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Original Article

Retinopathy of prematurity: applicability of international and national screening guidelines in the north of Iran

Yousef Alizadeh, Hassan Behboudi, Maryam Dourandeesh, Reza Soltani-Moghadam, Mitra Akbari, Abdolreza Medghalchi, Ebrahim Azaripour, Zahra Moravvej

Eye Research Center, Department of Eye, Amiralmomenin Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran.

ABSTRACT

Background. To determine the applicability of current international and national retinopathy of prematurity (ROP) screening guidelines and to identify a suitable community-based screening criterion.

Methods. A retrospective study on premature neonates (≤37 weeks gestation) referred to a tertiary eye hospital ROP clinic in the north of Iran was conducted over a 10-year period. Neonates were classified as no ROP, with ROP and type 1 ROP. Data consisting of birth weight (BW), gestational age (GA) and chief risk factors were evaluated. Various screening criteria and currently established screening guidelines were applied and compared for applicability using a receiver operating characteristic curve.

Results. A total of 716 neonates with a mean GA of 31.4 ± 2.8 weeks and BW of 1629 ± 502 grams were screened. The incidence of ROP was 22.9% and type 1 ROP requiring treatment was 0.28%. When applying the national Ministry of Health Guidelines, all neonates with type 1 ROP requiring treatment were identified; These criteria had a specificity of 7% for the diagnosis of type 1 ROP, and a large number of neonates (n=645) who are not at risk for type 1 ROP will be redundantly screened. Guidelines of the American Academy of Pediatrics and the UK would miss 4.5% of patients requiring ROP treatment. According to our data a threshold of GA≤32 weeks and/or BW ≤1600 grams demonstrated a sensitivity of 95.7% and specificity of 33.6% for the diagnosis of any ROP and a sensitivity of 100% and specificity of 26.8% for type 1 ROP requiring treatment.

Conclusions. The ideal ROP screening guideline is one that is very sensitive and identifies patients requiring treatment without delay. To minimize redundant screening while maintaining optimum ROP requiring treatment diagnosis, we proposed a new local evidence-based screening guideline.

Key words: retinopathy of prematurity, prematurity, screening guideline, neonate.

Retinopathy of prematurity (ROP), a vasoproliferative retinal disease in premature neonates, is a leading cause of avoidable childhood blindness and impaired vision.[1,2] The advancement of neonatal care in developing countries including Iran has led to an increase in the incidence of ROP.[3,4] The main preventive measure in these neonates is serial fundus examinations for timely diagnosis of vision-threatening ROP.

An adequate ROP screening program should be cost-effective, detect those in need of treatment and avoid redundant examinations which are stressful for infants and families. As various population-based and prenatal care factors influence ROP and its severity, the development of specific screening criteria tailored to the local population seem necessary.[5-7] The current ROP screening guideline of the American Academy of Pediatrics (AAP) has shown to be inadequate in developing countries.[5,6] Furthermore, the

✉ Maryam Dourandeesh
maryam.dourandeesh.dl@gmail.com

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current Iranian screening guideline which recommends screening neonates of birth weights (BWs) ≤2000 grams and/or gestational age (GA) <34 weeks seems to place a large burden on the health-care system.

The purpose of this study was to access the applicability of international guidelines (including the AAP's and United Kingdom's) and our current national screening guideline in premature neonates in the north of Iran. This study was carried out at the main referral hospital for ROP in the north of Iran and is one of the few of its kind in Iran. We aimed to modify and determine a screening threshold that would be safer and more efficient to identify type 1 ROP requiring treatment in neonates.

Material and Methods

Data were retrospectively collected from the records of all premature neonates (≤37 weeks gestation) examined in the ROP clinic from 2008 to 2018 at Amiralmomenin Hospital, a tertiary hospital in the Guilan province. The study was approved by our institutional ethics review board and was conducted in accordance with the tenets of the Declaration of Helsinki with the code of IR.GUMS.REC.1394.195. The patients were all referred from local neonatal intensive care units or by a pediatrician. The same protocol was applied for all neonates and patients were examined by retina specialists with expertise in ROP. After the instillation of mydriatic eye drops (0.5% tropicamide and 1% phenylephrine) indirect ophthalmoscopy was performed using a sterile eyelid speculum, depressor and 2.2 or 30 diopter lenses. The staging of ROP was recorded according to the International Classification of ROP.

