weight must be screened for ROP.[4] Infants between 1750 and 2000 g should also be screened if risk factors for ROP are present.[4] The large number of premature births, need for repeated ROP screening examinations, and paucity of experienced ROP surgeons poses a considerable challenge in India. Given this scenario, we need to look at alternative and innovative strategies for detecting ROP. Poor postnatal weight gain during the first few weeks of life is a strong predictor for the development of sight-threatening ROP[5] (Type 1 ROP requiring treatment according to the early treatment for ROP study).[6] Various algorithms such as WINROP, CHOP-ROP, and ROP score use a weight gain predictive model for the occurrence of treatable ROP.[7] These algorithms have demonstrated promise in accurately predicting ROP and reducing the number of ROP screening examinations in developed countries. However, these models have not been tested in Indian premature infants. The online monitoring tool, WINROP (https://winrop.com/), developed in Gothenburg, Sweden, is based on longitudinal weekly weight measurements and indicates an alarm if the infant is likely to develop Type 1 ROP requiring treatment.[8,9] The present study evaluates the efficacy of WINROP algorithm in predicting ROP in a cohort of Indian premature infants.

Methods

The use of WINROP algorithm requires that the infant's gestational age is from 23 to 32 gestational weeks at birth, weekly weight measurements, and physiological weight gain of <450 g/week. Infants with hydrocephalus must be excluded due to nonphysiological weight gain. Final ROP outcome data should be available. Data of preterm infants, who met the above criterion, born and managed at two urban Level II neonatal intensive care units (NICU) of North India between June 2014 and August 2016 was entered into WINROP (https://winrop.com/). Oxygen supplementation was monitored and oxygen saturation targeted between 90% and 95% in both NICUs. ROP screenings were started at 4 weeks of birth, by a single experienced ROP surgeon (GS). Infants with

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birth weight ≤2000 g or gestational age ≤34 weeks were screened for ROP based on Indian ROP screening criterion.[4] ROP was classified according to revised International Classification of ROP.[10] All treatments were done according to the ETROP study guidelines.[6] ROP screening was continued till treatment was required or complete vascularization of retina occurred. Data entered into the WINROP algorithm included birth weight, gestational age, and weekly weight measurements from birth until an alarm is signaled or a postmenstrual age of 35–36 weeks. Based on weekly weight measurements, WINROP signals either an alarm or no alarm. An alarm means that an infant is at risk for developing Type 1 ROP (requiring treatment according to ETROP guidelines). Based on actual ROP outcome, the sensitivity and specificity of WINROP alarm in predicting Type 1 ROP was calculated. The prevalence of type 1 ROP in the study cohort was further used to calculate the negative and positive predictive values of WINROP. 95% confidence intervals (CIs) were calculated.

Results

One hundred and ninety-nine infants were screened for ROP during the study period. Eight-seven infants who had a gestational age of ≥32 weeks were not eligible as WINROP algorithm requires that the infant's gestational age is from 23 to 32 weeks at birth. Of the remaining 112 infants with gestational age <32 weeks (eligible for WINROP), 36 with missing longitudinal weight data and 6 who did not complete ROP screening were excluded from the study. A substantial number of these were babies discharged early from NICU where successive weight data after discharge was not always possible. Remaining seventy infants with complete weight data and ROP outcome were enrolled in the study. None of these infants had nonphysiological weight gain. All included infants completed their final ROP screening follow-up. The median birth weight was 1075 g (range: 630–1610 g), and median gestational age was 28 weeks and 5 days(range: $24^{5/7}$ - $31^{6/7}$ weeks). Table 1 describes the overall demographic profile and ROP outcome of all infants screened during this period.

Of the seventy infants enrolled in WINROP, 31 (44.28%) developed Type 1 ROP, 12 (17.14%) had Type 2 ROP, and 27 (38.57%) had no ROP [Table 2].

WINROP alarm was signaled in 74.28% (52/70) of all infants and 90.32% (28/31) of infants treated for Type 1 ROP. The specificity was 38.46% (15/39). The positive predictive value was 53.84% and negative predictive value (NPV) was 83.3% [Table 3]. WINROP did not signal an alarm in three infants treated for Type 1 ROP. One of these infants was treated for aggressive posterior ROP (APROP) and two infants for high-risk prethreshold Stage 2 ROP in zone 2. The infant developing APROP was on a ventilator for 2 weeks, developed thrombocytopenia, and required blood transfusion.

