Original article

Comparative study of RetCamRetCam II vs. binocular ophthalmoscopy in a screening program for retinopathy of prematurity*,**

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A B S T R A C T

Objective: To determine the performance of RetCam vs. binocular ophthalmoscopy (BIO) in a screening program for retinopathy of prematurity (ROP).

Methods: Observational comparative study with prospective data collection. Examinations with RetCam (n = 169) were performed on 83 infants included in a screening program for ROP and stored for analysis at a later stage. An experienced ophthalmologist examined the ocular fundus with binocular indirect ophthalmoscopy (BIO). The Retcam images were assessed for the presence of ROP, zone, grade, and presence of plus disease. RetCam and BIO data were compared by visually to estimate sensitivity, specificity, positive (VPP) and negative (VPN) predictive values.

Results: ROP disease was detected in 108 eyes with BIO, and in 74 with RetCam. Out of 306 eyes examined with RetCam, false negative results were found in 34 eyes, with no false positives. Sensitivity of RetCam exam vs. BIO was 0.68, and specificity was 0.99. Positive predictive value was 0.93 and negative predictive value was 0.85. All 34 ROP cases not detected with RetCam were in zone III or outer zone II. They were all mild and regressed spontaneously. No threshold ROP was missed with RetCam.

Conclusion: Binocular indirect ophthalmoscopy is the reference method for the diagnosis of ROP. RetCam may be used as an alternative for ROP screening.

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Estudio comparativo de RetCam II frente a oftalmoscopía binocular en el cribado de la retinopatía de la prematuridad

RESUMEN

Objetivo: Conocer el grado de utilidad de la RetCam como alternativa a la oftalmoscopía binocular (BIO) en el cribado de la retinopatía de la prematuridad (ROP).

Métodos: Estudio observacional prospectivo comparativo. Se realizaron un total de 169 exámenes con RetCam II en 83 niños prematuros participantes en un programa de cribado de la ROP, exámenes que fueron almacenados en un archivo para análisis posterior. Un oftalmólogo altamente cualificado evaluó el fondo usando el oftalmoscopio binocular indirecto. El examinador evaluó posteriormente las fotografías en busca de la presencia o ausencia de ROP, la zona y el grado de la enfermedad, y la presencia o ausencia de enfermedad plus. Estos datos fueron comparados con los resultados de oftalmoscopía binocular indirecto para determinar la sensibilidad, especificidad y los valores predictivos positivo (VPP) y negativo (VPN) del método.

Resultados: Fue detectada ROP con oftalmoscopía binocular indirecto (BIO) en 108 ojos; en la exploración con RetCam se detectó ROP en 74 ojos. De los 306 ojos examinados con RetCam, se hallaron falsos negativos en 34 ojos y ningún falso positivo. La sensibilidad de RetCam fue de 0,68 y la especificidad del 0,99. El VPP fue de 0,93 y el VPN fue de 0,85. Treinta y cuatro casos de ROP no fueron diagnosticados por la RetCam. Todos estos casos fueron en la zona III o la zona II anterior, todas en grado leve y con mejoría espontánea. Ningún caso de ROP umbral se perdió.

Conclusión: Aunque el oftalmoscopio binocular indirecto continúa siendo el método gold standard para el diagnóstico de la ROP, la RetCam ofrece una alternativa al oftalmoscopio binocular indirecto para el cribado de la ROP.

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Introduction

CRYO-ROP (a multicenter group for studying cryotherapy in retinopathy of prematurity) defined the threshold disease as that which must be treated.1,2 The natural evolution of untreated threshold retinopathy of prematurity (ROP) is blindness in 50% of cases. In 1988 the first CRYO-ROP results on the efficacy of cryotherapy to halt the natural evolution of the disease were published.3,4 Subsequently, ETROP (a multicenter study for early treatment of ROP) demonstrated greater benefits with early treatment of the high risk pre-threshold disease or type 1 disease.5-8 This evidence, together with increased survival of immature infants, increased the need for ocular screening.

At present, scientific societies have issued recommendations on screening criteria for ROP and other screening aspects.9-12 Evidence shows that premature infants at risk of ROP requiring treatment are different in different countries, and that larger and more mature infants in developing countries develop severe ROP.14-17 Nowadays, developed and highly industrialized countries have excellent neonatal care and efficient screening and treatment programs that have significantly diminished blindness due to ROP.18-20 However, at present we are witnessing a ROP epidemic in middle income countries and emerging economies.21 In these countries, neonatal intensive care units are being developed, thus increasing survival rates for premature babies, but screening programs are not widely implemented and not enough ophthalmologists trained for treating ROP. All this has given rise to a significant number of premature infants surviving with severe ROP which eventually leads to blindness.22-23

In 2005, the International Classification of ROP (ICROP) was modified to include the concept of aggressive posterior ROP (AP-ROP) observed in children with lower weight at birth, which rapidly progresses to retina detachment. The characteristic signs of this type of ROP are its posterior location and the presence of prominent plus disease. AP-ROP is more frequently observed in zone I, although it can also occur in posterior zone II. A striking characteristic of this ROP is the low peripheral involvement but with marked congestion and vascular tortuosity. It is essential to recognize this morphological group, even more so with the increased survival rates of infants with very low weight and short gestational age.24