Medical data regarding gestational age (GA), birth weight (BW) and additional risk factors for the development of ROP, such as twin birth, O2 therapy, mechanical ventilation, acute respiratory distress syndrome, apnea, intra-ventricular hemorrhage and transfusion were extracted. ROP staging was done according to the International Classification of Retinopathy of Prematurity (2005). Neonates requiring treatment were indicated based on the early treatment of ROP (ETROP) study and included (Type 1 ROP): eyes with any stage of ROP with plus disease in zone 1, stage 3 without/with plus disease in zone 1, and stage 2 or 3 with plus disease in zone 2. Treatment included indirect diode laser pan-retinal photocoagulation for type 1 ROP and anti-VEGF injection or pars-plana vitrectomy when indicated.

Statistical analysis

Statistical analysis was performed using SPSS version 21 (SPSS Inc., Chicago, IL). Student t-test was used to compare the GA and BW of infants with no ROP, with ROP and type 1 ROP. The Chi-square test was used to compare categorical variables. To determine the appropriate GA and BW for screening of ROP and type 1 ROP, a receiver operating characteristic (ROC) plot was used. Different BW and GA thresholds were combined to establish sets of criteria and the sensitivity and specificity was determined in each setting. Also, the AAP, UK, and the national Iranian guidelines were applied to our patients to determine their efficacy. In the multivariate analysis, we used logistic models with the backward likelihood ratio method. All variables with significant levels less than 0.1 in multivariate analysis were entered in the logistic model. A p-value of less than 0.05 was considered to be statistically significant.

Results

A total of 716 neonates with a GA of ≤37 weeks were enrolled in this study. The mean GA ± SD of the patients was 31.4 ± 2.8 weeks (range: 24-37 weeks). The mean BW of the patients was 1629 ± 502 grams (range: 600-3360 grams).

ROP was observed in either one or both eyes of 164 (22.9%) patients, of which 22 patients (13.41%) required treatment. There was no significant difference for type 1 ROP patients in terms of gender (45.5% female vs. 54.5% male, p-value=0.67).

GA and BW of patients with and without ROP and type 1 ROP are compared in Table I.

Systemic factors and potential risk factors for ROP were compared between patients presenting with and without treatment requiring ROP (Table II). According to logistic regression analysis none of the investigated variables showed a significant effect on the development of type 1 ROP requiring treatment.

ROC curve analysis on GA for ROP detection demonstrated that the area under the curve (AUC) was 0.815 (95% CI 0.779 to 0.852). ROC curve analysis on BW for ROP detection confirmed that the AUC was 0.798 (95% CI 0.760 to 0.837). Also, the AUC for type 1 ROP was 0.745 (95% CI 0.673 to 0.818) and 0.773 (95% CI 0.709 to 0.837) for GA and BW, respectively.

According to our data, when a screening threshold of BW ≤2000 grams and GA≤35 weeks was considered; 100% sensitivity for the diagnosis of ROP and type 1 ROP was reached.

When applying the current national screening threshold for ROP (BW ≤2000 grams and/or GA<34 weeks), 99.9% of ROP patients would be diagnosed without any cases of type 1 ROP requiring treatment being missed. This threshold would result in a very weak specificity (8.6% for ROP and 7% for treatment requiring ROP diagnosis) and 645 neonates who are not at risk of type 1 ROP requiring treatment are screened. This screening factor results in a high burden on the health care system.

On the other hand, following the screening recommendations of the AAP, would demonstrate 84.1% and 95.4% sensitivity for ROP and type 1 ROP requiring treatment, respectively. The AAP threshold would miss the diagnosis of one (4.5%) patient requiring ROP treatment. Also, using the UK's screening criteria one patient requiring ROP treatment would be missed.

In order to determine an appropriate screening threshold, we investigated several potential screening criteria in terms of sensitivity and specificity (Fig. 1). The best option was a threshold of GA≤32 weeks and/or BW ≤1600 grams which demonstrated a sensitivity of 95.7% and specificity of 33.6% for the diagnosis of any ROP and a sensitivity of 100% and specificity of 26.8% for type 1 ROP requiring treatment.

Discussion

Improvement in neonatal care and the consequent rise in survival rates has led to an increase in the prevalence of ROP in middle-income countries. Early diagnosis and treatment of this disease is very important in preserving vision.[1,2,8-10]

Table I. Comparison of GA and BW of patients with and without ROP and type 1 ROP requiring treatment.

		Total	Group		Difference	95% CI		p-value*
			No-ROP	ROP		Lower	Upper	
GA	Mean ±SD	31.4 ± 2.8	32.1±2.51	28.9±2.3	3.1	2.7	3.5	< 0.001
	Range	24-37	25-37	24-35				
BW	Mean ±SD	1629 ±502	1739±485	1257±362	482	401	562	< 0.001
	Range	600-3360	600-3360	720-3000				
		Total	Group					
			No-ROP	ROP				
GA	Mean ±SD	31.4±2.8	31.4±2.7	29.0±2.0	2.3	1.1	3.5	< 0.001
	Range	24-37	25-37	24-32				
BW	Mean ±SD	1629±502	1642±503	1202±239	439	107	228	< 0.001
	Range	600-3360	600-3360	750-1600				

*Student t-test
GA: gestational age; BW: birth weight

Table II. Comparison of associated risk factors in ROP requiring (Type 1 ROP) and not requiring treatment groups.

