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Systematic Review of Digital Imaging Screening Strategies for Retinopathy of Prematurity

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Abstract

BACKGROUND—Retinal imaging with remote interpretation could decrease the number of diagnostic eye examinations that premature infants need for the detection of retinopathy of prematurity and thus decrease the time demand on the relatively small pool of ophthalmologists who perform retinopathy of prematurity examinations.

OBJECTIVE—Our goal was to review systematically the evidence regarding the reliability, validity, safety, costs, and benefits of retinal imaging to screen infants who are at risk for retinopathy of prematurity.

METHODS—We searched Medline, the Cochrane library, CINAHL, and the bibliographies of all relevant articles. All English-language studies regardless of design with primary data about our study questions were included. We excluded (1) studies that only included subjects with retinopathy of prematurity, (2) hypothetical models other than cost-effectiveness studies, and (3) validity studies without sufficient data to determine prevalence, sensitivity, and specificity or that only evaluated subjects for 1 component of retinopathy of prematurity (eg, plus disease only).

RESULTS—Studies of only 1 retinal imaging device (RetCam [Clarity Medical Systems, Inc, Pleasanton, CA]) met the inclusion criteria. There was a wide range in reported sensitivity, but specificity was high. There were several important limitations noted, including the eye as the unit of analysis instead of the individual or variations in the criteria for determining a true-positive or true-negative screening result. The risk of retinal hemorrhage resulting from imaging is low, and systemic effects (eg, bradycardia, hypertension, decreased oxygen saturation) are mild. No generalizable cost-effectiveness data were found.

CONCLUSIONS—The evidence base is not sufficient to recommend that retinal imaging be routinely adopted by NICUs to identify infants who have serious retinopathy of prematurity.

Keywords

retinopathy of prematurity; photography; image interpretation; telemedicine; evidence-based medicine; review

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Well-timed peripheral retinal ablation for cases of severe retinopathy of prematurity (ROP) can lead to significant improvements in visual outcomes.¹ In the United States, binocular indirect ophthalmoscopy examinations are recommended for infants at risk for the development of ROP (ie, birth weight of <1500 g, gestational age of ≤ 30 weeks, birth weight between 1500 and 2000 g or gestational age of >30 weeks and an unstable clinical course). Serial diagnostic examinations are performed until each eye is considered no longer at risk for developing serious ROP (ie, full retinal vascularization, postmenstrual age of 45 weeks, and no prethreshold disease, zone III retinal vascularization without previous zone I or II ROP, or regression of ROP).²

Regional shortages in the availability of ophthalmologists to provide ROP diagnostic examinations are an important barrier to ensuring appropriate ROP care.³ One potential solution is to decrease the number of indirect ophthalmoscopy examinations by first screening with some other method. Retinal photography to evaluate ROP was described nearly 4 decades ago⁴ and has been used to monitor outcomes from an intervention trial.⁵ Digital retinal cameras that can be used in the NICU are now commercially available. In general, they can be categorized as wide-angle cameras (eg, RetCam [Clarity Medical Systems, Inc, Pleasanton, CA]) and narrow-angle cameras (eg, NM-200D [NIDEK, Inc, Fremont, CA]). Wide-angle cameras provide a greater view of the retina (eg, 130° field of view) than narrow-angle cameras (eg, 30° field of view). However, compared with narrow-angle cameras, wide-angle cameras are currently more expensive and less portable and require that the camera lens be in direct contact with the cornea. Both types of cameras can produce digital images that could be transferred remotely for evaluation. Computer-assisted algorithms have been developed to assist with the interpretation of the images.^{6–15}

There is significant interest in the use of retinal imaging devices for ROP screening, and some NICUs have already purchased such devices. One example of the current use of these devices is a telemedicine-based ROP-screening program that has been developed at Stanford University (Stanford, CA) for area NICUs.¹⁶ To help provide guidance to NICU directors about whether they should purchase a retinal camera and participate in a remote evaluation system for digital images of infants at risk for ROP, we conducted a systematic review to evaluate the potential impact of incorporating retinal imaging into the system of ROP care. We had 3 key questions: (1) What is the reliability and validity of retinal imaging for the detection of ROP? (2) What are the risks associated with retinal imaging? and (3) What are the costs and benefits of using retinal imaging to detect ROP?

