DOI 10.5935/0034-7280.20190007

Application of the WINROP model in Retinopathy of Prematurity (ROP) screening in a Portuguese cohort of premature infants

Aplicação do modelo WINROP no rastreio de Retinopatia de Prematuridade (ROP) numa amostra de prematuros portugueses

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Abstract

Objective: *To evaluate the sensitivity and specificity of the WINROP algorithm for predicting retinopathy of prematurity (ROP) in a population of Portuguese preterm infants.* ***Methods:*** *Retrospective study of all newborns who underwent ROP screening at Hospital Universitário do Porto from January 2010 to May 2016. Gestational age (GA), birthweight and weekly postnatal weight measurements of the newborns, up to a postmenstrual age of 35-36 weeks, were entered in the online application of WINROP, which signals with an alarm the newborns who are at risk of developing ROP type 1, which requires treatment.* ***Results:*** *Of a total of 496 RN undergoing ROP screening, 20 were excluded from the study by incomplete records and 101 by GA ≥32 weeks. Of the newborns with a GA≥32 weeks, one developed ROP type 1 and was treated. Of the 375 newborns introduced in the WINROP application, 231 recorded an alarm signal. All the newborns with type 1 ROP were identified by the alarm signal. The WINROP algorithm presented a sensitivity and a negative predictive value of 100% and a specificity of 41%. The mean time between the alarm signal and the treatment was 10 weeks plus 6 days.* ***Conclusion:*** *The WINROP model was 100% sensitive in the detection of preterm infants requiring treatment for ROP. Besides its lower specificity, WINROP application can reduce substantially the number of exams in ROP screening. One of the limitations of the model is the exclusion of newborns with GA≥32 weeks.*

Keywords: *Retinopathy of prematurity; Weight gain; Gestational age; Birth weight; Infant, premature*

Resumo

Objetivo: Avaliar a sensibilidade e especificidade do algoritmo WINROP na deteção de retinopatia de prematuridade (ROP) numa amostra de prematuros portugueses. **Métodos:** Estudo retrospetivo que incluiu todos os recém-nascidos prematuros (RN) submetidos a rastreio de ROP no Centro Hospital Universitário do Porto entre Janeiro de 2010 a Maio de 2016. A idade gestacional (IG), peso à nascença e os pesos semanais dos RN, até uma idade pós-menstrual de 35-36 semanas, foram introduzidos na aplicação online do WINROP, que sinaliza com uma mensagem de alarme os RN em risco de desenvolver ROP tipo 1, que requer tratamento. **Resultados:** De um total de 496 RN submetidos a rastreio de ROP, 20 foram excluídos do estudo por registos incompletos e 101 por IG≥32 semanas. Dos RN com uma IG≥ 32 semanas, um desenvolveu ROP tipo 1 e foi submetido a tratamento. Dos 375 RN introduzidos no modelo WINROP, 231 (62%) registaram um sinal de alarme. Todos os RN com ROP tipo 1 foram identificados pelo sinal de alarme. O tempo médio entre o sinal de alarme e o tratamento foi de 11 semanas. O algoritmo WINROP apresentou uma sensibilidade e um valor preditivo negativo de 100% e uma especificidade de 42%. **Conclusão:** O modelo WINROP demonstrou ser sensível na deteção de prematuros com necessidade de tratamento. Embora com um valor de especificidade menor, a aplicação do algoritmo pode ajudar a reduzir substancialmente o número de exames realizados. Uma das limitações do modelo consiste na exclusão de RN com IG≥32 semanas.

Descritores: Retinopatia da prematuridade; Ganho de peso; Idade gestacional; Peso ao nascer; Recém-nascido prematuro

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The authors declare no conflicts of interests.
Received for publication 31/08/2018 - Accepted for publication 07/12/2018.

Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative disease secondary to abnormal proliferation of developing retinal blood vessels of premature newborns (NB).[1,2] According to the World Health Organization, it is the leading preventable cause of childhood blindness in developed countries.[3]

Epidemiological studies reveal variable rates of ROP prevalence in different countries, varying according to the gestational age (GA) included in the studies and the characteristics of the care provided in the Neonatal Intensive Care Units.[4] In developed countries, improved neonatal and perinatal care led to a change in the viability limit of premature newborns to declining gestational ages, thus increasing the number of children at risk for ROP.[5]

Most cases of ROP are low grade, and regress spontaneously without treatment. However, severe cases of ROP can progress rapidly to tractional retinal detachment with irreversible loss of sight.[1,2,5]

ROP screening involves multiple observations of the ocular fundus until the retinal vascularization of the newborn is complete without development of complications or need for treatment. Ophthalmologic screening tests are an important stress factor for NBs[6] and their parents, and imply a high demand of human resources. It is therefore imminent to create and validate screening protocols with high sensitivity and specificity rates allowing the identification and targeting of screening for newborns at higher risk of developing ROP in need of treatment[7] (ROP type 1 according to the study of the Cooperative Group of Early Treatment for Retinopathy of Prematurity [8]).

The WINROP algorithm (weight-insulin-like growth factor 1, neonatal, retinopathy of prematurity) developed in Gothenburg - Sweden evaluates the weekly weight gain of premature newborns to identify the cumulative risk of an NB developing severe ROP. Initially, it was based on studies demonstrating a correlation between postnatal weight measurements and serum levels of insulin-like growth factor-1 (IGF-1) with the development of ROP.[9-12] IGF-1, whose serum levels in premature newborns are lower, plays a permissive role for the vascular endothelial growth factor (VEGF) to work on normal retinal vascularization.[13] As IGF-1 levels begin to increase, abnormally accumulated VEGF causes massive vasoproliferation of the hypoxic retina. Several studies have shown that low levels of postnatal IGF-1 are correlated with low weight gain during the first weeks after birth.[7,14,15] Based on this relation, the WINROP model was later simplified to evaluate only weekly postnatal weight gain as an indirect measure of IGF-1 serum levels.

After simplifying the model, its results were primarily validated successfully in Sweden[16], and over time have been retrospectively validated in several populations of premature newborns worldwide.

The objective of the present study was to apply the WINROP model retrospectively to a sample of Portuguese premature infants in order to determine their sensitivity and specificity levels.

Methods

Population

The study included all premature newborns with a gestational age of less than or equal to 32 weeks, or birth weight (BW) less than or equal to 1500 grams or with an unstable clinical course, regardless of GA and BW, undergoing ROP screening at Centro Hospitalar Universitário do Porto between January 2010 and May 2016.

Data was collected retrospectively using clinical processes. The collection and review of individual cases were done respecting the confidentiality of each NB.

The following data was collected for all NB included in the study: demographic data, GA, BW, and weekly weight gain until they completed a postmenstrual age (PMA) of 35-36 weeks. The highest ROP grade reported in ophthalmological observations and the presence or absence of plus disease were also recorded. In cases of ROP type 1, we evaluated PMA at the time of diagnosis and treatment of ROP, the type and number of treatments carried out, and the progression of ROP. All NBs included were assessed for ROP screening until complete retinal vascularization or ROP regression.

The criteria for the online application of the WINROP model implies that the GA of the NBs included was between 23 and 31 weeks plus 7 days for BW recording, of weekly weights and a physiological weight gain <450 g/week.

Thus, newborns with incomplete weekly weight records and/or GA≥32 weeks and/or a physiological weight gain <450 g/week were excluded from our standard population.

ROP screening

The ROP screening protocol in CHUP is followed on NBs with GA lower than or equal to 32 weeks, or birth weight of less than or equal to 1500 grams, and also on NBs with an unstable clinical progression regardless of the value of GA and BW. The first exam happens between the 4th and 6th week of life, or at 31-33 weeks of PMA if the GA at birth is less than 27 weeks. Subsequent exams happen weekly or at a longer time, according to the findings of the last ophthalmic examination until the retina is completely vascularized or until ROP regression. The exam consists of observing the ocular fundus using an indirect ophthalmoscope with lens of +20D or +28D under scleral indentation and after pupil dilation with phenylephrine 2.5% and tropicamide 0.5% instilled every 10 minutes for 30 minutes.

Ophthalmologic examinations were carried out by 3 specialists in pediatric ophthalmology with experience in ROP screening.