		Total	ROP requiring Treatment		p-value*
			No	Yes	
Intubation	Yes	63 (8.8)	61 (8.8)	2 (9.1)	0.961
	No	653 (91.2)	633 (91.2)	20 (90.9)	
Transfusion	Yes	131 (18.3)	121 (17.4)	10 (45.5)	0.001
	No	585 (81.7)	573 (82.6)	12 (54.5)	
O2 Therapy	Yes	476 (66.5)	454 (65.4)	22 (100)	0.001
	No	240 (33.5)	240 (34.6)	0 (0)	
Phototherapy	Yes	367 (51.3)	349 (50.3)	18 (81.8)	0.004
	No	349 (48.7)	345 (49.7)	4 (18.2)	
ARDS	Yes	459 (64.1)	438 (63.1)	21 (95.5)	0.002
	No	257 (35.9)	256 (36.9)	1 (4.5)	
IVH	Yes	32 (4.5)	29 (4.2)	3 (13.6)	0.035
	No	684 (95.5)	665 (95.8)	19 (86.4)	
Apnea	Yes	82 (11.5)	76 (11)	6 (27.3)	0.018
	No	634 (88.5)	618 (89)	16 (72.7)	
Twin birth	Yes	189 (26.4)	185 (26.7)	4 (18.2)	0.37
	No	527 (73.6)	509 (73.3)	18 (81.8)	

*Chi-square test
ARDS: acute respiratory distress syndrome, IVH: intraventricular hemorrhage

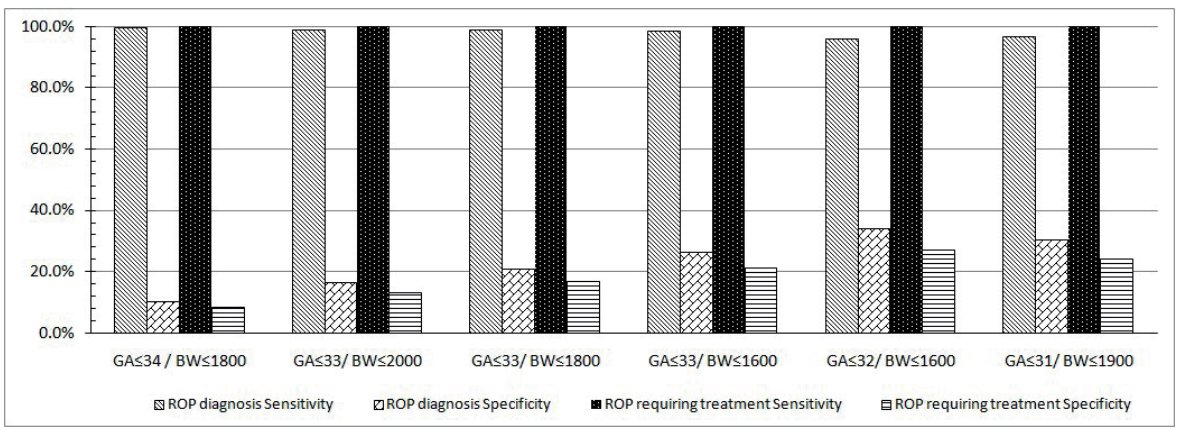

Fig. 1. Sensitivity and specificity for ROP and ROP requiring treatment diagnosis at different gestational age (GA) and birth weight (BW) thresholds using receiver operating characteristic curves.

The present study was conducted at the Amiralmomenin Hospital; the only tertiary hospital to specialize in ROP management in the Guilan province, north of Iran. The hospital is the main referral hospital for ROP in the north of Iran.