METHODS

Data Sources

We searched Medline (1950 through October 2007), the Cochrane library (through October 2007), and CINAHL (Cumulative Index for Nursing and Allied Health Literature; 1982 through October 2007) for English-language articles by using the following search strategy with Medical Subject Headings (MeSH) terms and key words: “retinopathy of prematurity” and (“photography”; “image interpretation, computer-assisted”; “image processing, computer-assisted”; or “telemedicine”). We also searched the bibliographies of all identified articles.

Study Selection

We included all studies regardless of design that included primary data about our key questions of reliability, validity, risks, costs, and benefits. Although editorials and commentaries were not included in the data synthesis, we did review such publications for other potential articles. Because we were primarily interested in evaluating ROP screening, we excluded those studies that focused only on evaluating ROP progression after diagnosis or treatment. We excluded

studies based on hypothetical models other than cost-effectiveness studies. We excluded studies of screening accuracy that did not present sufficient data to determine prevalence, sensitivity, and specificity or that only evaluated the validity of 1 component of ROP (eg, plus disease).

Data Extraction and Analysis

Identified studies were reviewed and data from eligible studies were abstracted by a single reviewer (Dr Kemper), who extracted relevant information from the included studies. Any uncertainties were resolved by discussion with the other authors.

For studies of screening validity, we preferentially used the finding of “referral-warranted ROP” on dilated fundus examination as the gold-standard criterion. Referral-warranted ROP, the level of severity proposed by Ells et al¹⁷ to identify children who should be evaluated by an ophthalmologist, is defined as the presence of any of the following: any ROP in zone 1, plus disease, or any stage 3 ROP; this is equivalent to prethreshold or worse ROP.¹⁷ If there were insufficient data available in the reports to determine this criterion, we used the standard described in the report; for those studies with more than 1 standard, we used the one that was most similar to referral-warranted ROP. Wherever possible, our unit of analysis for test characteristics was the infant, not the eye, reflecting the role of screening to identify which infants should receive additional evaluation.

When 95% confidence intervals (CIs) were not provided in an article, we calculated them by using Stata 8.2 software (Stata Corp, College Station, TX). These calculated CIs are noted as CI^c.

RESULTS

Validity and Reliability

RetCam—The earliest published study that met our inclusion criteria was from 2000¹⁸ (reported also in 2002¹⁹). This study evaluated RetCam screening over time at 2 different postmenstrual ages: 32 to 34 weeks (examination 1) and 38 to 40 weeks (examination 2). The main outcomes were the accuracy of detecting any ROP at both times and the accuracy of using the images to predict the progression to prethreshold ROP. A total of 23 infants (46 eyes) were included at examination 1, and 25 infants (50 eyes) were included at examination 2. The unit of analysis was the eye, and all photographs were masked for interpretation. The training and experience of the reader were not described. The prevalence of any ROP was 26% at examination 1 and 85% at examination 2, and the prevalence of prethreshold ROP was 14% at examination 1 and 28% at examination 2. The sensitivity and specificity for any ROP were, respectively, 46% (95% CI: 17%–77%) and 100% (95% CI: 89%–100%) at examination 1 and 76% (95% CI: 59%–89%) and 100% (95% CI: 54%–100%) at examination 2. The sensitivity and specificity of predicting progression to prethreshold ROP were, respectively, 33% (95% CI: 4%–78%) and 100% (95% CI: 90%–100%) between examinations 1 and 2 and 64% (95% CI: 31%–89%) and 97% (95% CI: 82%–100%) between examination 2 and 6 to 8 weeks later.

The next RetCam study we identified that met our inclusion criteria was published in 2001.²⁰ This study was based on 100 RetCam evaluations, which included up to 6 images each, and eye examinations from a total of 59 eyes of 32 infants. The outcome was the presence of any ROP, and the unit of analysis was the eye. Images were interpreted in a masked fashion by 2 of the study authors. ROP was present in 68% of the eyes. The overall sensitivity was 82% (95% CI^c: 71%–90%), and the specificity was 94% (95% CI^c: 79%–99%).

A report from 2003 was based primarily on a longitudinal cohort of 36 infants (72 eyes), with each infant receiving between 2 and 11 examinations while enrolled in the study.¹⁷ A total of

356 RetCam photographic sets were generated. Six percent were not readable; although subsequent readable photographs were obtained, the time period was up to 4 weeks. The unit of analysis was the eye. The prevalence of referral-warranted ROP over the entire study period was 32%. The overall sensitivity was 100% (95% CI: 85%–100%), and specificity was 96% (95% CI: 86%–100%). There was some variation in the timing of the identification of referral-warranted ROP: RetCam photography findings preceded examination findings by at least 1 week in 43% (95% CI: 23%–66%) of the eyes with referral-warranted ROP but lagged examination findings by up to 2 weeks in 13% (95% CI: 3%–34%) of the eyes with referral-warranted ROP.

