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Restricted universal guidelines for ROP screening: A possible misguidance for middle income countries

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Aim: The objective of all studies evaluating retinopathy of prematurity (ROP) screening criteria has been to minimize the number of infants screened while missing no patients with ROP who required treatment. Studies supporting the recommendation that screening for ROP could be restricted to infants born at less than 30 weeks of gestation with birth weights of less than 1250 g have been reported recently, especially from Western countries. However, with the lack of local outcome data, application of the new restricted screening guidelines to infants in middle income countries may lead to misguidance. We aimed to investigate ROP screening requirements in infants born at more than 30 weeks of gestation with birth weights above 1250 g in our unit and to compare them with different countries' screening guidelines to assess the possible risk of restricted guidelines in our unit.

Materials and methods: Retinopathy screening results were analyzed in relevance to the birth weight, gestational age, and contributing clinical factors. Infants who had a gestational age of 30 weeks or less and a birth weight less than or equal to 1250 g (Group 1) were compared to those who had a gestational age greater than 30 weeks and a birth weight greater than 1250 g (Group 2).

Results: Among 226 live premature infants, 51 (22.5%) of them required laser treatment. No patient developed blindness. The majority of patients who required laser treatment (n = 27, 53%) belonged to Group 2.

Conclusion: This study showed that applying developed countries' guidelines might lead to a misdiagnosis of many patients who require treatment. Restriction criteria in retinopathy screening guidelines should be based on local population studies of the disease, not on results from other regions like high income countries.

Key words: Premature, retinopathy of prematurity, screening

ROP taraması için kısıtlı evrensel rehberler: orta gelirli ülkeler için muhtemel bir yanlış yönlendirme

Amaç: Prematüre retinopatisi tarama kriterlerini değerlendiren tüm çalışmaların hedefi tedavi gerektiren retinopati hastalarını kaçırmadan taranacak hasta sayısını azaltmaktır. Son zamanlarda, özellikle batı ülkelerinden ROP taramasının tamamlanmış 30 hafta ve doğum ağırlığı 1250 gramdan az olan prematüre bebeklere sınırlanabileceğini öneren çalışmalar yayınlanmıştır. Bu çalışmada ünitemizdeki >30 hafta üzeri ve >1250 g doğum ağırlığı olan prematüre bebeklerde retinopati tarama gereksinimi araştırmayı ve elde ettiğimiz sonuçları değişik ülkelerin tarama rehberleri ile karşılaştırmayı ve kısıtlı tarama programının muhtemel riskini değerlendirmeyi amaçladık.

Yöntem ve gereç: Retinopati tarama sonuçları doğum ağırlığı, gestasyon haftası ve klinik bulgularla bağlantıları açısından analiz edildi. Gestasyon haftası ≤30 hafta ve doğum ağırlığı ≤1250 g (Grup 1) olan bebekler, gestasyon haftası >30 hafta ve doğum ağırlığı >1250 g (Grup 2) olan bebekler ile karşılaştırıldı.

Bulgular: 259 prematüre bebeğin 51'inde cerrahi gereksinim tespit edildi ve Evre ≥3 prematüre retinopatisi olan bebeklerin çoğunluğu (n = 27, % 53) Grup 2'ye aitti. Gelişmiş ülkelerin rehberlerinin uygulanmasının tedavi gerektiren birçok hastanın tanı alamamasına neden olabileceği görüldü.

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Sonuç: Bu çalışma gelişmiş ülke rehberlerinin uygulanmasının tedavi gerektiren birçok hastanın tanı alamamasına neden olabileceği göstermiştir. Retinopati tarama kriterlerinin kısıtlanması başka bölgelerden, özellikle de gelişmiş ülkelerden elde edilen verilere değil, yerel topluluktan elde edilen çalışmalara dayandırılmalıdır.

Anahtar sözcükler: Prematüre, prematüre retinopatisi, tarama

Introduction

Screening of populations at risk of developing a specific disease or health outcome is a common part of current medical practice. For screening to be cost-effective, the disease has to be worth screening for, the screening methodology has to be sufficiently effective to detect those at risk of developing the disease, and there needs to be an effective treatment for the disease. Retinopathy of prematurity (ROP) is a disease that fulfills these requirements; the health outcome to be avoided is blindness in a premature infant. The cost effectiveness of avoiding this outcome is immense, especially in human terms (1,2). Therefore, screening guidelines for those requiring an ocular examination that includes all infants at risk is mandatory for managing ROP. Many studies have evaluated and proposed criteria for ROP screening. The objective of all studies was to minimize the number of infants screened while missing no patients with ROP who required treatment (3).