Definition of ROP

The classification of ROP was based on the International Classification of Retinopathy of Prematurity revised in 2005.(17) The degree of ROP was defined as the most severe stage in the most posterior zone in the worst eye. The recommendations of the Cooperative Group on Early Treatment for Retinopathy of Prematurity8 were followed for treatment. According to these recommendations, ROP type 1 requiring treatment is defined as any stage of ROP in zone I with plus disease; ROP 3 in zone I with or without plus disease; and ROP in zone II, stage 2 or 3 with plus disease. In the present study, we evaluated the ability of the WINROP algorithm to predict the presence of ROP type 1.

WINROP Algorithm

The online application of the WINROP algorithm evaluates weekly weight gain to identify premature NBs at risk of developing severe ROP by a statistical analysis that takes place over several stages: the weight of the NB is compared weekly with a normalized growth curve for NBs who did not develop ROP

or developed mild ROP; the differences or deviations between the expected weight and the actual weight are accumulated from week to week, and when such cumulative deviations exceed a threshold value an alarm is signaled to indicate that the NB is at risk of severe ROP.

The GA data of each premature newborn, BW, and weekly weights measured every 7 days were retrospectively introduced in the online application until an alarm signal was recorded or up to an PMA of 35-36 weeks. For NBs with alarm signal, the week to which the message was signaled was recorded. Then, the newborns were classified into 2 groups: with or without an alarm signal. The results were compared to the highest ROP recorded for each NB, and with the presence or absence of ROP type 1.

Statistical analysis

The process of recording alarm messages by the WINROP online application was evaluated for sensitivity (probability of an alarm signal being triggered in a NB with ROP type 1) and specificity (probability that an alarm signal not being triggered in an NB without ROP type 1). Negative and positive predictive values were calculated using the sensitivity, specificity and prevalence of ROP type 1 for the group study. Data analysis was performed using the 23rd edition of the software SPSS (IBM®, USA).

Results

A total of 496 NBs with gestational age of less than or equal to 32 weeks, or birth weight less than or equal to 1500 grams underwent ROP screening between January 2010 and May 2016 at Centro Hospitalar Universitário do Porto. The average GA at birth was 30.1 weeks, and the average BW was 1222.4 grams.

Of the 496 NBs screened, 20 were excluded from the study due to incomplete weekly weight records, and 101 due to GA ≥32 weeks. No NB was excluded due to physiological weight gain <450 g/week.

Table 1 shows the averages of the GA and BW of the NBs analyzed in the study.

Of the 496 NBs, 64.1% developed any degree of ROP detected in ophthalmologic screening exam, and 5.8% developed ROP type 1. The prevalence of ROP grade 1 was 52.0%, ROP grade 2 was 6.7%, ROP grade 3 was 4.6%, ROP grade 4 was 0.4%, and ROP grade 5 was 0.6%.

The average GA and BW were significantly lower in the NBs who developed ROP compared to the NBs without ROP (GA: 29.3 vs 31.5 weeks, respectively, ANOVA test, p≤0,0001 and BW: 1119.2 vs 1404.5g, respectively, ANOVA test, p≤0,0001).

Table 1
Descriptive analysis of the GA and BW of the newborns analyzed in the study.

	Total of 496 RN	20 NBs with incomplete records	101 NBS with GA≥32 weeks	375 NBs evalued in WINROP algorithm
GA, weeks (average±SD)	30.1±0,1	29.3±0.4	33.0±0.1	29.3±1.0
(Max-Min)	36-24	31-25	36-32	31-24
BW, grams (average±SD)	1222.4	1252.3	1448.2	1158.7
(Máx-Min)	2250-325	1845-665	2250-810	2250-325

GA: gestational age; BW: Birth weight; SD: standard deviation

Of the 20 NBs excluded from the study due to incomplete weekly weights, 2 developed ROP type 1 and underwent treatment with an unfavorable progression for inoperable ROP 5. The characteristics of the two NBs and the type of treatments are shown in table 2.