In 2005, a report described the development of a retinal image atlas consisting of 163 digital RetCam images from 63 infants (81 right eyes and 82 left eyes) at risk for developing ROP obtained from 1999–2000.²¹ Each eye also received a dilated eye examination around the time of imaging. This retinal image atlas was the basis for 2 subsequent reports of the validity and reliability of image grading by 3 ophthalmologists (the 2 later studies described the atlas as having 64 infants but the same number of right and left eyes).^{21–23} For all studies, the unit of analysis was the eye. In the second report,²² 2 retina specialists and 1 general ophthalmologist interpreted the images to identify “mild or worse” ROP. Referral-warranted ROP was present in 21% of the eyes. The 2 retina specialists and the general ophthalmologist were similarly sensitive (83% [95% CI: 71%–95%], 75% [95% CI: 61%–89%], and 72% [95% CI: 58%–87%]) and specific (90% [95% CI: 85%–95%], 99% [95% CI: 94%–100%], and 99% [95% CI: 96%–100%]) for the detection of referral-warranted ROP. Interobserver agreement based on a 4-level scale ranging from no ROP to ROP requiring treatment found substantial to almost perfect agreement (weighted κ range: 0.67–0.83). Intraobserver agreement based on 7 duplicated images and the same 4-level scale found substantial agreement overall (weighted κ = 0.78). Insufficient data were presented to calculate the 95% CI around the κ scores or to determine the level of agreement based only on the presence of referral-warranted ROP. In the third report,²³ the 3 readers were asked to use 3 different “internal cutoffs” for interpreting the images: mild or worse ROP (as with the second report²²), referral-warranted ROP, or ROP requiring treatment. When evaluating for referral-warranted ROP, none of the readers reported a false-positive result for identifying referral-warranted ROP (ie, specificity was 100%; there were insufficient data to calculate CIs). However, the sensitivity decreased for all 3 readers (42% [95% CI: 27%–56%], 28% [95% CI: 12%–44%], and 27% [95% CI: 11%–43%]).

One recent study was based on a prospective cohort study and modeled how retinal photography might decrease the number of ROP examinations.²⁴ Each infant received eye examinations and underwent digital imaging with a RetCam according to a typical clinical schedule (eg, between 30 and 34 weeks postconceptional age, then biweekly for those with no ROP or weekly for those with ROP, until discharge, transfer, treatment, or maturation of the retinal vasculature). After images of the peripapillary, nasal, temporal, superior, and inferior fundus were obtained, a composite image was developed, if possible, by using specialized software. The composite images were then interpreted by 1 of the study authors who was masked to the results of the examination and to the infant’s identifiers. The reader made the decision about whether the image demonstrated referral-warranted ROP. A total of 43 infants (86 eyes) were enrolled, and the unit of analysis was the eye. No data were provided regarding the total number of eye examinations or RetCam images that were obtained. Although ROP developed in 42% of the cases, the severity was not specified. Twenty-one percent of the images could not be interpreted because of poor quality. Insufficient data were provided to determine the CI. No cases of referral-warranted ROP were missed (100% sensitivity). The specificity for referral-warranted ROP was reported as 97.5%, but we calculated 95% on the basis of the reported false-positive rate of 5%. Insufficient data were presented to directly calculate this value or determine the CI. No data were provided regarding the impact of the software to

produce the composite images. The authors did not report the potential decrease in the number of eye examinations that resulted from implementing retinal photography.

A report from 2008 described a multi-center trial to evaluate a telemedicine-based approach to ROP screening with the RetCam conducted in 2001 and 2002.²⁵ The criteria used in this study, termed “clinically significant ROP,” included referral-warranted ROP the presence of additional features (zone II, stage 2 with up to one quadrant of vascular dilatation and tortuosity), those cases of any vascular dilation and tortuosity for which ridge characteristics were not interpretable, or those cases of ROP for which plus disease was not interpretable. Subjects had a gestational age less than 31 weeks and a birth weight less than 1000 grams, and were followed for up to 10 weeks. Images were interpreted by a reading center, and the readers were masked to the results of the eye exam. Analyses were conducted separately for left and right eyes. We present combined data for right and left eyes. A total of 51 study eligible infants (102 eyes) were enrolled. Of the 300 total image sets taken, 8% were not interpretable. Overall, 58% of the eyes developed clinically significant ROP. The sensitivity was 92% (95% CI: 81%–97%) and specificity was 37% (95% CI: 23%–53%).