The rate of blindness caused by ROP varies greatly among countries, depending on their level of development, the availability of evidence-based neonatal care, the assessment of visual and neonatal outcomes, and the existence of effective screening and treatment programs. The population of infants who develop severe ROP in developed, high income countries differs from that affected in middle income countries (4). The American screening guidelines for ROP, which we have also been using, suggests that infants of 1500 g of birth weight (BW) or below, or 32 weeks gestational age (GA) or younger, must be screened, while those infants above 1500 g or older than 32 weeks should be screened at the discretion of the attending neonatologist (5). Recently, a few studies supporting the recommendation that screening for ROP could be restricted to infants younger than 30 weeks GA with a BW of less than 1250 g have been reported, especially from Western countries (6-8). However, with the lack of local outcome data, application of the new restricted screening guidelines to infants in middle income countries may lead to misguidance.

In this retrospective study, we sought to find out whether a BW of less than 1250 g or a GA of less than 30 weeks could provide a safe and efficient screening criterion for detecting treatable ROP in our neonatal intensive care unit (NICU) setting. Screening guidelines recommended previously for developed middle income and high income countries were reviewed, the prevalence of ROP that required treatment was defined, and data were compared with the international outcomes.

Materials and methods

The study was conducted in a 25-bed, Level III NICU in Ankara that serves as a referral unit for central Anatolia, especially for sick, very low birth weight (VLBW) premature infants. Oxygen saturation targets were used to set to higher limits (92%-96%) than those recently accepted (88%-92%), and it was difficult to keep within those limits because of an insufficient number of nurses in shifts for ventilated VLBW infants during the study period (9). The study was approved by the Ethics Committee and a retrospective review of NICU computer-based data collection for 6 years (2000-2005) was undertaken. This study included all of the premature infants who were screened for ROP. In our center, infants with a BW of less than 1500 g or a GA of 32 weeks or less, and selected infants with a BW of 1500-2000 g or a GA of more than 32 weeks with an unstable clinical course (as defined by the attending neonatologist) were screened. The first eye examination was performed at the postnatal age of 3-4 weeks by a staff ophthalmologist at the bedside. Follow-up was continued at least every second week until full retinal vascularization was documented. Infants with pathological findings were examined more frequently, depending on the severity of retinal changes. At each examination, dilation of the pupils was done using phenylephrine (2.5%) and cyclopentolate (0.5%).

Indirect ophthalmoscopy was performed using a 20 D lens and scleral depression. Findings were classified according to the international classification of ROP (5). Laser photocoagulation was performed with the diagnosis of threshold disease.

Patients who required surgery were divided into 2 groups, depending on the BW and GA. Infants who were less than or equal to 30 weeks of gestation with a BW equal to or less than 1250 g constituted Group 1, whereas Group 2 included infants born at more than 30 weeks of gestation with BWs greater than 1250 g. The prevalence of ROP and the clinical characteristics and perinatal risk factors (BW, GA, prolonged premature rupture of membranes, respiratory distress syndrome, mechanical ventilation, early neonatal sepsis, late neonatal sepsis, patent ductus arteriosus, and bronchopulmonary dysplasia) of all of the infants were assessed. The probable number of missed patients, according to the application of our NICU's results to the reported guidelines and local studies from around the world, was determined.

Statistical analysis was performed using SPSS version 12 (SPSS Inc., Chicago, IL, USA). These data were analyzed using the Mann-Whitney U and chi-square tests. $P < 0.05$ was considered significant for all tests.