Of the 101 NBs excluded due to GA≥32 weeks, 1 (GA 33 weeks + 2 days, PN 1200g) developed ROP type 1. Regarding the clinical history, we emphasize the presence of intrauterine and postnatal growth restriction, the presence of cranial intraventricular hemorrhage, and the development of neonatal sepsis. Bilateral laser photocoagulation was performed at 41 weeks plus 1 day with favorable ROP regression.

Thus, a total of 375 NBs (75.6%) were evaluated by the WINROP algorithm. The average GA and BW were 29.3 weeks

Table 2
Characteristics and type of treatments carried out for NBs with ROP type 1 excluded by incomplete weekly weight records

	NB 1	NB 2
GA (weeks + days)	25 + 4	25 + 0
BW (grams)	680	665
PMA diagnosis of ROP type 1 (weeks + days)	38 + 5	41 + 0
PMA during 1st treatment	39 + 0	41 + 1
Total number of treatments	4	5
LASER photocoagulation	2	2
Intravitreal injection of anti-VEGF	1	1
PPV	1	2

GA: gestational age; BW: birth weight; anti-VEGF: anti-vascular endotelial growth factor; PPV: pars plana vitrectomy.

and 1158.7g, respectively. 26.4% did not develop any degree of ROP, 58.9% developed ROP 1, 8% ROP 2, 5.6% ROP 3, 0.8% ROP 4, and 0.3% ROP 5. Plus disease was also present in 1.9% of newborns. The diagnosis of ROP type 1 was made in 6.9% of the NBs.

The alarm signal was recorded in 231 (61.6%) of the 375 NBs enrolled in the online application, with an average PMA of 29 weeks plus 6 days (between 26-32 weeks). The alarm signal was recorded on average 1 week and 2 days after birth (between 0-3 weeks after birth). An alarm signal at week 0 only with the introduction of birth weight was recorded in 52 NBs (22.5%).

The most recent alarm signal occurred at 32 weeks of PMA in 20% (47/231) of newborns, and the earliest at 26 weeks of PMA in 1.7% (4/231) of newborns.

The average of GA and BW and the characterization of ROP in premature infants with alarm signal and without alarm signal record are shown in table 3.

The analysis of these results showed that all NBs with ROP≥3, ROP type 1, and with Plus disease were identified with an alarm signal.

An alarm signal was also recorded in 39.4% of NBs without ROP, in 63.8% of NBs with ROP 1, and in 86.7% of NBs with ROP 2. Graph 1 analyzes the percentage of NBs without ROP or with ROPs≤2 (low-grade) identified with alarm signal.

In NBs with ROP type 1, the average time between alarm signal record and treatment was 11 weeks plus 1 day (between 6-17 weeks). In all of them, the alarm signal was recorded at least 6 weeks

Table 3
Gestational age, birth weight, and ROP characterization of premature infants with and without an alarm signal in the WINROP online application

	Alarm (n=231)	Without Alarm (n=144)	Total (n=375)
GA, weeks (average±SD)	28.6±1.8	30.5±0.1	29.3±0.1
BW, grams (average±SD)	971.4±211.9	1459.2±18.3	1158.7±16.5
Without ROP n (%)	39 (16.8)	60 (41.6)	99 (26.4)
ROP 1	141 (61.0)	80 (55.5)	221 (58.9)
ROP 2	26 (11.2)	4 (2.8)	30 (8.0)
ROP 3	21 (9.0)	0 (0)	21 (5.6)
ROP 4	3 (1.3)	0 (0)	3 (0.8)
ROP 5	1 (0.4)	0 (0)	1 (0.3)
Plus disease	7 (3.0)	0 (0)	7 (1.9)
ROP type 1	26 (11.3)	0 (0)	26 (6.9)
Treated	26 (11.3)	0 (0)	26 (6.9)

GA: gestational age; BW: Birth weight; SD: standard deviation

before treatment. Table 4 presents the average gestational age and the average postmenentual ages of NBs with ROP type 1: at the date of the alarm signal, at the date of diagnosis, and at the date of the first treatment (in weeks). The average BW of NBs with ROP type 1 was 654.8g (between 520-770g).

All NBs diagnosed with ROP type 1 underwent treatment.