NIDEK—We found no study of a narrow-angle camera that met the inclusion criteria for this review. We did identify 1 abstract from a study that evaluated the NIDEK narrow-angle digital camera for the detection of plus disease in a sample of 95 examinations from the right eye of 37 infants.²⁶ On the basis of image analysis by 2 independent and masked reviewers, both of whom were experts in ROP screening, the sensitivity was 83% and specificity was 94% (insufficient data to calculate the 95% CIs).

Other Imaging Modalities—Video indirect ophthalmoscopy has been used to collect retinal images for analysis but only during the course of an examination by an ophthalmologist.²⁷ Currently, therefore, this is not a screening method.

We identified 2 studies that used ultrasonography to detect ROP.^{28,29} These studies were excluded from our review because ultrasonography cannot detect threshold or plus disease and, thus, cannot be used for ROP screening.

Risks

We found 1 case report of retinal hemorrhages in association with use of the RetCam.³⁰ However, a subsequent study found no cases of retinal hemorrhages in 25 infants screened with the device.³¹ On the basis of this cohort, the 95% CI^c for the risk of developing a retinal hemorrhage is 0% to 14%.

One small study (15 infants) evaluated risk by randomizing the order of 3 different screening strategies (the RetCam and indirect ophthalmoscopy with and without a speculum) used for each study subject.³² On average, blood pressure increased by 18% after screening with the RetCam and by 16% after indirect ophthalmoscopy with a speculum. However, blood pressure did not change after indirect ophthalmoscopy without a speculum. There were too few subjects for a meaningful statistical analysis. After screening with the RetCam, there were a total of 6 episodes of decreased blood oxygen saturation that required additional supplemental oxygen. All subjects returned to baseline after 30 minutes.

A larger study compared 67 infants who were screened with the RetCam to 36 infants who underwent indirect ophthalmoscopy with scleral depression.³³ There was a small increase in the heart rate for all subjects but less for those who were screened with the RetCam (increase of 23 vs 14 beats per minute; $P = .04$). The respiratory rate increased during indirect ophthalmoscopy (increase of 11 per minute) but did not increase during RetCam screening ($P = .01$). There were no statistically significant changes in oxygen saturation or blood pressure.

Bradycardia associated with the oculocardiac reflex was noticed in 12% of those who were screened with the RetCam and 8% who underwent indirect ophthalmoscopy. All subjects returned to baseline by 1 hour.

Costs and Benefits

We identified 1 cost-effectiveness evaluation of ROP screening strategies.³⁴ This study was a hypothetical evaluation comparing indirect ophthalmoscopy and 4 different strategies based on the RetCam: (1) images obtained by a neonatal intensive care nurse who then either (a) interpreted the images or (b) forwarded them to an ophthalmologist for interpretation or (2) images obtained by a special visiting nurse using a portable device who then either (a) interpreted them or (b) forwarded them to an ophthalmologist for interpretation. This study was conducted from the perspective of the British National Health Service. Under the base-case scenario, the RetCam and indirect ophthalmoscopy were modeled to have equal accuracy (sensitivity: 90%; specificity: 99%). Although 1-way sensitivity analyses were presented (ie, evaluation of the impact of changes in RetCam sensitivity or specificity), no 2-way sensitivity analyses were reported (ie, changes in both sensitivity and specificity). The disutility of visual impairment related to ROP was adopted from a study of adults with cataracts. The authors concluded that under most situations, a visiting nurse who obtains and interprets the images would be the most cost-effective strategy. Because most inputs into this model were hypothetical and based on limited primary data, actual cost-effectiveness is likely to be different. For example, we are unaware of any data regarding the accuracy of image interpretation by visiting nurses. Furthermore, we are not aware of any program that uses visiting nurses for both screening and image interpretation.

