Current Practice Patterns for Screening and Treatment of Retinopathy of Prematurity in Portugal

Práticas de Rastreio e Tratamento da Retinopatia da Prematuridade em Portugal

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ABSTRACT

INTRODUCTION: The screening and treatment of retinopathy of prematurity (ROP) may vary significantly between providers. The aim of the study is to determine preferred practices in screening, diagnosis and treatment of ROP.

MATERIAL AND METHODS: Portuguese ophthalmologists that perform ROP screening were invited to complete an electronic anonymous questionnaire regarding screening, treatment and the use of telemedicine (n=26).

RESULTS: In 76.9% of the responders, ROP screening is made if ≤ 32 weeks of gestational age or ≤ 1500 g of birth weight or if > 32 weeks / > 1500 g with an unstable clinical state, starting at 4 weeks' chronologic age or at a corrected gestational age of 31 weeks in 65.4%, using topical 2.5% phenylephrine + 0.5% tropicamide and binocular indirect ophthalmoscopy in 84.6%. After the diagnosis of type 1 ROP, 46.2% performed the treatment. The initial treatment for type 1 ROP was anti-VEGF intravitreal injection if ROP in zone I and laser photocoagulation if ROP zone II in 65.2%. No complications were reported in 72.2% of laser treatments and in 73.3% of anti-VEGF injections. The use of telemedicine for ROP screening is considered to be helpful by 88.5%.

CONCLUSION: Most Portuguese ophthalmologists use a more inclusive criteria of gestational age to screen ROP and mostly perform it with a binocular indirect ophthalmoscope. The treatment of choice for type 1 ROP is mostly dependent on the zone of ROP. Screening of ROP with telemedicine seems a reliable option for most ophthalmologists.

KEYWORDS: Portugal; Retinopathy of Prematurity/diagnosis; Retinopathy of Prematurity/epidemiology; Retinopathy of Prematurity/therapy; Surveys and Questionnaires

RESUMO

OBJETIVOS: O rastreio e tratamento da retinopatia da prematuridade (ROP) varia significativamente entre unidades hospitalares. O objetivo deste estudo é sintetizar as práticas atuais no rastreio, diagnóstico e tratamento da ROP em Portugal.

MATERIAL E MÉTODOS: Os oftalmologistas portugueses com prática no rastreio de ROP foram convidados a preencher um questionário online anónimo relacionado com o rastreio, tratamento e aplicação da telemedicina (n=26).

RESULTADOS: A maioria dos participantes rastreia ROP se ≤ 32 semanas de idade gestacional ou ≤ 1500 g de peso ao nascimento ou um estado clínico instável, iniciando às 4 semanas de idade cronológica ou 31 semanas de idade gestacional, utilizando fenilefrina a 2,5% + tropicamida a 0,5% e com oftalmoscopia indireta. Após o diagnóstico de ROP tipo 1, o tratamento é realizado pelo próprio inquirido em 46,2% dos casos. O tratamento inicial para ROP tipo 1 é injeção intravítrea de anti-VEGF se ROP zona I ou fotocoagulação laser se ROP zona II em 65,2%. A maioria não reportou complicações secundárias ao laser ou à injeção de anti-VEGF. A maioria reconhece a utilidade da telemedicina no rastreio da ROP, com a aplicação de um sistema ocular digital, realizado por oftalmologistas e revisto num centro especializado.

CONCLUSÃO: A maioria dos oftalmologistas inquiridos utilizam um critério mais inclusivo de idade gestacional para rastrear ROP, utilizando mais frequentemente oftalmoscopia binocular indireta. O tipo de tratamento da ROP tipo 1 está dependente da zona de ROP na maioria dos casos. O rastreio por telemedicina é uma opção viável para a maioria dos inquiridos.