The first treatment carried out in 92.3% (24/26) of NBs was the LASER photocoagulation of the ischemic retina, and in 7.7% (2/26) cryoablation of the ischemic retina. In 84.6% (22/26) of NBs, a favorable regression of ROP was observed with only one treatment. The remaining 4 evolved to ROP 4a despite the reinforcement of LASER photocoagulation in two of them. They were subsequently submitted to pars plana vitrectomy with endolaser, and only 1 progressed to inoperable ROP 5.

Table 4
Analysis of the average gestational age and the average postmenentual ages of NBs with ROP type 1 at the date of the alarm signal, the diagnosis of ROP type 1, and the date of the first treatment in weeks.

Age, weeks	Average ± SD
GA	26.4±1.8
PMA alarm signal	28.0±1.6
PMA diagnosis of ROP type 1	38.1±2.8
PMA during 1st treatment	38.4±3.1

GA: gestational age; PMA: post-menstrual age

The WINROP algorithm presented a sensitivity of 100% (26/26), a negative predictive value of 100% (144/144), a specificity of 41.7% (144/349), and a positive predictive value of 11.3% (26/231), table 5.

Discussion

Of a total of 496 NBs undergoing ROP screening between January 2010 and May 2016 at Centro Hospital Universitário do Porto, 64.1% developed any degree of ROP, and 5.8% developed ROP type 1, requiring treatment.

Studies report that the incidence of ROP among premature NBs may be as high as 70%, however, the incidence of ROP type 1 represents only a small percentage of the total, ranging from 5% to 35% in different studies.(8,18,19)

For the identification of this important fraction of NBs, multiple screening ophthalmologic examinations are carried out on all premature NBs who meet the criteria for inclusion in the ROP screening program.

Observations of the ocular fundus made in the ROP screening are not risk-free for the NB.(6) For funduscopic observation, it is necessary to use eye drops with sympathomimetic or parasympatholytic properties which, although rarely, can be absorbed systemically causing adverse effects for the NB. In addition, the discomfort caused during the exam is a moment of stress for the NB, which may interfere with its clinical situation that

Table 5
Calculation of the sensitivity, specificity and positive and negative predictive values of the WINROP model.

	Alarm signal		%			
	Yes	No	Sensitivity%	Specificitye%	Positive Predictive Value%	Negative Predictive Value%
ROP type 1	26	0	100	41.7	11.3	100
Without ROP type 1	205	144				
Total	231	144				

Current guidelines for ROP screening are based on gestational age and birth weight of newborns. Based on these two variables, on the one hand, a large number of NBs are included in the screening, and, on the other hand, all NBs are treated at a common risk level for the development of severe ROP.

Other variables such as weight gain after birth or the presence of systemic complications known as risk factors for the development of more aggressive forms of ROP have been applied in the creation of new ROP screening protocols such as the WINROP algorithms, ROPscore, and CHOP ROP.[7]

These models may incorporate other risk factors and help in the risk stratification of the NBs, directing the screening for the NBs at greater risk of developing severe ROP.

The WINROP algorithm is based on the correlation between the risk of the NB developing ROP with its birth weight and the increased weekly weight after birth (as an indirect measure of serum IGF-1 levels). The online application evaluates the weekly weight gain of premature NBs with GA ranging from 23 to 31 weeks plus 7 days to signal the cumulative risk of a NB with a given birth weight developing severe ROP.

This model has been tested in several countries. Table 6 presents the results obtained in some of these studies carried out in different populations. From its analysis, we can see records of very different sensitivity and specificity rates from population to population. The differences in the characteristics of the premature NB samples, the perinatal care provided, as well as the differences in the study designs and the inclusion criteria explain many of the discrepancies found in these results.

This Portuguese sample is similar to other developed countries, and the WINROP algorithm presented a sensitivity rate of 100%, but a much lower specificity rate of 42%.

The algorithm reliably identified all NBs that developed ROP type 1 (100% sensitivity). In addition, it identified NBs in a timely manner prior to the diagnosis of ROP type 1 and the need for treatment, and thus well before the development of any complication with long-term functional repercussion. The average time between the alarm signal and the treatment was 11 weeks plus 1 day.

On the other hand, the algorithm presented a negative predictive value of 100%, which allows us to safely identify which premature NBs are not at risk of developing severe ROP.

