original article

Screening premature infants for retinopathy of prematurity in a tertiary hospital in Saudi Arabia

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BACKGROUND: Early detection of retinopathy of prematurity (ROP) in preterm infants is critical, especially with advancements in neonatal care and improved survival rates. However, a balance should be found between not missing any ROP requiring treatment and minimizing workload, saving resources, and reducing unnecessary examinations to fragile neonates.

OBJECTIVE: Ascertain whether our current inclusion criteria in screening ROP could be modified to ≤1250 g (while keeping the gestational age at ≤30 6/7 weeks) to reduce the number of screened babies without missing any type I ROP requiring treatment.

DESIGN: Retrospective, record-based study.

SETTING: Referral center.

MAIN OUTCOME MEASURES: ROP outcome and risk factors.

PATIENTS AND METHODS: Neonates screened for ROP in the neonatal intensive care unit of our institution between January 2016 and November 2018 were included. Data collected for each neonate included demographics, ROP details and risk factors. We used a revised version of ROP screening guidelines by the American Academy of Pediatrics.

SAMPLE SIZE AND CHARACTERISTICS: 155 neonates (median birth weight, 1035 g; range, 527–1982 g; and gestational age range, 23–39 weeks).

RESULTS: Of 1393 live births, 155 babies met the inclusion criteria. ROP occurred in 60/155 (38.7%) screened babies while sixteen developed threshold ROP. All 16 babies who required treatment had both a birthweight ≤1000 g and a gestational age ≤30 weeks. Using the screening recommendations of the Canadian Policy, more infants would have been screened without diagnosing a case of ROP of any stage, and no case of ROP requiring treatment would have been missed compared to the AAP recommendations.

CONCLUSION: ROP requiring treatment is a rare occurrence in premature infants with a gestational age >30 weeks and body weight >1000 g at our institute. Nonetheless, this is not an attempt to alter national screening guidelines. A multicenter prospective study with an adequate sample size is needed to assess whether guidelines for ROP screening should be altered in this category of neonates.

LIMITATIONS: Retrospective design.

CONFLICT OF INTEREST: None.
Retinopathy of prematurity (ROP) has been reported as the primary cause of preventable visual impairment among premature infants. Early detection of ROP in preterm and very low birth weight (BW) infants is critical, as several studies have reported a heightened risk of ROP in these infants. However, ROP screening is not only challenging to master, but is also time-demanding to conduct and may be unsafe for the patient. Nonetheless, blindness is prevented through this process by identifying the threshold ROP for treatment. Despite the small proportion of treated to screened cases, outcomes are markedly improved, and every successful case represents years of prevented blindness. On these grounds, ROP screening has been shown to be cost-effective as well as beneficial in clinical terms. At our institute, we are currently following the 2013 American Academy of Pediatrics policy for ROP screening, which states the following criteria for screening: all infants ≤1500 g and/or born at ≤30 weeks, and selected infants either with 1500 to 2000 g BW or >30 weeks gestational age (GA) with an unstable clinical course or noted by the attending pediatrician to be at high risk of ROP. The recommendations of the Canadian Pediatric Society (2010) state the evidence indicates that the likelihood of an unscreened patient developing advanced ROP requiring treatment is small, if screened infants are ≤30 6/7 weeks GA, regardless of BW, and/or have a BW ≤1250 g. Thus, we conducted this retrospective study on ROP screening at an institute in Jeddah to ascertain whether the ROP screening inclusion criteria might be safely reduced (while keeping the GA at ≤30 6/7 weeks) without missing any ROP requiring treatment.

SUBJECTS AND METHODS
ROP screening records between 1 January 2016 and 31 November 2018 were retrospectively analyzed. All the electronic files of the preterm infants from the neonatal intensive care unit (NICU) of our institute were reviewed. Participants were included if they had a BW ≤2000 g, regardless of GA, satisfied the current ROP screening guidelines, and survived until screening. The following criteria were used for exclusion: no final ROP outcome documentation, death before examination, or loss to follow up.

During the study period, all ROP screening was performed by ophthalmologists who were specially trained in ROP screening. Once an infant either reached four weeks old or 31 weeks corrected GA, screening was initiated. Cyclopentolate (0.5%) and phenylephrine (2.5%) eye drops were used three times to achieve pupil dilation. These were done five minutes apart and at least 45 minutes before the infant was examined. A topical anesthetic was applied, and then indirect ophthalmoscopy was performed with a 28-diopter lens and lid speculum. A scleral depressor was used for routine ocular rotation. The details of the examination were recorded in adherence with the revised International Classification of ROP. Any infant with stage 1 ROP or higher was considered to have any stage ROP while a case with any stage III was labelled as having severe ROP. Any neonate who had type 1 ROP or higher in either eye (high-risk prethreshold ROP) was considered a patient with ROP requiring treatment. Follow-up exams were done at weekly intervals at the ophthalmologist's discretion until the peripheral retina was vascularized normally. The same pediatric ophthalmologist or vitreoretinal surgeon performed treatment.