The median time to alarm was 2 weeks from birth (range: at birth to 5 weeks). Forty-eight (92.3%) of the 52 alarms went off in the first 3 weeks of birth (i.e., before first screening at 4 weeks age), 3 alarms (5.7%) coincided with first screening at 4 weeks age, and 1 alarm (1.9%) occurred after first screening date. The median time from alarm to treatment for Type 1 ROP was 6 weeks (range: 2–11 weeks) [Figs. 1 and 2].

Discussion

In the present study, the sensitivity of the alarm for Type 1 ROP was 90.32%. This is comparable to results from other developing countries, majority of which show sensitivity ranging from 80% to 90% [Table 4].[8,9,11-19] In contrast, data from Sweden and the USA show a sensitivity of 100%.[8,9] This difference may be due to diverse populations and NICU protocols. The alarm missed an infant with APROP in the present study. This infant had prolonged oxygenation and thrombocytopenia which have been reported as risk factors for APROP in the Indian subcontinent.[20,21] It is likely that due to a complicated clinical course, APROP was missed by the alarm.

The overall specificity was low due to high false-positive rate. A recent resetting of the WINROP alarm leads to a modest increase in the specificity of the alarm.[22] Due to low specificity/high false-positive rate, we need to do ROP screening as usual for infants with positive alarm.

Alarm was triggered at birth in five infants. Recent studies suggest low birth weight as an independent predictor of ROP outcome. However, only one of the five infants with positive alarm at birth in the present study developed treatable ROP.

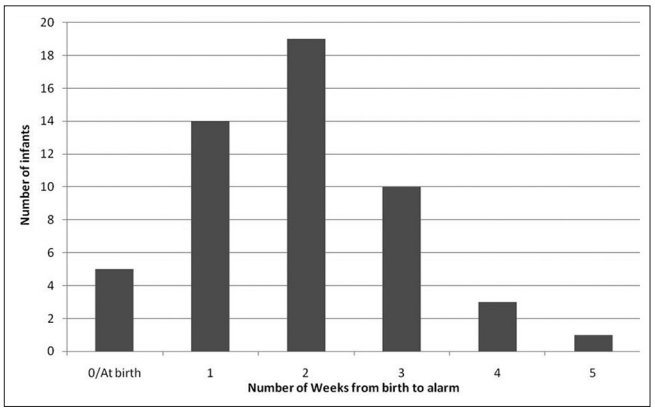

Figure 1: Distribution of infants in relation to the timing of alarm from birth

Table 1: Profile of infants screened and completing retinopathy of prematurity screening during the study period*

	Number of infants	Birth weight (g), median (range)	Gestational age (weeks), median (range)	Incidence of ROP (%)	Incidence of Type 1 ROP (%)
≥32 weeks	84	1777.5 (1060-2700)	$31^{2/7}$ (32-$36^{5/7}$)	11.9	4.76
<32 weeks excluded from WINROP due to missing longitudinal weight data	36	1390 (780-1950)	$30^{6/7}$ (26-$31^{6/7}$)	38.88	22.22
<32 weeks (WINROP)	70	1075 (630-1610)	$28^{5/7}$ ($24^{5/7}$-$31^{6/7}$)	61.42	44.28
Total	190	1400 (630-2700)	31 ($24^{5/7}$-$36^{5/7}$)	35.26	22.63

*Of the 199 infants screened, nine were lost to follow up and not included in subgroup analysis. ROP: Retinopathy of prematurity

Most alarms (92.3%) occurred before first screening (3 weeks) and 5.7% at first screening (4 weeks). With more experience, we may be able to decrease the number of examinations for infants with no alarm till first 4 weeks.

