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Telemedicine for Retinopathy of Prematurity in 2020

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Introduction

Retinopathy of prematurity (ROP) is a disorder of the developing retinal vasculature in premature infants and is the leading cause of visual impairment in prematurely born children.[1,2] Considerable resources are devoted to screening premature infants for ROP, as timely diagnosis and treatment, if needed, can prevent visual impairment in the vast majority of infants.[3] ROP meets the criteria for successful screening programs because the prevalence of disease is high, it typically progresses in a stepwise manner, and there are effective treatments.[1] ROP continues to be a major cause of morbidity in high-income nations because of continued advances in neonatal care, allowing greater survival rates of severely premature infants.[4] We now more frequently encounter aggressive posterior disease owing to these advances.[5,6] Today's greatest burden of ROP, however, is in middle-income nations, who are experiencing epidemic-levels of the disease.[7] This is because many hospitals in these nations are only recently developing neonatal intensive care units (NICUs), but without sophisticated means of delivering and monitoring supplemental oxygen.[8] Therefore many middle-income nations are currently facing a similar situation that high-income nations faced at the onset of the first ROP epidemics in the 1940s and 1950s when oxygen was unregulated.

In the United States, the screening recommendations set forth by the American Academy of Pediatrics, American Academy of Ophthalmology, American Association for Pediatric Ophthalmology and Strabismus, and the American Association of Certified Orthoptists, are to examine infants with birth weight (BW) ≤ 1500 grams or gestational age (GA) ≤ 30 weeks, and infants with BW 1500-2000 grams or GA > 30 weeks with an unstable clinical course, as determined by the neonatologist. Screening examinations entail bedside dilated

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binocular indirect ophthalmoscopic (BIO) examinations.[1] However, there are increasing logistic difficulties of bedside examinations and the conventional ROP screening system is becoming stressed.

There is a limited supply of ophthalmologists who have expertise in evaluating ROP, and many of these ophthalmologists profess that the logistical challenges of covering multiple NICUs, neck and back strain, low reimbursement, and high medico-legal risks lower their desire to make ROP screening a part of their practice.[9–11] Many of these systems issues are particularly compounded in middle-income nations where the number of infants requiring screening outnumber the capacity of ROP screeners.

Telemedical diagnosis of infants with ROP has the potential to address the above issues. Images can be obtained by the local NICU staff, for example, while the ophthalmologist reader can remotely provide interpretations and perform bedside examinations only for high-risk characteristics, for treatment, or for infants who were difficult to image, vastly decreasing the travel burden. Additionally, telemedical screening programs would allow more NICUs to offer screening, decreasing NICU to NICU transfers. Beyond addressing the above issues, telemedicine may even improve certain aspects of care, discussed later in body of this paper. The aforementioned factors, among others, spurred interest in the development of telemedical systems of remote digital fundus imaging (RDFI) evaluation for ROP.[1]

The purpose of this paper is to review the evidence regarding the use of RDFI in the evaluation of ROP, to outline considerations that can be taken into account in developing or for currently active telemedical ROP care structures, and to identify potential areas of further study.

Goals of ROP Screening

“Referral-warranted ROP” (RW-ROP) is a relatively new telemedical ROP concept initially defined as eyes with plus disease, ROP in zone I, or ≥ stage 3 ROP, as these eyes would benefit from a bedside examination and possible treatment.[12,13] These findings are posterior enough to capture by wide-angle cameras in the majority of infants in the NICU.[2,13,14] The thresholds for requiring a bedside examination can subtly differ from program to program, depending on the logistics and comfort levels of the NICU and ROP screener. Thus, the goal of an ROP telemedical program is to capture all infants who have a high likelihood of requiring imminent treatment, while safely minimizing the number of bedside examinations. It is compulsory to have predetermined methods of referring infants for bedside examinations and potential treatment within an acceptable time frame.

Effectiveness of RDFI Systems

Investigations into the feasibility of telemedical systems for the evaluation of ROP have been performed in numerous contexts.[2,15–19] These studies, which while limited by the lack of a reference standard in calculating sensitivities and specificities, have resulted in a large body of evidence regarding the accuracy and reliability of fundus image analysis.