PALAVRAS-CHAVE: Inquéritos e Questionários; Portugal; Retinopatia da Prematuridade/diagnóstico; Retinopatia da Prematuridade/epidemiologia; Retinopatia da Paturidade/tratamento

INTRODUCTION

Retinopathy of prematurity (ROP) is a pathologic process that occurs in immature retinal tissue of premature newborns with abnormal proliferation of developing retinal blood vessels, which can progress to more severe forms and result in functional or complete blindness.[1] In fact, ROP is the leading preventable cause of childhood blindness in developed countries, according to World Health Organization.[2]

Current screening guidelines are primarily based on two risk factors: birth weight (BW) and gestational age (GA).[1] Current guidelines by the American Academy of Pediatrics, American Academy of Ophthalmology and American Association for Pediatric Ophthalmology and Strabismus specify that all infants ≤30 weeks GA or ≤1500 g BW should be screened for ROP, as well as selected infants based on clinical course.[3] The recommendations regarding the gestational age has changed twice in 2006[4]: in February 2006, the criterion was changed from 28 weeks or less to 32 weeks or less[5] and in September 2006, a correction of the recommendations decreased the criterion to 30 weeks or less.[6] The incidence of any degree of ROP among infants with a gestational age of greater than 30 weeks has been estimated to be at least 2%.[7] In Portugal, current national guidelines specify that all infants ≤32 weeks GA or ≤1500 g BW should be screened for ROP, as well as specific referrals by Neonatology.[8,9]

Furthermore, many investigators have suggested other risk factors, including maternal factors, prenatal and perinatal factors, demographics, medical interventions, comorbidities of prematurity, nutrition, and genetic factors.1 An ideal screening algorithm for ROP must have near-100% sensitivity so as not to miss a single case of treatment-requiring ROP.[10,11] The WINROP program is an example of an algorithm risk model for the detection of premature infants requiring treatment for ROP[12] that has already been studied in the Portuguese population.[13,14]

The ROP examination should be performed after pupillary dilation by using binocular indirect ophthalmoscopy with a lid speculum and scleral depression (as needed) to detect ROP.[3] The use of digital photographic retinal images that are captured and sent for remote interpretation is a developing approach to ROP screening.[15,16] However, outcomes comparison between large-scale operational digital-imaging systems with remote interpretation versus binocular indirect ophthalmoscopy has not been published yet.[3]

The sequential nature and rapid evolution of ROP requires that at-risk preterm infants be examined at proper time and intervals to detect the changes of ROP, before they become permanently destructive.

Laser photocoagulation has replaced cryotherapy as the gold standard for peripheral retinal ablation,[17,18] resulting in an improved visual outcome for these patients.[19] However, in a small but significant proportion of preterm infants, the disease progresses despite laser treatment.[20] Additionally, visual fields are slightly smaller in eyes subjected to peripheral retinal ablation as compared to 'control' eyes,[20] the ablation techniques are uncomfortable and usually require sedation/general anesthesia. This led to a quest for simpler and more effective treatment strategies. A recent Cochrane review 21 evaluated the efficacy and safety of intravitreal bevacizumab/ranibizumab, compared with conventional laser therapy in ROP in infants requiring treatment for ROP, named as type 1 ROP (Zone I ROP: any stage with plus disease, Zone I ROP: stage 3 without plus disease, Zone II ROP: stage 2 or stage 3 with plus disease).[22] Monotherapy with intravitreal bevacizumab or ranibizumab reduces the risk of refractive errors during childhoodbut did not reduce the risk of retinal detachment or recurrence of ROP, as compared with conventional laser therapy.[21]

Intravitreal bevacizumab monotherapy in infants with stage 3+ ROP showed a significant benefit for zone I but not zone II disease, as compared with conventional laser therapy.[22,23] While the intravitreal treatment might reduce the risk of recurrence of ROP in infants with zone I ROP, it can potentially result in higher risk of recurrence requiring retreatment in those with zone II ROP.[21]

Therefore, both the screening and the treatment of ROP may vary significantly between providers.

The aim of the present study is to determine preferred practices in screening, diagnosis and treatment of ROP by surveying Portuguese ophthalmologists.

MATERIAL AND METHODS

Portuguese ophthalmologists that perform ROP screening in one or more hospitals of the Portuguese public health system were invited from July to August 2020 to complete an electronic anonymous questionnaire (Annex 1), without including their specific location of practice. All procedures and data collection were conducted according with the Declaration of Helsinki.

The survey was made in the Google Form® platform that automatically collected the submitted information. The questionnaire had a total of 21 multiple choice questions with the option to free-text responses, regarding screening (inclusion criteria, examination), treatment (indications, use of laser, use of anti-VEGF, follow-up) and application of telemedicine.

Data analysis was performed with the Statistical Package for the Social Sciences for Windows, version 23 (IBM SPSS Statistics®). Descriptive statistics and frequency distributions were calculated for specific variables. Missing data were taken into account when analyzing the data.