DISCUSSION

We found insufficient data to recommend that retinal imaging be adopted by NICUs to identify those at-risk infants who should receive an examination by an ophthalmologist experienced in the care of ROP. Although retinal imaging could decrease the number of eye examinations that would require an evaluation by an ophthalmologist, the approach should not be expected to obviate completely the need for such examinations. The number of examinations that could potentially be eliminated depends directly on the prevalence of significant ROP. In the studies included in this review, the prevalence of referral-warranted ROP was high, which implies that retinal imaging would not substantially decrease the need for regular NICU rounds by ophthalmologists. Furthermore, retinal imaging would almost surely miss some cases of sight-threatening ROP. Although most infants would undergo serial imaging evaluations, making it unlikely that a child with severe ROP would be completely missed, no data are available regarding the impact of such a delay in diagnosis. The Early Treatment for Retinopathy of Prematurity Study found that waiting until an eye develops threshold ROP (as defined in the Cryotherapy for Retinopathy of Prematurity [CRYO-ROP] trial) rather than treating at the development of high-risk prethreshold ROP increases the likelihood of unfavorable visual outcome at 9 months' corrected age from 14.5% to 19.5% ($P = .01$).¹

Because of differences in study methods, it is difficult to directly compare findings across studies. We have specific study-design recommendations to fill in critical gaps in knowledge. Future studies should more reflect patient-level processes of care by measuring the impact of screening on health care utilization including the induced costs associated with establishing a screening program, changes in the number of eye examinations, and the harms of delayed or missed cases of ROP. Such future studies will need to consider the infant as the unit of analysis, not the eye. If correlation of ROP status between the eyes is not considered in analysis,³⁵ as the case in the studies we found, then using the eye as the unit of analysis may double the sample size and, thus, dramatically increase the apparent statistical power. However, this

approach neglects the true impact of a positive screening result. With a patient-level approach, a positive screening result in either eye would identify a child as needing an examination of both eyes. In addition, studies need to take into account the impact of those eyes that cannot be imaged and would, therefore, likely lead to an infant requiring an eye examination. We propose that assessment should be prospective and longitudinal, as was done in some of the RetCam studies noted above. Such a study design will allow determination of the cost-effectiveness of retinal imaging for ROP screening, including factors such as the reduction in the number of needed diagnostic eye examinations and the impact of missed cases. Cohort studies should reflect the current recommendations for identifying those children at risk for the development of ROP.² Across all studies, there should be a rigorously defined approach to interpretation of the diagnostic eye examination, including the criteria for those retinal findings that should be detected through screening. As described in this review, we support the concept of using referral-warranted ROP as proposed by Ells et al.¹⁷

The only studies of retinal imaging that met the criteria for this review used the RetCam for imaging, and only 1 of these studies²⁴ incorporated software to help with image processing. We recommend that future studies consider other approaches to retinal imaging (eg, narrow-angle cameras and video-indirect ophthalmoscopes) and the emerging computer-based approaches to image interpretation.

The utility of retinal imaging devices will vary on the basis of the needs and the sample of infants within the NICU. NICUs associated with academic medical institutions may not have a great need to reduce the number of eye examinations because of the high availability of ophthalmologists. Other NICUs, in contrast, may have a greater need for access to a telemedicine-based approach to retinal imaging, but some may not be able to identify image readers. Up-front cost of the digital camera imaging system, which can be approximately \$60 000, may also be a barrier; however, there are financing and other leasing programs available. In addition, training for personnel who perform the imaging procedure and quality control are factors that must be taken into account. The overall cost-effectiveness of retinal imaging will depend on complex factors related to access to ophthalmologic expertise in ROP and patient case mix. Future studies, therefore, should be conducted in a large number of different sites to reflect this heterogeneity.

CONCLUSIONS

Although there is likely variation among ophthalmologists in the diagnosis of ROP with indirect ophthalmoscopy,^{36,37} such clinical examinations are the current standard of care for identifying ROP.²⁵ Until the evidence base for digital imaging improves, we do not recommend that those NICUs with access to ophthalmologists experienced in ROP transition to use of retinal imaging to detect eyes with ROP. NICUs with poor access to experienced ophthalmologists should first attempt to improve such access by working with the local ophthalmologic community and hospital administration before adopting retinal imaging. Finally, we strongly recommend that all NICUs that elect to adopt retinal imaging collect outcome data to expand the evidence base and monitor for any cases of potentially preventable visual impairment.

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Abbreviations

ROP

retinopathy of prematurity

CI

confidence interval

CI^c

calculated confidence interval

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