In 2003 Ells *et al.* obtained wide-angle fundus images immediately after bedside examinations and compared the findings in a masked fashion. RW-ROP was successfully diagnosed in all eyes where it was identified via BIO examinations.[12] The positive predictive value (PPV), meaning the proportion of eyes diagnosed with RW-ROP via RDFI that actually had RW-ROP, was 92%.[12] The negative predictive value (NPV) was 100%, meaning that no eyes which had RW-ROP went undiagnosed by RDFI examination.[12] The telemedical approach had a sensitivity of 100% and a specificity of 96%.[12] Also of interest, the majority of RW-ROP was diagnosed either at the same time-point (43%) or even earlier (43%) by RDFI compared to bedside BIO examinations.[12]

In 2006. Chiang *et al.* enlisted three RDFI readers (1 general ophthalmologist and 2 retina specialists) to take part in a comparison with one pediatric ophthalmologist's BIO examinations.[14] They found that the sensitivities of the RDFI examinations ranged from 85-90% and the specificities ranged from 95.3-97.3%.[14] Intrareader reliability for identifying low-risk prethreshold ROP was 100%.[14] The accuracy and intra/interreader reliability of RDFI examination diagnosis of RW-ROP was determined to be high.

Wu *et al.* also compared the results of RDFI to BIO examinations and found that RDFI readers missed no cases of prethreshold or threshold disease.[21] RDFI had a sensitivity of 100% and specificity of 97.5% in identifying prethreshold and threshold ROP.[21] The PPV of this study was 67%, which indicated that the readers could be conservative in their interpretation of the images.[21] This overestimation of ROP, combined with occasional poor image quality, led to BIO examinations being recommended in 20% of cases that did not meet the criteria for RW-ROP.[21] However, in line with the goals of ROP screening, no cases of RW-ROP went unidentified by the readers.

Chiang and colleagues also performed a similar comparison of RDFI interpretations and BIO interpretations with a larger cohort of 248 eyes that underwent nurse-captured fundus images.[22] For the diagnosis of type 2 prethreshold or worse ROP, at 35 to 37 weeks post-menstrual age (PMA), the sensitivities were 100% and the specificities ranged from 85.7-94.3%.[22] Images were rated as "adequate" or "possibly adequate" for diagnosis in 93.3% of eyes.[22] The intergrader reliability for the detection of type 2 prethreshold or worse was 79.1-88.9%.[22]

The Photo-ROP study was the first prospective, multicenter, masked clinical trial to assess RDFI screening for ROP.[23] One hundred and two eyes were analyzed between 2001 and 2002.[23] An ophthalmologist captured the fundus images that were evaluated by two masked retina specialists. RDFI evaluation identified clinically significant ROP with a sensitivity of 92% and a specificity of 37%.[23]

The e-ROP study examined 1257 infants in 13 North American NICUs between 2011 and 2013.[16] Digital imaging was performed by nonphysician staff and read by two trained, masked, nonphysician readers. Their evaluations of RW-ROP were compared to BIO examinations performed by an ophthalmologist. When both eyes were considered for the presence of RW-ROP, the RDFI system had a sensitivity of 90% and a specificity of 87%, and an NPV of 97.3%.[16]

Most recently, i-ROP is a multicenter ROP imaging consortium that is further evaluating various analytical aspects of RDFI. Several findings from the consortium are discussed in subsequent sections below.

Live RDFI ROP Screening Programs

As evidence for the effectiveness of telemedical screening for ROP grew, several live telemedical programs were implemented. Weaver and Murdock implemented a telemedical screening program for ROP out of necessity in Great Falls, Montana.[19] There were no ROP screeners available to examine infants in the NICU within 200 miles. Fundus images were evaluated by one of two pediatric ophthalmologists. From 2007 to 2011, 137 infants were examined and 13 were transferred for RW-ROP, which they defined as type 2 or greater, any plus disease, or zone 2 stage 2 eyes with pre-plus disease.[19] Nine of these 13 ultimately required laser treatment.[19] There were no adverse outcomes (progression to retinal detachment) in the RDFI screened cohort.[19]

The Stanford University Network for Diagnosis of Retinopathy of Prematurity (SUNDROP) published their 6-year results in 2015.[18] SUNDROP is a telemedical ROP screening program for 6 NICUs in California that utilizes RDFI. The images are collected by nonphysician staff in the NICUs and are uploaded for evaluation by a pediatric retina specialist. A total of 608 infants had participated.[18] Compared with BIO examinations, RDFI evaluation had a sensitivity of 100%, a specificity of 99.8%, and a NPV of 100%.[18]