RESULTS

A total of 26 ophthalmologists (Table 1) answered the questionnaire (response rate of 89.7%).

For twenty out of 26 responders (76.9%), the screening criteria for ROP was ≤ 32 weeks of gestational age or ≤ 1500 g of birth weight or an unstable clinical state with > 32 weeks / > 1500 g, while for 5 out of 26 (19.2%) the criteria was ≤ 30 weeks of gestational age or ≤ 1500 g of birth weight or an unstable clinical state with > 30 weeks / > 1500 g and in one case the criteria was < 32 weeks of gestational age and/or < 1500 g of birth weight or an unstable clinical state.

For seventeen out of 26 responders (65.4%), the first examination was performed at 4 weeks' chronologic (postnatal) age or at a corrected gestational age of 31 weeks, whichever is later (but not later than 6 weeks' chronological age). For five out of 26 (19.2%), the first examination was performed at 4 weeks' chronologic (postnatal) age in infants with ≥ 27 weeks of gestation age at birth or at 33 weeks of corrected gestation age in infants with < 27 weeks of gestation age at birth. In 3 out of 26 (11.5%), the first examination was scheduled by the neonatologist. One out of 26 performed the first examination at 4 weeks' chronologic (postnatal) age or at 32 weeks of corrected gestational age, whichever is sooner.

The mean number of ROP examinations per month was < 5 examinations/month in 34.6% of the experts (9 out of 26), 5-15 examinations/month in 38.5% (10 out of 26) and > 15 examinations/month in 26.9% (7 out of 26). Three out of 26 doctors (11.5%) made the screening in more than one hospital, one of them (33.3%) by a telemedicine screening.

Pharmacological mydriasis with topical 2.5% phenylephrine plus 0.5% tropicamide was used by 84.6% of the sample (22 out of 26), while 7.70% of the sample (2 out of 26) use 0.2% cyclopentolate plus 1% phenylephrine, 3.86% of the sample (1 out of 26) use 0.25% cyclopentolate plus 1% phenylephrine and 3.86% if the sample (1 out of 26) use the ophthalmic insert Mydriasert®.

ROP examination with the use of a binocular indirect ophthalmoscope was made in 84.6% (22 out of 26) of the cases, 90.9% (20 out of 22) of them with the use of a lid speculum, 54.5% (12 out of 22) of them with the use of a scleral depression.

Binocular indirect ophthalmoscopy added to a retinal digital system was used by 26.9% (7 out of 26) of the sample, with less than 10 minutes per examination in 14.3% of the cases (1 out of 7) and 10 to 20 minutes in 85.7% of the cases (6 out of 7). When the binocular indirect ophthalmoscope was used in isolation (57.7%, 15 out of 26), 26.7% (4 out of 15) spent less than 10 minutes in the examination, 60% spent 10 to 20 minutes (9 out of 15) in the examination and 13.3% (2 out of 15) spent more than 20 minutes in the examination (Fig. 1).

Table 1 Characteristics of ROP examinations

	Examinations / month % (*n*)		Pharmacological mydriasis % (*n*)		Instruments % (n)	
***n* (%)**	< 5	34.6 (9)	2.5% Phenylephrine + 0.5% Tropicamide	84.6 (22)	Binocular indirect ophthalmoscope	57.7 (15)
26 (89.7%)	5-15	38.5 (10)	0.2% Cyclopentolate + 1% Phenylephrine	7.70 (2)	Binocular indirect ophthalmoscope + retinal digital imaging	26.9 (7)
			0.25% Cyclopentolate + 1% Phenylephrine	3.86 (1)	Retinal digital imaging	15.4 (4)
	> 15	26.9 (7)	Mydriasert®	3.86 (1)		

ROP = retinopathy of prematurity. n = number of subjects

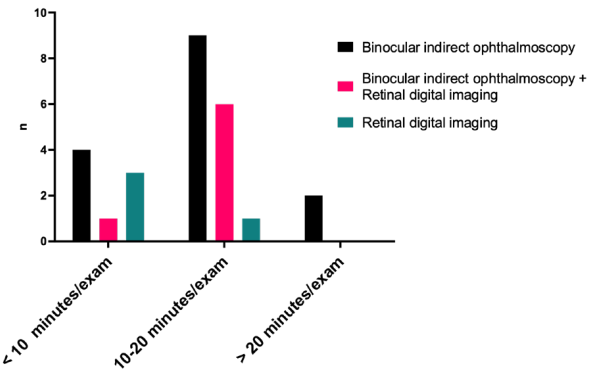

Figure 1: Time spent on each examination.