ROP was detected in 22.9% of the premature neonates. This rate was somewhat lower than the previous studies from Iran, reporting incidences of 33.3%, 42.1%, 37.2% and 26.2% from Tehran, Shiraz, Southern and North-east Iran, respectively.[11-14] We also noted lower rates compared to countries such as Turkey (27%), Oman (40.4%), Saudi Arabia (38.7%), India (25.3%), Egypt (34.4%) and Canada (40.4%).[9,15-19] In comparison lower incidence was reported

from China (15.9%), Bahrain (20.4%) and the United States (19.88%).[20-22]

Among neonates with ROP, the frequency of type 1 ROP requiring treatment in this study was 13.41%, which was higher than previous studies reported from Iran. Various studies from several provinces of Iran have reported rates from 7.5 to 11.1%.[11,12,23,24] The mean GA (29.0 ± 2.0 weeks) and BW (1202 ± 239 grams) of neonates with type 1 ROP in this study was similar to previous studies from Iran and in moderately developed countries.[11]

This difference between countries can be associated with genetics, NICU care facilities, socioeconomic status and the criteria set out in screening guidelines. Maintaining a balance between identifying all ROP infants in need of treatment and minimizing unnecessary examinations, as well as saving financial and human resources is very challenging.[9,25] Therefore, assessing screening criteria and determining criteria justified to each countries resources and requirements seems necessary.[8,19,26]

When applying the AAP and UK's guidelines to our data, we noticed that they would miss the diagnosis of one (4.5%) ROP infant in need of treatment. According to the latest regulations of the Ministry of Health and Medical Education of Iran, it is recommended that all infants with a GA of less than 34 weeks (33 weeks and 6 days or less) or a BW of 2000 grams or less, as well as infants born at birth more than or equal to 34 weeks gestation or weighing >2000 g if clinically unstable or are diagnosed as high-risk by a physician, should be examined for retinopathy. When we used our current national Ministry of Health Guidelines, all neonates with ROP in need of treatment were identified. However, when using these criteria, a large number of neonates (645) who are not at risk for type 1 ROP are being screened.

The most suitable ROP screening criteria would be one that does not miss any neonates with ROP that require treatment while limiting the burden on the health-care system and minimizing examinations of infants with mild or no ROP. By evaluating several potential screening criteria in terms of sensitivity and specificity, we reached a cut-off point of GA≤32 weeks and/or BW ≤1600 grams as the ideal criteria. This criterion has 100% sensitivity and 26.8% specificity for type 1 ROP. Roohipoor et al.[8] in 2016 showed that using the guidelines of other countries in Iran can lead to missing cases requiring treatment, so they suggested a cut-off point of G ≤32 weeks or BW≤2000 grams as the basis screening in Iran. A recent study from Tehran has proposed a cut-off point of GA≤32 weeks or BW≤1750 grams.[11] Findings of our study are in accordance with both mentioned studies and this suggests that national guidelines may need regular re-evaluation, especially in developing countries. In comparison to the two studies from Tehran, the lower cut-off BW reached in our study may be due to the larger number of patients referring to Tehran (a countrywide referral center), different socioeconomic status, different neonatal care and diagnostic facilities (e.g. ultrasound for accurate determination of GA and precision of weight scales).[27]

Evidence-based screening criteria are essential for ROP screening and are ongoing in various countries. A study in China found that using optimized criteria (GA <32 weeks or BW <1600 g) in comparison to China's Ministry of Health criteria (GA ≤34 weeks or a BW ≤1750 g) can reduce 43.2% of the examinations.[20] A study in Saudi Arabia showed that by using the Canadian criteria (GA ≤30 weeks or BW ≤1250 g) all ROP cases in need of treatment can be identified with 100% sensitivity and 13.6% specificity. These GA and BW values are lower than the values specified by the National Eye Health Program of the Saudi Ministry of Health (BW ≤1500 g or GA of ≤32 weeks).[9] A cohort study in Germany showed that in the absence of a specific risk factor, the risk of developing type 1 ROP in neonates with a GA ≥30 weeks is very low or zero.[10] This number is also lower than the current German national guideline (GA<32 weeks).[10] The newly defined criteria in these studies indicated a lower cut-off than the previously established values. The present

study and similar aforementioned studies indicate the need for periodic revision of criteria and even generating provincial specific criteria.

This study had some limitations, including the retrospective design and the relatively small sample size. Although our hospital is the primary referral center for ROP in the north of Iran, the short distance to the country's capital city medical centers may have limited the accuracy of populational demographics.

In conclusion, the most ideal ROP screening guideline is one that is very sensitive and does not miss any patients requiring treatment. Owing to different ethnic, diagnostic and therapeutic facilities and socioeconomic statuses in different countries and different regions of a country, it seems reasonable to determine local or even institutional evidence-based screening criteria. According to the present study for timely detection of type 1 ROP in this geographic region, it seems reasonable to screen for ROP at GA≤32 weeks or BW ≤1600 grams.

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Ethical approval

The study was approved by our institutional ethics review board and was conducted in accordance with the tenets of the Declaration of Helsinki with the code of IR.GUMS. REC.1394.195.

Author contribution

The authors confirm contribution to the paper as follows: study concept and design: YA; data collection: YA, HB, MD, RSM, MA, AM, EA; analysis and interpretation of data: MD, ZM; writing the paper: MD. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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