In line with the goals of an RDFI screening program for ROP, the negative predictive values are very high. Thus, the adoption of RDFI screening programs, when implemented properly, can prevent infants with RW-ROP from going undetected and untreated, which is the overarching goal of any ROP screening program. There are numerous other live programs in the United States and internationally.[16,17,20]

Considerations and Limitations of RDFI

Many studies have demonstrated the efficacy of RDFI systems in the NICU setting.[12,14,16,18–24] This efficacy is a prerequisite, but alone is not sufficient for the implementation of RDFI programs. These programs must also be demonstrated to be cost effective, timely, not lead to greater errors, and not lead to unintended adverse outcomes. A number of considerations should be taken into account when assessing an RDFI program.[12,14,16,18–24] Additionally, limitations must be acknowledged and addressed in order to successfully create and/or maintain a program. Five main categories of considerations and limitations will be discussed: image quality, logistics, available treatments, upfront costs, and the use of computer-assisted documentation and analysis.

A full set of acceptable quality images must be obtained. As Morrison *et al* found, accuracy and reliability of detection of RW-ROP is decreased when fewer than four out of the series of five retinal images are captured with high image quality.[25] In their study, more than 90% of patients had at least 4 images of acceptable quality.[25] This indicates that close to 10% of patients may have their care compromised if they are not evaluated either by BIO or new images of sufficient quality. This finding underscores the requirement for training of those

designated to capture the images, as well as the prospects that better cameras in the future may further improve the screening process.

Additionally, there needs to be a clearly defined workflow in order to avoid adverse outcomes. As mentioned in the most recent SUNDROP report, there are numerous potential breakdowns when setting up an RDFI system beyond technical expertise.[18] One logistical workflow concern is the timing of RDFI reads. The image grader should ideally return the RDFI read back to the NICU within a day. This way there is enough lead-time to coordinate care if intervention is required, since timing of diagnosis and therefore treatment are essential in ROP management.[1,2] The e-ROP study examined the feasibility of grading and returning the results to the NICU within 24 hours of the images being submitted.[55] They found that this goal was accomplished in more than 95% of image sessions.[55] Upon amending the suggested schedule of the readers, this number went up to 99%, showing that 24-hour turnaround time is feasible and recommended.[55] All developing RDFI ROP screening programs would be advised to monitor this metric since guidelines can be updated in response to the data collected.

Another logistic concern is the coordination of care surrounding the imaging sessions. The timing of imaging should be semi-automated independent of the ophthalmologist's schedule. Before screening, ROP programs should have a meticulous system in place to identify the infants who need screening. At the conclusion of inpatient screening, the most important handoff is the scheduling of the outpatient follow-up examination and continued ROP screening until termination criteria are met. This essential transition requires multiple verbal and written handoffs, to assure that appropriate care is continued. This also requires human decision-making and can be susceptible to error. Furthermore, either physicians willing and able to travel to examine high-risk infants must be identified, or transport of high-risk infants must be prearranged. Finally, if there are any changes to the imaging schedule due to the infant's health or logistic issues, protocols need to be in place to get the RDFI screening back on track as soon as possible.

Vascular endothelial growth factor (VEGF) plays an important role in the pathogenesis of ROP and studies have demonstrated the efficacy of anti-VEGF treatment in ROP regression.[26,27,28] The use of anti-VEGF treatment has been increasing especially in rural hospitals without access to laser therapy. However, anti-VEGF treatment has been associated with unpredictable reactivation of ROP, systemic exposure (but no high quality evidence for systemic sequelae at the current time), and progressive retinal detachment in some eyes.[29,30,31,32,33,34] In an international multicenter study, progression to retinal detachment was noted a mean of 70 days after anti-VEGF injection; 11% within 1 week, and 49% within 4 weeks.[32] Given the risk and difficulty of repair of these detachments, RDFI screening should occur frequently to monitor infants treated with anti-VEGF therapy. A clear workflow of transferring infants who develop retinal detachments to a pediatric retinal surgery practice should also be in place.[33]

Research has also suggested a role for computer-assisted analysis.[35–45] Patel *et al* found that compared to analysis of multiple individual photographs, analysis of "computer-generated mosaic" images led to an increase in the sensitivity for diagnosing stage 2 ROP, plus disease,

and treatment-requiring ROP.[35] It also improved intergrader agreement. Moreover, software programs have been shown to be effective in helping to diagnose plus disease.[36–43] Furthermore, funduscopic findings are currently documented via physician-produced sketches with conventional bedside screening, whether on paper or on electronic medical records.[46] The International Classification of ROP was a significant step forward in the standardization of the diagnosis of ROP, but a documentation system that utilizes funduscopic photographs (images) as opposed to hand-drawn ones could be advantageous for more accurately assessing subtle retinal and vascular changes over time by allowing side-by-side comparisons.[47] This would be valuable information in the continued monitoring of disease, particularly when more than one ophthalmologist is involved in the screenings, and especially in assessing plus disease.[48] Accurate documentation may also provide protection in cases of ROP litigation, as the subjectivity of the examination is less questioned.