ROP = retinopathy of prematurity. n = number of subjects.

A retinal digital imaging system without ophthalmoscopy was used by 4 out of 26 subjects (15.4%), 75% of them spending less than 10 minutes and 25% of them spending 10 to 20 minutes per examination.

Infants requiring treatment for ROP had Type 1 ROP (21 out of 24, 87.5%) or posterior aggressive ROP (3 out of 24, 12.5%). After the diagnosis of type 1 ROP, 46.2% (12 out of 26) performed themselves the treatment, 42.3% (11 out of 26) referred the patients to a specialized treatment center and 11.5% (3 out of 26) referred the patients to another specialist from the same hospital.

The standard initial treatment for type 1 ROP was anti-VEGF intravitreal injection if zone I ROP and laser photocoagulation of the avascular retina if zone II ROP in 65.2% (15 out of 23) of the sample. In 26.1% (6 out of 23), laser photocoagulation was the preferred treatment and in 8.70% (2 out of 23) the anti-VEGF was the preferred treatment (Fig. 2).

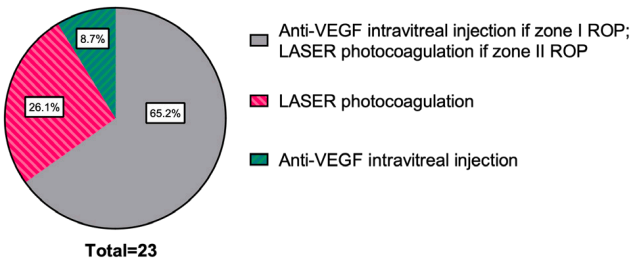

Figure 2: The standard initial treatment for type 1 ROP

(Zone I ROP: any stage with plus disease, Zone I ROP: stage 3 without plus disease, Zone II ROP: stage 2 or stage 3 with plus disease). ROP = retinopathy of prematurity.

Regarding laser photocoagulation, most of the sessions were made in the operation room (71.4%, 10 out of 14). After one session, 41.2% (7 out of 17) of the doctors wait 10 days, 41.2% (7 out of 17) of the doctors wait 14 days and 5.88% (1 out of 17) wait 14 to 21 days before doing another intervention, while 11.8% (2 out of 17) change the observational time according to the evolution. In refractory cases after one laser session, 70% (14 out of 20) made another laser only in the presence of skip lesions, 20% (4 out of 20) referred to another specialist, 5% (1 out of 20) made one anti-VEGF injection and 5% (1 out 20) performed laser even without skip lesions. Most of the sample did not report any complication after laser (72.2%, 13 out of 18). The reported complications after laser were leucoma (16.7%, 3 out of 18), intraocular hemorrhage (5.56%, 1 out of 18), glaucoma (5.56%, 1 out of 18) and cataract (5.56%, 1 out of 18).

Regarding anti-VEGF injection, bevacizumab was injected in 80% (4 out of 5), bevacizumab or aflibercept were injected in 20% (1 out of 5). The procedure was made in the operation room in 64.3% (9 out of 14), with an injection located at 1.5 to 2 mm from limbus in 66.7% (10 out of 15). After one injection, 40% (6 out of 15) of the doctors wait 10 days, 6.67% (1 out of 15) wait 5 days, 6.67% (1 out of 15) wait 14 days and 6.67% (1 out of 15) wait 14 to 21 days before doing another intervention, while 13.3% (2 out of 15) change the observation time according to the evolution, 6.67% (1 out of 15) change the observation time according to the type of anti-VEGF and 20% (3 out of 15) stated that there is always an improvement. In refractory cases after one injection, 41.2% (7 out of 17) made laser, 39.4% (5 out of 17) referred to another specialist, 17.6% (3 out of 17) repeat another injection of the same anti-VEGF and 11.8% (2 out 17) change the option according to the ROP zone. The limit of 2 anti-VEGF injections per eye was stablished by 53.8% (7 out of 13) of the sample, while 46.2% (6 out of 13) only perform one anti-VEGF injection per eye. Most of the sample did not report any complication after injection (73.3%, 11 out of 15). The only reported complication after anti-VEGF injection was intraocular hemorrhage (26.7%, 4 out of 15).