Results

Of the 259 premature infants who were candidates for ROP screening, 33 (12.7%) died prior to retinal examination. Among the 226 VLBW infants who fit the screening criteria, threshold ROP was detected and laser photocoagulation was performed in 51 (22.5%) (Figure). The majority of patients with Stage 3 or above ROP belonged to Group 2. Percentages of infants with prolonged premature rupture of membranes, early neonatal sepsis, late neonatal sepsis, and patent ductus arteriosus were as high in Group 1 as in Group 2 (Table 1). The GA of 3 patients in Group 2 was greater than 32 weeks, but none of these patients had a BW above 1500 g. On the other hand, although 7 patients had BWs greater than 1500 g, all of them had GAs of 32 weeks or less. When the criteria of a GA less than or equal to 32 weeks and a BW of less than or equal to 1500 g were used together, no patient with Stage 3 or above ROP was missed.

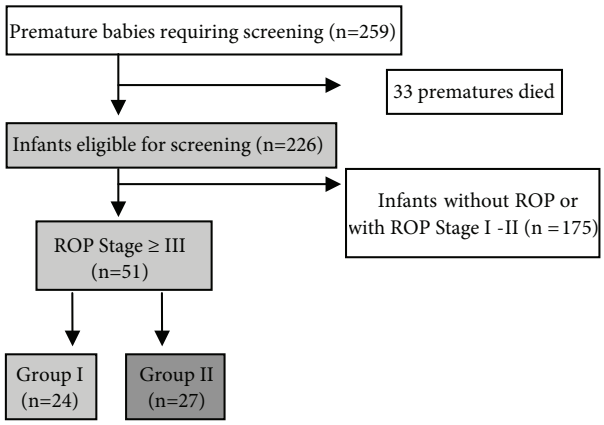

Figure. Number of screened infants and stages of defined retinopathy of prematurity (ROP).

When the Western guidelines or guidelines suggested by studies from other countries supporting the recommendation that screening for ROP could be restricted to infants with a GA below 30 weeks and a BW below 1250 g (4,6-8) were applied to our NICU population, the restriction of ROP screening caused some of the Stage 3 or above ROP patients to be missed (Table 2).

Discussion

Improved survival of premature infants has resulted in an increased incidence of ROP and an increase in blindness. A recent report showed that the incidence of ROP-related severe visual impairment or blindness in middle income countries ranged between 0% and 38.6% (10).

Screening infants at risk is a fundamental first step in the prevention of blindness. Due to differences in neonatal care protocols and the socioeconomic status of each country, the ROP screening criteria followed in higher income countries might not be appropriate in middle or low income countries. In addition, infant health assessment varies among centers within the same country, leading to intercenter differences in ROP prevalence rates (11). Recently, the International NO-ROP group suggested that each country should adopt its own screening program based on the characteristics of infants with ROP seen in its own population (4). Several studies have evaluated and proposed criteria for ROP screening. The objective of

Table 1. The characteristics and perinatal risk factors of both groups.

Clinical characteristics or risk factors	Group 1 (n = 24)	Group 2 (n = 27)	P-value
Mean birth weight (g)	1006 ± 140 (760-1245)	1358 ± 253 (1260-1780)	<0.001
Mean gestational age (weeks)	27.4 ± 1.2 (25-30)	31.1 ± 1.3 (30-33)	<0.001
Sex (male/female)	11/13	12/15	>0.05
Prolonged premature rupture of membranes (n, %)	15 (62.5%)	18 (66.7%)	>0.05
Early neonatal sepsis (n, %)	13 (54.2%)	12 (44.2%)	>0.05
Late neonatal sepsis (n, %)	14 (58.3%)	16 (59.2%)	>0.05
Patent ductus arteriosus (n, %)	6 (25%)	8 (29.6%)	>0.05
Respiratory distress syndrome (n, %)	21 (87.5%)	12 (44.4%)	<0.01
Mechanical ventilation (n, %)	21 (87.5%)	14 (51.9%)	<0.01
Bronchopulmonary dysplasia (n, %)	9 (37.5%)	2 (7.4%)	<0.01

Table 2. The number of probable missed patients, according to the application of our NICU's results to the some guidelines and local studies from around the world (4,6-8,12-16).