Sample size was determined by assuming that at least 91.0% of a given population (BW 1250 to 1500 g) are over-screened, sample size of 1393 live births and an expected response rate of 95% were considered. Thus, the study would require a sample size of 122 eligible babies to estimate the expected proportion with an absolute precision of 5% and 95% confidence limits. In this study, however, we included 155 infants in the analysis, which is larger than the ideal sample size. Nine neonates were excluded as no final ROP outcome was recorded. Data collected for each neonate included gender, GA, BW, history of multiple births, ROP details in both eyes, postmenstrual age at detection of ROP, ROP treatment if given, and the date of treatment. Other risk factors included necrotizing enterocolitis (NEC), intraventricular hemorrhage, bronchopulmonary dysplasia, patent ductus arteriosus, congenital heart defect, anemia, blood transfusion, sepsis, respiratory distress syndrome, phototherapy, birth defects, hyperglycemia, surfactant, steroids, artificial ventilation, and length of hospital stay. The institute’s Research Ethics Committee gave ethical clearance for the chart review.

Statistical analysis
This study was analyzed using IBM SPSS version 23. Descriptive statistics were used to define the characteristics of the study variables by showing central tendencies (mean) and dispersion (standard deviation), and the distribution by showing the counts and percentages. Sensitivity/specificity and receiver operating characteristic (ROC) curve analysis was used to determine the diagnostic ability of the Canadian Criteria and AAP Criteria in detecting ROP. The chi-square test was used to establish the relationship of ROP to demographic factors and other systemic risk factors. Additionally, GA age and birth weight was analyzed by ROP using
the independent t test. These tests were conducted on the assumption of normal distribution using Levene's statistic. Severe ROP was defined as a binary outcome (marking samples under the criteria of severe ROP with 1, otherwise marked 0). A binary logistic regression model (BLRM), with backward conditional elimination, was used with enter criteria=0.05 and elimination=0.10 to create a model including all infants with any severe ROP comprising infants with GA <30 weeks and/or BW <1250 g, with at least one of the following risk factors: intraventricular hemorrhage, sepsis, necrotizing enterocolitis (NEC), steroids and blood transfusion. A conventional P value < .05 was the rejection criteria for the null hypothesis.

RESULTS
Of 164 neonates who underwent ROP screening during this three-year period, 155 (71 males) were included. Nine were excluded because no final ROP outcome was recorded. Neonates with a BW ≤2000 g, regardless of GA, were referred to the NICU for ROP screening at our institute. The mean and standard deviation for BW of the infants was 1071.1 (273.0) g, and their GA was 28.3 (2.3) weeks. Fifty-three percent of the infants were Saudis. A total of 1393 infants (1011 inborn and 382 outborn transferred from other hospitals) were cared for in our hospital during the study period. Of the 155 infants, 58 (37%) were screened in 2016, 46 (30%) in 2017 and 51 (33%) in 2018 (P<.05).

Sixty of 155 (38.7%) babies had ROP on screening—37 (61.7%) had stage 1, 17 (28.3%) had stage 2, and 6 (10.0%) had stage 3 ROP, with 6/60 (10.0%) having plus disease when examined before hospital discharge. None of the infants were diagnosed with stage 4 or 5 ROP. Sixteen (26.7%) required treatment either by laser therapy (13/16 [21.7%]), anti-vascular endothelial growth factor (anti-VEGF) (1/16 [1.7%]) or both anti-VEGF and laser therapy (2/16 [3.3%]). The mean corrected GA at detection of ROP was 33 weeks. The distribution of GA and BW for patients treated and not treated are shown in Figures 1 and 2, respectively. The total number of babies <31 weeks GA and <1251 g in 2016-2018 were 122 (78.7%) and 114 (73.5%), respectively, out of the total number of preterm births. Table 1 shows the distribution of GA and BW for any stage of ROP and without ROP and those requiring and not requiring treatment. The ROC curves for gestational age and birth weight predicting ROP requiring treatment are shown using the American Academy of Pediatrics criteria (Figure 3, Table 2) and the Canadian criteria (Figure 4, Table 2).