It seems that the presence of the plus disease is the most noteworthy clinical sign of ROP. However, it can be difficult to assess the degree of vascular changes in the posterior pole of an infant. It would be useful to have computer programs measuring tortuosity and dilatation in comparison with standard photographs of plus disease and to determine by
means of calculations weather an eye has sufficient alterations to be classified as plus disease. One of the computer programs being developed is the «ROP tool» which appears to display excellent sensitivity and specificity in the detection of sufficient tortuosity to determine plus and preplus disease (RetCam digital retinograph images were analyzed and compared with the conclusions of 5 expert ROP ophthalmologists). Accordingly, said tool has the potential to reduce the subjectivity in the plus disease and become an aid for screening.26,27

Even though the reference method or gold standard in ROP diagnostic continues to be indirect binocular ophthalmoscopy (IBO), it seems necessary to develop alternative methods and new technologies for making screening easy, safe and cost effective. ROP screening with IBO is difficult and requires specialized training and a learning curve involving a high number of patients. Many hospitals do not have trained personnel for effective ROP screening, although telemedicine could be an opportunity to improve this. At present, the digital retinography RetCam system enables premature retina image captures by trained personnel that need not be ophthalmologists, and the images can be e-mailed through the Internet for assessment by expert ophthalmologists. Telemedicine could be very useful in regions with few ophthalmologists or in hospitals with few premature infants where it is not possible to obtain sufficient experience for their management.

The present study aims at establishing the degree of usefulness of RetCam as an alternative to binocular ophthalmoscopy in ROP screening. To this end, the digital images captured with RetCam II were compared with indirect binocular ophthalmoscopic exploration for screening ROP, assessing its diagnostic efficacy.

Methods

A prospective and comparative study comprising 83 consecutive infants screened for ROP in the Neonatology Unit of a reference hospital between November 2007 and May 2008. The criteria for inclusion in the screening program were a gestational age of 30 weeks or less and a weight of 1250 g or less.

Indirect binocular ophthalmoscopic exploration was carried out by an ophthalmologist with ample experience with this condition. The RetCam II digital system was utilized to capture digital images. For each patient, gestational age and weight at birth were registered and, in each exploration, the degree of midriasis and the application of any type of breathing support or other causes which could hinder the exploration were also registered.

The pupils were dilated with a combination of 0.5% cyclopentolate and 2.5% phenylephrine. Topical anesthesia was applied for the exploration utilizing a sterile blepharostat. For the IBO explorations, a 28 D lens was utilized together with a pediatric scleral indenting device. RetCam II was utilized to capture a number of images, including a posterior pole image and the largest possible peripheral retina area.

The presence or absence of ROP and disease or plus were recorded in each exploration. If ROP was identified, the zone and degree of ROP were also recorded. A modification was adopted, classifying zone II in zone II anterior and zone II posterior, taking into account that the latter tends to perform like that of zone I, while zone II anterior is most similar in behavior to zone III, if ROP was absent, the zone reached by vascularization was recorded.

The explorations continued up to complete retinal vascularization or until slight ROP improved or the state of the treated threshold ROP scar was verified. The explorations with indirect binocular ophthalmoscope were compared with the RetCam images. The latter were assessed at a different time and in a masked manner (without identifying the personal or clinical patient data).

Sensitivity and specificity for RetCam was calculated, taking into account the clinical examination with indirect binocular ophthalmoscope as the reference diagnostic method to assess the clinical usefulness of the digital images.

Overall, 408 consecutive explorations (816 eyes) were carried out with RetCam and the indirect binocular ophthalmoscope. As it was necessary to compare both to assess the validity of the method, the RetCam explorations had to be paired with the corresponding indirect binocular ophthalmoscope explorations.

The sensitivity and specificity for RetCam was calculated taking into account the clinical examination with indirect binocular ophthalmoscope as the diagnostic method of reference. In addition, the positive (PPV) and negative (NPV) values were calculated.

Results

For the 83 infants of the study, the mean weight at birth was of 1151.17 g (SD ± 384.27 g), with a mean gestational age of 28.12 weeks (SD ± 2.74 weeks), and a mean amount of postnatal birth up to the exploration of 79.67 (SD ± 42.12 days).

Overall, 408 consecutive explorations (816 eyes) were performed with RetCam and indirect binocular ophthalmoscope. Of these, 387 right eye explorations and 386 left eye explorations were taken as valid (total 773 eyes). The rest of eyes were excluded for several reasons such as medium opacity or low midriasis. Of the 773 valid eyes, ROP was detected in 286.

Exploration with indirect binocular ophthalmoscope revealed ROP in 200 eyes (96 right eyes, 104 left eyes, 90 bilateral) out of 478 eyes (239 explorations). RetCam revealed ROP in 88 eyes (42 right eyes, 46 left eyes, 34 bilateral) out of 338 eyes (169 explorations). Due to the need to compare the validity of the methods, the RetCam explorations had to be paired with the matching indirect binocular ophthalmoscope. Overall, 153 explorations were matched corresponding to 306 eyes. Indirect binocular ophthalmoscope explorations detected ROP in 108 eyes (46 infants with bilateral disease) and RetCam explorations detected ROP in 74 eyes (27 bilateral).