Additionally, the cost of current fundus imaging systems can be a burden, particularly for small healthcare organizations, which are often precisely the ones that need to participate in RDFI screening programs. This burden is largely mitigated in the long term by cost savings associated with switching to an RDFI system.[19,44] Weaver and Murdock initiated their RDFI program out of necessity, as the NICUs geographical area was unserved. Their report described the associated costs as approximately $80,000 for equipment, plus wages for those who obtained the images and for those who read them, as well as necessary upgrades to their computer systems.[19] They also noted that during the study period they incurred a cost of $138,960 for 16 air ambulance transports.[19] Without the RDFI program, they would have been required to arrange 137 air ambulance transfers which would have cost an estimated $1.1 million.[19] Furthermore, RDFI screening examinations are more economical than traditional BIO screening examinations, with a cost of $3,193 versus $5,617 per quality-adjusted life year.[56] RDFI programs have also suggested promise in decreasing medio-legal costs.[10,11] Additionally, NICUs financially benefit from offering ROP screening as it allows them to avoid transferring patients who are driving revenue. Nonetheless, there is a real and significant upfront cost that can be an obstacle for many NICUs and hospitals. We hope and expect more cost-effective cameras will be offered in the future.

In establishing an RDFI screening program, one must take care in examining the system as it is implemented to limit human error in the process. As Quinn *et al* examined, and SUNDROP along with others demonstrated, it is possible to set up the workflow so that there are no adverse effects introduced by virtue of human error, but these systems must be intelligently crafted and diligently maintained.[18,55] Data on the time between image upload and response should continually be monitored. Additionally, accuracy decreases when there are not enough images of sufficient quality, so there must be an emphasis on capturing high quality images.[25] If high quality images cannot be obtained from a particular infant, that infant needs to be referred for BIO examination. For best results, a system in which images are selected at the bedside immediately after photography, “mosaicized” (per the methods of Patel *et al*) automatically, and then sent to the reader, is suggested.

Future Research

While RDFI programs have enough evidence to support their implementation, there is need for research that could bring further improvements. Technological advances will allow image quality to increase while decreasing the cost of equipment.[1] These trends promise increased capabilities and ease for RDFI ROP screening programs. Beyond equipment improvements, current research has suggested steps that could be taken to make RDFI programs more effective, such as with the integration of artificial intelligence.[57–59]

Computer based image analysis programs have shown great capacity as tools in the screening of infants for ROP, but no clinical trials using computer assisted image analysis have thus far been carried out. Studies are needed to explore the effectiveness and potential unexpected issues related to using programs to help physicians in their assessment of ROP. Other imaging modalities, such as optical coherence tomography (OCT) and OCT angiography, show promise in identifying retinal changes in ROP that fundus photos are unable to detect and that may be relevant to the evaluation of ROP. Further research in this area would be valuable.[60–63]

Conclusions

RDFI systems seek to address a number of challenges that healthcare systems generally and ophthalmologists specifically face in carrying out appropriate ROP screening on every infant who meets screening guidelines. In certain geographical areas, ophthalmologists who are willing and able to carry out BIO examinations to screen for ROP are in short supply.[9–11] RDFI ROP screening programs have been demonstrated to be accurate and reliable in the detection of RW-ROP.[12,14,16,18–24] They show great promise in resolving many current issues regarding the screening of infants for ROP, specifically including overcoming geographic barriers and physician availability challenges. Additionally, they provide superior ability to track subtle retinal changes over time and to accurately document a patient's disease state. While there is a non-trivial financial cost to beginning an RDFI screening program, they have been demonstrated to be cost-effective in comparison to current systems.[19,56]

When designing ROP RDFI programs, the unique needs and strengths of the specific healthcare system it will serve must be considered. There are many examples of successful programs that are well-adapted to the environment they operate within, and these examples should be used as guideposts instead of as rigid roadmaps.

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