The ROC curves for gestational age and birth weight predicting ROP requiring treatment are shown using the American Academy of Pediatrics criteria (Figure 3, Table 2) and the Canadian criteria (Figure 4, Table 2). For the Canadian criteria, a GA threshold of ≤30 weeks and/or BW ≤1250 g yielded sensitivity and specificity rates of 90.0% and 42.1%, respectively, for identifying any ROP, and sensitivity and specificity rates of 100% and 13.6%, respectively, for identifying patients with ROP requiring treatment. The Canadian criterion was considered the best option because it had 100% sensitivity for predicting ROP requiring treatment. Based
on the screening recommendations of the Canadian Policy, more infants would have been screened without diagnosing a case of ROP of any stage, and no case of ROP requiring treatment would have been missed compared to the AAP recommendations. Fewer babies (25%) would have been examined had the tested inclusion criteria (Canadian Neonatal Network 2010) been used.

The relationship between ROP and the risk factors involved was assessed by using binary logistic regression. The risk factors for any stage ROP included artificial ventilation, multiple births, blood transfusion, respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, sepsis, gender, and length of hospital stay and phototherapy. Only the length of hospital stay (>90 days) was statistically significant ($P<.001$, 95% CI 0.51–0.82). A higher frequency of ROP of any stage was associated with a longer hospital stay (Figure 5). BW was the best predictor for the development of any stage ROP ($P<.001$, CI 1.001–1.004), as determined using the binary logistic regression model with backward conditional elimination (Table 3).

### Table 1. Distribution of gestational age and body weight for participants with any stage of retinopathy of prematurity and without retinopathy of prematurity and for participants requiring and not requiring treatment for retinopathy of prematurity.

| Variables                  | All participants | ROP of any stage | Mean difference | 95% CI | P value |
|----------------------------|------------------|------------------|-----------------|--------|---------|
|                            | No (n=95)        | Yes (n=60)       |                 |        |         |
| Gestational age (weeks)    | 28.3 (2.3)       | 29.0 (2.3)       | 27.2 (1.8)      | 1.796  | 1.110–2.481 | <.001 |
| Body weight (g)            | 1071.1 (288.1)   | 1168.7 (273.0)   | 916.5 (241.4)   | 1.796  | 167.107–337.346 | <.001 |

ROP requiring treatment

| Variables                  | No (n=130) | Yes (n=16) |
|---------------------------|-----------|-----------|
| Gestational age (weeks)    | 27.18 (1.8) | 27.50 (1.7) | 26.3 (1.9) | 1.188 | 0.186–2.189 | .02   |
| Body weight (g)            | 916.5 (241.4) | 970.1 (244.3) | 769.1 (162.7) | 200.966 | 68.866–333.066 | .003  |

Data are mean (SD) and range. ROP: retinopathy of prematurity.
**DISCUSSION**

A total of 155 neonates born with birth weight ≤2000 g were screened for ROP between January 1, 2016 and November 30, 2018, regardless of GA. The number of neonates referred annually for screening did not differ significantly. Additionally, during the three-year study period, the incidence of ROP did not change significantly, as the study had a near consistent ROP incidence (38.7%) with respect to other published results both locally⁹ and internationally—Egypt (152 participants, 34.4%),¹⁰ Oman (73 participants, 34.4%),¹¹ and India (165 participants, 47%).¹² A comparable proportion of ROP requiring treatment (16%) has been reported in another study conducted in the region.¹³ During the three-year study period, 16 babies (10.3 %) showed threshold disease and none progressed to stage 4 or 5 in either eye. Several factors contribute to this variability in ROP incidences and outcomes, such as survival rate, the standard of care, genetic factors and ethnicity.¹⁶⁻¹⁸

The importance of using BW,¹⁵ GA,¹⁶ or both¹⁷ as part of ROP screening inclusion criteria is well established. In our study, BW was the best predictor of the development of any stage ROP (P<.001, CI 1.001–1.004), of the other risk factors had a significant correlation except for the length of hospital stay >90 days (P<.001, CI 0.51–0.82). Nonetheless, we advocate using both GA and BW as the basis for screening inclusion criteria.