Out of the 306 eyes examined with RetCam, false negatives were identified in 34 eyes, with no false positives. RetCam sensitivity with 95% confidence interval was of 0.68 (0.59–0.76) and specificity was 0.99 (0.97–1.00). PPV was of 0.93 (0.93–0.99) and NPV was of 0.85 (0.80–0.89).
Analyzing the distribution of ROP per zone, the 2 eyes with ROP in zone II posterior were detected by the indirect binocular ophthalmoscope explorations as well as the RetCam explorations, and the false negatives observed with RetCam correspond to ROP in zone II anterior or zone III (zone II anterior with indirect binocular ophthalmoscope in 49 eyes with ROP, zone II anterior with RetCam in 40 eyes with ROP; zone III with indirect binocular ophthalmoscope in 57 eyes with ROP, zone III with RetCam in 32 eyes with ROP).

In addition to providing instantaneous documentation by creating a permanent record of digital images, the system allows the comparison of images in different times to observe patient evolution between different explorations and optimize the diagnostic, as ROP is a disease in which small changes could involve the need of treatment in a very short timeframe.

The disadvantages of RetCam include the difficulty of capturing images with small pupils which cannot dilate sufficiently, the fact of being a contact method which requires corneal support, and the lack of peripheral ROP detection in addition to the initial cost of the equipment.

In the present study, RetCam has exhibited insufficient sensitivity for overall ROP detection, as already demonstrated in other studies.28,29 This is mainly because it is not able to photograph the peripheral retina up to the ora serrata, in addition to requiring adequate midriasis.

However, the sensitivity and specificity of RetCam for detecting severe ROP is high, which also matches the results of previous studies such as Chiang, PHOTO-ROP and SUNROP.30

In Spain there are data about the usual clinical practice in ROP which illustrates the problem caused by delays in decision-making and application of treatment in severe ROP, as well as the transfer of infants for diagnostic confirmation. Both ophthalmologists and neonatologists have shown interest in telemedicine.31-35

Improvements in screening involve the deployment of telemedicine in hospitals which do not have qualified personnel for screening and referring to reference hospitals only infants exhibiting ROP which requires treatment. RetCam paves the way for telemedicine for ROP patients, with the possibility of optimizing and minimizing costs derived from patient transfers as well as the difficulties involved in transport because captured images can be transmitted through networks and examined by a specialist who could indicate the protocol to be followed.36-38

Even though indirect binocular ophthalmoscope continues to be the gold standard for diagnosing ROP, RetCam holds the promise of becoming an alternative to IBO for screening ROP as part of a telemedicine program.39,40

**Discussion**

Any new method with the potential to substitute the reference diagnostic methods, in this case IBO, should comprise acceptable sensitivity and specificity. In the present study, RetCam sensitivity was of 0.68 (0.59–0.76) and specificity was of 0.99 (0.97–1.00), similar to the numbers reported in a previous study by Roth.28 In the present study, 34 ROP cases were not detected with RetCam. The majority of “missed” ROPs were degree one or 2 without plus in zone III, with some in zone II anterior. All improved spontaneously. Said “missed” ROPs are already shown in previous studies such as in Roth, Yen and Shah.

The present study did not include any missed ROP with RetCam in cases located in zone I or II posterior. Accordingly, RetCam has shown to be useful in the detection and documentation of posterior ROP susceptible to be treated. The study carried out by Schwartz29 did not include either threshold ROP cases which went undiagnosed. PPV was of 0.93 (0.93–0.99) and NPV was of 0.85 (0.80–0.89), respectively, similarly comparable with the Roth study.

Sensitivity and NPV of RetCam are not sufficient. This is mainly due to its inability to capture the entire peripheral retina up to the ora serrata due to the obstacles encountered in the camera lens movement due to its size in such a small palpebral fissure as that of premature infants.

IBO achieves a thorough examination of the peripheral retina, enabling the diagnosis of all peripheral ROP cases. However, it requires dedicated and experienced ophthalmologists for an adequate screening and management of ROP. The scarcity of qualified ophthalmologists is due to the low frequency of the disease and the lower incidence of stages requiring treatment, thus making it difficult to obtain sufficient experience. The probability of prescribing treatment after an exploration is under 3%, and the challenge of maintaining a high concentration level during a difficult exploration with a low incidence of positive cases is well known. Another frequent disadvantage is the scarcity of ophthalmologists’ availability and time.

The use of the RetCam system in the Neonatology Dept. features significant advantages. Ease of management and maneuverability allow a trained technician (not necessarily an ophthalmologist) to capture images. A single capture examines a very broad area of the retina (120°). Images remain stored in digital format and can be reviewed by one or more ophthalmologists at any place and time. The RetCam system enables connection to a standard network to transmit images through e-mail.

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**Conflict of interest**

No conflict of interests has been declared by the authors.

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