Recommendations based on country or study	Criteria for screening	No. of probable missed patients
Joint Statement of the AAP, AAPOS, and AAO, 2002	GA ≤28 weeks or BW ≤1500	7 (13.7%)
United Kingdom	GA <32 weeks or BW <1500	4 (7.8%)
Sweden	GA ≤32 weeks	3 (5.9%)
Denmark	GA ≤32 weeks or BW ≤1750	0 (0%)
Canada	GA ≤30 weeks or BW ≤1500	5 (9.8%)
Singapore	GA <32 weeks or BW <1250	13 (25.4%)
Japan	GA <31 weeks or BW <1500	5 (5.9%)
Chile	GA <32 weeks or BW <1750	1 (2%)
Brazil and Latin America	BW <1750	1 (2%)
India	GA <35 weeks or BW <2000	0 (0%)
Argentina	GA ≤32 weeks or BW ≤1500	0 (0%)
Lithuania	GA ≤32 weeks or BW ≤1500	0 (0%)
Restricted screening criteria applied to our patients	GA ≤30 weeks or BW ≤1250	27 (52.9%)

all studies was to minimize the number of infants screened while missing no patients with ROP who required treatment (3). Many studies from Western countries suggested that the criteria of a BW below 1250 g and a GA below 30 weeks could be safely and efficiently used to screen infants without missing a diagnosis of sight-threatening ROP (6-8,12). According to Ho et al., when the new restricted criteria for screening were applied, 44% of infants would not have been examined, and this would result in savings in time, money, and stress to the infants (7).

Our study revealed that the prevalence of ROP was very high, and severe ROP was diagnosed among larger and more mature infants, as well. In our setting, the criteria of a BW of less than 1250 g and a GA of less than 30 weeks could not be safely or efficiently used to screen infants without missing a diagnosis of sight-threatening ROP. Relatively restricted criteria to identify premature infants eligible for routine ophthalmoscopic screening for ROP may result in some infants going unexamined and their ROP remaining undetected (Table 2).

In the USA, screening for ROP is recommended for infants born with any of the following characteristics: a BW of less than 1500 g, a GA of 30 weeks or less, or a BW of 1500-2000 g or GA of more than 30 weeks and an unstable clinical course (5). Although the BW criterion has not changed, the recommendations regarding the GA criterion for the ROP screening of infants was corrected twice in 2006: in February 2006, the criterion was changed from 28 weeks or less to 32 weeks or less, and in September 2006, a correction of the recommendations decreased the criterion to 30 weeks or less (5,12). However, only 19% of NICUs in the USA use the currently recommended GA criterion of 30 weeks; instead, 6% use a lower, more restrictive criterion, and 74% use a higher, more inclusive criterion (12).

There are wide variations in screening guidelines in developing middle income countries and low income, underdeveloped countries (3,4) (Table 2). This variation may be the result of a possible lack of access to advanced neonatal care units in many developing and underdeveloped countries. We believe that the higher ROP rate in larger premature infants in our unit is related to a cumulative ratio due to the higher chance of survival with advanced gestational weeks and the liberal use of supplemental oxygen, in spite of the availability of pulse oximeters at the bedside.

As in our setting, because larger and more mature infants had developed threshold ROP, ophthalmologists in Latin America suggested widening the inclusion criteria for diagnostic screening. In Ecuador, the ROP screening program started in 1994, and initially only infants with BWs below 1500 g were examined. The criteria were changed the following year to less than 1901 g BW and/or less than 37 weeks GA because several unexamined infants with BWs greater than 1500 g presented with inoperable Stage 5 ROP. Since adoption of the wider criteria, no infant has become blind from ROP because of screening failure (4). A recent publication from Thailand supports the findings of our study: the authors suggested region-specific criteria of less than 1500 g BW or less than 33 weeks GA (3). Based on our results and data from developing countries, although the screening criteria of less than 1500 g or less than 32 weeks seem to be better, we suggest a regional assessment of patients to develop optimal screening criteria for ROP.

Even in developed countries in which there is access to advanced neonatal care units for most, there is a wide variation in the screening guidelines for ROP (Table 2) (4,13-17). The purpose of a screening protocol is to capture all positive instances of the problem under surveillance, while minimizing the number of negative exams. The balance of cost versus benefit to society is one that must be weighed by all participants. Screening does involve a cost to the community. The cost to the individual, family, and community of one child blind from ROP would most likely be greater than that of the cost saved by reduced screening (6,8,18). Given the current medical-legal climate and the liability faced by neonatologists and pediatricians for ROP screening, there seems to be no reason for not liberalizing ROP screening guidelines, at least in Turkey.