Considering these results in this NB sample, we could suggest a reduction in the number of ophthalmologic examinations performed in 144 NBs not identified by the algorithm out of a total of 375 NB (38%) screened, increasing the time interval between re-observations of these premature infants according to the clinical judgment appropriate to each case.

The confirmation of these results with a more representative sample of the Portuguese premature population could allow a significant reduction in the number of exams carried out per NB, avoiding unnecessary exams and allowing an equally efficient but more effective screening strategy to be used with a better use of available resources.

One of the limitations of the algorithm is the exclusion of NBs with gestational ages equal or superior to 32 weeks, which led to the exclusion of one NB with ROP type 1 (GA 33 weeks + 2 days, BW 1200g).

Table 6
Sensibilidade e especificidade do algoritmo WINROP em diferentes populações

Author, year	Country	Nº NB	Sensitivity %	Specificity %
Hellstrom et al., 2009[1]	Suécia	353	100	84.5
Wu et al., 2010[20]	E.U.A	318	100	81.7
Hård et al., 2010[21]	Brasil	366	90.5	55
Wu et al., 2012[22]	Canada	1706	98.6	36,2
Zepeda-Romero et al., 2012[23]	México	352	84.7 (IG<32s) 5.3 (IG>32s)	26.6(IG<32s) 88.3(IG>32s)
Sun et al., 2013[24]	China	590	89.3	89
Choi et al., 2013[25]	Coreia do Sul	314	90	52.6
Lundgren et al., 2013[18]	Suécia	407	95.7	23.9
Piyasena et al., 2014[26]	Reino Unido	410	87.5	63.4
Eriksson et al., 2014[27]	Suécia	104	100	58.6
Ko et al., 2015[28]	Taiwan	148	64.7	55
Koçak et al., 2016[29]	Turquia	223	84.3	52.8
Timkovic et al., 2016[30]	Republica Checa	445	100	69.7
Piermarocchi et al., 2017[31]	Itália	377	83.6	55.2
Jung et al., 2017[32]	E.U.A	483	88.6	53.3
Estudo atual	Portugal	375	100	42

The criteria for the online application of the WINROP model implies that the GA of the NBs is between 23 and 31 weeks plus 7 days, regardless of the BW. However, these criteria may exclude NBs with higher GA, but with low BW and possible systemic pathologies implying a limitation of postnatal growth with risk of development of ROP in later PMA. This limitation is particularly evident in developing countries where the incidence of ROP in higher PMAs is higher, reflecting the lower quality of neonatal care provided in these countries. [21,23]

In many developed countries, ROP is screened on NBs with GA less than or equal to 30 weeks or BW less than or equal to 1500g [33] In the present study, the later alarm signal record occurred at 32 weeks, which occurred in 20% of the NBs with an alarm signal. Thus, the establishment of a maximum GA limit of 32 weeks even for inclusion in the ROP screening seems reasonable, in addition to the inclusion of NBs with BW of less than or equal to 1500g.

In conclusion, the WINROP algorithm in this sample of Portuguese premature infants showed a sensitivity of 100% in the identification of NBs with ROP 1 with an early alarm signal, which allows us to optimize the ROP screening strategy in these NBs. In spite of the high number of false positives, the algorithm may also be an important tool in reducing the number of screening ophthalmologic exams to be performed in NBs with low risk for the development of severe ROP not identified with an alarm signal by the algorithm.

However, it will not be sensible to extrapolate these results to the Portuguese population of premature infants considering the greater heterogeneity of both NBs and neonatal care provided at the country level.

Conclusion

Given the results obtained, the Authors of the present study suggest the extension of the same to the several Portuguese centers where ROP is screened for a future design of a mathematical model with values adapted to the Portuguese population.

Acknowledgements

The authors would like to thank Dr. Jorge Breda, head of the Ophthalmology Service at Centro Hospitalar de São João and responsible for the Pediatric Ophthalmology and Strabismus Unit of the Ophthalmology Service at Centro Hospitalar de São João, Porto, Portugal, for his contribution to the screening of retinopathy of prematurity at Centro Hospital do Porto until July 2014.

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