Under the 2013 American Academy of Pediatric guidelines, 32 (20%) fewer babies would have been screened without missing any ROP requiring treatment.
if the criteria BW ≤1250 g and/or GA ≤30 weeks were utilized. This suggests that it is possible to adjust the BW threshold from 1500 g to ≤1250 g, allowing for a focus on visually-threatening stages. This finding is in agreement with several studies that observed no threshold ROP in children weighing more than 1250 g.7,18 Other authors have even suggested lowering the BW and GA threshold to less than 1000 g and 28 weeks, respectively.20,26 ROP screening guidelines are set higher in several developing countries in order to avoid missing ROP requiring treatment based on some reports that suggested more mature babies can experience threshold ROP.19,20 Two babies with stage III and with BW greater than 1000 g and GA higher than 30 weeks would have been missed with BW greater than 1000 g and GA higher than 30 weeks in a study from Denmark.21 Keith and Doyle reported that blindness developed in 16 infants with BW >1250 g and six with GA ≥31 weeks in Australia.19 Two babies requiring treatment weighed >1250 g in a Jordanian cohort.22 Of note, ROP requiring treatment can occur in heavier babies falling outside the Canadian criteria; however, the Canadian Pediatric Society still recommends its practice point regarding the recommendations for ROP screening published in 2010,7 which requires a cut-off point of 1250 g. Canadian Neonatal Network data spanning five years (2009–2014) showed that 2171 neonates with a BW >1250 g were screened for ROP, and three (0.14%) were treated for the condition.23

A local study conducted between 2003 and 2004 found a higher mean GA in infants developing any stage ROP; the investigators recommended that the current GA threshold be increased to 34 weeks GA.10 However, the recommendation to include larger babies was to avoid missing any stage ROP and none of those who developed threshold ROP requiring treatment were above 800 g or 28 weeks. A study on Saudi preterm infants did not clearly state the upper limit of BW of treated ROP cases.18 However, another study conducted in Saudi Arabia reported that no infant with BW exceeding 1350 g or GA >31 weeks was treated for ROP.24 With advanced neonatal care, failure to detect any ROP requiring treatment in more mature infants might be more generalizable to our current practice than in previous studies. Nonetheless, it is still possible that some babies may fall outside the criteria and might end up developing severe ROP. Therefore, high-risk babies are included in the screening at the neonatologist’s discretion, in addition to numerous algorithms25,26 being validated to capture these neonates.

Figure 5. Number of cases with retinopathy of prematurity of any stage and without retinopathy of prematurity by length of neonatal intensive care unit stay (percentages are total for each group, P<.001 chi-square: 20.23)

ROP IN PREMATURE INFANTS

Practical national guidelines for screening and treatment of ROP in Saudi Arabia have recently been published to provide a framework for local ophthalmologists to follow. These guidelines, led by the National Eye Health Program of the Saudi Ministry of Health, recommended screening neonates with birth weight of ≤1500 g and/or GA of ≤32 weeks; however, efforts are being made to implement them across the country.27 Currently, different ROP screening protocols with a wide range of variability are followed by different institutes in Saudi Arabia. However, it is imperative to conduct that a prospective, population-based, multi-center study to ensure that ROP cases requiring treatment would all remain detectable despite lowered screening criteria before our suggestion is implemented. The emphasis on conducting further studies also highlights the dangers of altering the indications for national screening on the basis of one study population.

There are several limitations to our study. The numbers in our study were relatively small. Additionally, not all the babies were examined by the same ophthalmologist, and they did not necessarily follow the same threshold for treating type 1 ROPs. This non-uniformity is known to cause some discrepancy in diagnoses; however, it is less likely in severe ROP stages than milder cases.28 Furthermore, not all preterm infants born at our NICU may have been screened, and some might have been followed up elsewhere, thereby not reflecting the actual frequency of ROP. On the other hand, this study is the first to explore the validity of our local institute’s current ROP screening criteria. The significance of our study is, firstly, to explore the possibility of focusing our screening resources on neonates with
ROP IN PREMATURE INFANTS

vision-threatening stages of ROP and, secondly, to possibly avoid the pain and stress inflicted by unnecessary examinations of neonates who are at low risk of ROP requiring treatment. Slevin et al reported that participants showed increased neurobehavioural activity, as well as crying, during the invasive part of the screening, concluding that among preterm infants, ROP screening is distressing.4 Finally, to find a balance between efficiency and targeting populations at risk only, various authors have emphasized the inherent costs of over-screening premature babies, as well as the increased workload in the ophthalmic department.8,29

In conclusion, ROP requiring treatment is a rare occurrence in premature infants with a GA > 30 weeks and birth weight >1000 g. Ideally, one should not miss any ROP requiring treatment while minimizing the cost, saving resources, and reducing stressful unnecessary examinations to fragile neonates. While the adoption of the Canadian Neonatal Network guidelines would likely yield a high specificity in limiting unnecessary examinations without compromising sensitivity in identifying ROP participants, such a strategy cannot be applied to all neonatal populations without first carrying out a prospective population-based multicenter study. If other institutions in Saudi Arabia can confirm our findings, only then would it seem appropriate to reconsider our current ROP screening inclusion criteria to be safely reduced without missing any ROP requiring treatment. Additionally, it may be beneficial to conduct more studies that consistently verify whether the risk factors identified in our logistic regression model are the same, or if there are more that are relative to ROP outcomes.

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