Neonatologists serve a central role in coordinating the care for infants at risk of ROP, but there is lack of neonatologists in countries like Turkey. Although the recommendations specify the BW and GA criteria for ROP screening, they also state that "unit-specific criteria with respect to BW and GA for examination for ROP should be established for each NICU by consultation and agreement between neonatology and ophthalmology services" (5,12).

We conclude that individual prospective data for countries or units need to be collected and analyzed to ascertain screening criteria for ROP. Before applying international screening criteria to individual settings, potentially better available and applicable evidence-based care practices and resource provisions should be sought.

References

1. Andruscavage L, Weissgold DJ. Screening for retinopathy of prematurity. Br J Ophthalmol 2002; 86: 1127-1130.

2. Elder JE. Is it time to review the screening guidelines for retinopathy of prematurity? J Paediatr Child Health 2008; 44:159-160.

3. Trinavarat A, Atchaneeyasakul L, Udompunturak S. Applicability of American and British criteria for screening of the retinopathy. Jpn J Ophthalmol 2004; 48: 50-53.

4. Gilbert C, Fielder A, Gordillo L, Quinn G, Semiglia R, Visintin P. Characteristics of infants with severe retinopathy of prematurity in countries with low, moderate, and high levels of development: implications for screening programs. Pediatrics 2005; 115: 518-525.

5. Section on Ophthalmology American Academy of Pediatrics; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus. Screening examination of premature infants for retinopathy of prematurity. Pediatrics 2006; 117: 572-576.

6. Ahmed MAT, Duncan M, Kent A. For the NICUS Group. Incidence of Retinopathy of Prematurity requiring treatment in infants born greater than 30 weeks' gestation and with a birth weight greater than 1250 gm from 1998 to 2002: A regional study. J Paediatr Child Health 2006; 42: 337-340.

7. Ho SF, Mathew MRK, Wykes W, Lavy T, Marshall T. Retinopathy of prematurity: an optimum screening strategy. J AAPOS 2005; 9: 584-588.

8. Lee SK, Normand C, McMillan D, Ohlsson A, Vincer M, Lyons C, for the Canadian Neonatal Network. Evidence for changing guidelines for routine screening for retinopathy of prematurity. Arch Pediatr Adolesc Med 2001; 155: 387-395.

9. Sears JE, Pietz J, Sonnie C, Dolcini D, Hoppe G. A change in oxygen supplementation can decrease the incidence of retinopathy of prematurity. Ophthalmol 2009; 116: 513-8.

10. Gilbert C, Rahi J, Eckstein M, O'Sullivan J, Foster A. Retinopathy of prematurity in middle-income countries. Lancet 1997; 350: 12-14.

11. Carden SM, Lan LN, Huynh T. Zone 1 retinopathy of prematurity in a transitional economy: a cautionary note. Am J Ophthalmol 2006; 141: 1128-1129.

12. Kemper AR, Wallace DK. Neonatologists' practice and experience in arranging retinopathy of prematurity screening services. Pediatrics 2007; 120: 527-531.

13. Holmstrom G, el Azazi M, Jacobson L, Sachs D, Sule J, Lennerstrand G. Epidemiology of retinopathy of prematurity in the Stockholm area of Sweden. Acta Ophthalmol Suppl 1993; 210: 44-47.

14. Fledelius HC, Rosenberg T. Retinopathy of prematurity. Where to set screening limits? Recommendations based on two Danish surveys. Acta Paediatr Scand 1990; 79: 906-10.

15. Canadian Association of Pediatric Ophthalmologists Ad Hoc Committee on Standards of Screening Examination for Retinopathy of Prematurity. Can J Ophthalmol 2000; 35: 251-252.

16. See JLS, Wong TY, Yeo KT. Trends in the pattern of blindness and major ocular diseases in Singapore and Asia. Ann Acad Med 1998; 27: 540-546.

17. Ikeda N, Hayasaka S, Yano H, Kadoi C, Matsumoto M, Imamura H et al. Retinopathy of prematurity in Toyama area of Japan. Ann Ophthalmol 2001; 33: 303-308.

18. Yanovitch T, Siatkowski M, McCaffree MA, Corff KE. Retinopathy of prematurity in infants with birth weight >1250 grams - incidence, severity, and screening guideline cost-analysis. J AAPOS 2006; 10: 128-134.