The present study had certain limitations. First, the observer was not masked to the outcome of the WINROP alarm. This could introduce bias. Second, WINROP is not currently available for infants ≥32 weeks of gestation. This has implications in Indian scenario, where older and heavier premature infants can develop severe ROP.[23] Further, WINROP misses the older premature infants (≥32 weeks) who are small for gestational age, sick, and likely to develop ROP. Inferences may not be accurate for large for gestational age infants >1500 g at birth. Third, the overall specificity of WINROP alarm is low due to a high false-positive rate. The positive predictive value was low at 53.84%. Hence, infants with positive alarm need ROP screening as usual. The NPV was modest at 83.3%. A negative

Table 2: WINROP outcome

Alarm category (*n*)	ROP type (*n*)	ROP classification (*n*)	Treated (*n*)
Total infants (70)			
Alarm (52)	Type 1 ROP (28)	APROP (7)	Treated (28)
		ROP Stage 2+ (17)	
		ROP Stage 3+ (4)	
	Type 2 ROP (12)	ROP Stage 1 (1)	Spontaneous regression (9)
		ROP Stage 2 (11)	Treated (3)
	No ROP (12)		
No alarm (18)	Type 1 ROP (3)	APROP (1)	Treated (3)
		ROP Stage 2+ (2)	
	Type 2 ROP (2)	ROP Stage 2 (2)	Spontaneous regression (1) Treated (1)
	No ROP (13)		

APROP: Aggressive posterior retinopathy of prematurity, +: Plus disease

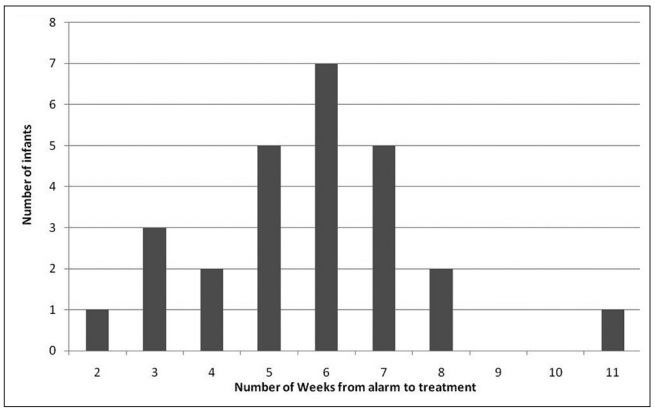

Figure 2: Distribution of infants in relation to the weeks elapsed from alarm to treatment

Table 3: Sensitivity, specificity, predictive values and likelihood ratio of WINROP alarm

	Alarm status			Percentage (95% CI)	
	Alarm	No alarm	Total	Sensitivity	Specificity
ROP categories, number of infants					
Type 1 ROP	28	3	31	90.32 (73.09-97.46)	38.46 (23.81-55.34)
Type 2/no ROP	24	15	39		
Total	52	18	70		
Predictive value, % (95% CI)					
PPV	53.84 (39.59-67.53)		Positive likelihood ratio 1.47 (1.12-1.93)		
NPV		83.3 (57.73-95.59)	Negative likelihood ratio 0.25 (0.08-0.80)		

NPV: Negative predictive value, PPV: Positive predictive value, CI: Confidence interval, ROP: Retinopathy of prematurity

Table 4: Comparative results of WINROP algorithm in various studies

Authors	Year	Country	Sensitivity (%)	Specificity (%)	NPV (%)
Löfqvist *et al*.[8]	2009	Sweden	100	54	100
Wu *et al*.[9]	2010	USA	100	81.7	100
Hård *et al*.[11]	2010	Brazil	90.5		
Wu *et al*.[12]	2012	multicentre	98.6		
Zepeda-Romero *et al*.[13]	2012	Mexico	84.7	26.6	
Choi *et al*.[14]	2013	Korea	90	52.55	
Sun *et al*.[15]	2013	China	87.5		
Lundgren *et al*.[16]	2013	Sweden	95.7	23	97.7
Piyasena *et al*.[17]	2014	UK	87		
Ko *et al*.[18]	2015	Taiwan	64.7		
Koçak *et al*.[19]	2016	Turkey	84.3	52.8	
Present study	2016	India	90.3	38.4	83.3

NPV: Negative predictive value

result is useful in identifying those babies that are at lower risk for progression to ROP. An ideal scenario would need a NPV of 100% so as to confidently reduce the ROP screening examination for infants with no alarm. Finally, our study is limited by a small sample size. Longitudinal weight data were not available for a significant proportion of infants. A study involving a larger number of infants and addressing the pitfalls of the present study is required.

Conclusion

This is the first study from India using a weight gain-based algorithm for prediction of ROP. The sensitivity of WINROP algorithm in detecting Type 1 ROP was 90.32% and specificity was 38.46%. The results of the study are comparable to data from previous studies. Population-specific tweaking of algorithm may improve result and practical utility for ophthalmologists and neonatologists.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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