Twenty three out of 26 experts (88.5%) recognized that it would be helpful to use telemedicine for ROP screening. Most ophthalmologists (95.7%, 22 out of 23) thought that screening in small units without trained ophthalmologists could be made by telemedicine. Most of them also agreed that telemedicine could centralize and maximize experience (56.5%, 13 out of 23), while 13% of them (3 out of 23) thought that telemedicine will be more cost-effective. An ocular digital screening made by ophthalmologists and evaluated in a specialized reading center was the preferred option (54.5%, 12 out of 22), while 27.3% (6 out of 22) select an ocular digital screening made by nurses and evaluated in a specialized reading center, 13.6% (3 out of 23) choose an ocular digital screening made by orthoptists and evaluated in a specialized reading center and 4.5% (1 out of 22) prefer an ocular digital screening made by general medical doctors and evaluated in a specialized reading center.

DISCUSSION

With the advancement of neonatal care, more premature infants with earlier gestational age and lower birthweights are surviving. Therefore, ROP continues to be a significant cause of visual morbidity worldwide.

Regarding criteria for ROP screening, the majority of the sample use the national guidelines regarding gestational age (≤32 weeks).[8,9]. In fact, the cut-off of ≤32 weeks was initially defined in 2006,[4] but corrected to ≤30 weeks in an erratum[6] and also readjusted to ≤30 weeks in international guidelines for ROP screening.[3] However, the national gui-

delines use the cut-off of ≤32 weeks.[8,9] The trend of the present study is in accordance with other international survey of neonatologists,[24] which represent a more conservative approach in order to avoid missing infants who may develop sight-threatening ROP.

The majority of the ophthalmologists perform the first ROP examination at 4 weeks' chronologic (postnatal) age or at a corrected gestational age of 31 weeks, whichever occurs later (but not later than 6 weeks' chronological age), which is in accordance to the most recent guideline.[3]

Most of the doctors apply topical 2.5% phenylephrine plus 0.5% tropicamide, as stated by the Royal College guideline.[25] However, a systematic revision concludes that one drop of phenylephrine 1% and cyclopentolate 0.2% is also effective and are more likely to be associated with a safer adverse effect profile.[26] Furthermore, the use of Mydriasert® appears to be safe to use in neonates without a history of increased vagal tone or gastrointestinal reflux.[27]

For most of the responders, the screening of ROP was made through binocular indirect ophthalmoscopy without a retinal digital system, which is similar to the findings of Jain *et al*.[28] The most common duration per ROP examination is 10 to 20 minutes, regardless of the complementary use of a retinal digital system.

In a recent international study, the first treatment of type 1 ROP is laser in 68.3% of the sample, bevacizumab in 32.7% of the sample, with only 29% stating that their decision is dependent on the zone of ROP involvement.[28] On the other hand, one study from the USA demonstrates a higher preference for bevacizumab than for laser (46.2% *versus* 39.3%).[29] Therefore, the treatment of ROP is not standardized and can vary significantly between providers.

In the present study, the treatment of type 1 ROP is mostly dependent on the zone of ROP involvement (65.2%), favoring anti-VEGF intravitreal injection in Zone I ROP since the bevacizumab eliminates the angiogenic threat of retinopathy of prematurity (BEAT-ROP) study showed that intravitreal bevacizumab is more effective than laser photocoagulation in zone I ROP.[23]

Multiple prospective and retrospective studies have shown that digital photography may be a valuable tool to detect clinically significant ROP and referral-warranted ROP,[30,31,32] although it does not replace indirect ophthalmoscopy as the gold standard.[3,33] In the present study, most of the responders recognized that telemedicine would be helpful in ROP screening. The preferred approach is a ROP screening made by ophthalmologists and revised in a specialized reading center.

In conclusion, most of the Portuguese ophthalmologists stablish a more inclusive criteria of gestational age to screen ROP, as stated by the national guidelines.[9,8] The ROP screening is mostly performed with binocular indirect ophthalmoscopy, using retinal digital system only in a minority of cases. The treatment of type 1 ROP is mostly dependent on the zone of ROP involvement, favoring anti-VEGF intravitreal injection in Zone I and laser treatment in zone II. There are few complications after laser treatments or anti-VEGF injections. Screening of ROP with the use of telemedicine seems a reliable option for most of the ophthalmologists.

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Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

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