Journal of Perinatology (2018) 38:381–385
https://doi.org/10.1038/s41372-017-0030-6

ARTICLE

Retinopathy of prematurity practices: a national survey of Canadian Neonatal Intensive Care Units

Kourosh Sabri[1,2,3] · Mary Angela Woodward[4] · Bethany Easterbrook[3] · Sandesh Shivananda[4] on behalf of the Canadian Neonatal Network

Received: 4 May 2017 / Revised: 7 November 2017 / Accepted: 9 November 2017 / Published online: 2 January 2018

Abstract

Objective To examine current level three Neonatal Intensive Care Unit (NICU) practices related to ROP screening and treatment.

Study design A cross-sectional survey was sent to 29 level three NICU's across Canada to survey current screening inclusion criteria, treatment options, supportive care and post-screening events for ROP.

Result 22/29 (76%) level three NICU's responded. Ten different ROP screening inclusion criteria were found to be in use with significant variation in gestational age and birth weight criteria. Many other national variations also exist regarding the supportive and procedural protocols surrounding ROP screening as well as mode of treatment for ROP.

Conclusion Despite national guidelines, significant variation in ROP screening inclusion criteria practices exist among neonatal units in Canada. Therefore, there is an urgent need for better evidence-based screening guidelines as well as a need to standardize supportive measures surrounding ROP screening and treatment.

Introduction

Retinopathy of prematurity (ROP) is a multifactorial vaso-proliferative disorder that increases in incidence with decreasing gestational age (GA) [1]. Advances in the field of neonatal care over the last several decades have led to improved outcomes for preterm infants as well as a rapidly decreasing minimum limit of viability. Recognizing the burden and impact of this disease, there has been an increased impetus towards early prevention, detection, screening and treatment of ROP. The Royal College of Paediatrics and Child Health along with the Royal College of Ophthalmologists in association with the British Association of Perinatal Medicine developed a guideline for screening that recommended all infants <32 weeks GA at birth or less than 1501 gm birth weight should be screened for ROP [2]. The Canadian Pediatric Society (CPS) and Canadian Ophthalmological Society (COS) in 2010 recommended screening all preterm infants whose birth GA was ≤30 + 6 weeks or whose birth weight was ≤1250 g [1]. The American Academy of Pediatrics (AAP) and American Academy of Ophthalmology (AAO) recommends screening of all infants with GA at birth <30 weeks or birth weight ≤1500 g as well as infants with a birth weight between 1500 and 2000 g who have had an unstable clinical course [3]. Recognizing the challenges that guideline adherence presents, we conducted a survey to characterize not only ROP screening criteria but also other relevant current practice patterns in use.

Methods

This project used a cross-sectional survey to obtain data from centers across Canada. Following ethics exemption from the local research ethics board, the survey was distributed across all level three Neonatal Intensive Care Unit

✉ Kourosh Sabri
sabrik@mcmaster.ca

1 Division of Ophthalmology, Department of Surgery, McMaster University, Hamilton, ON, Canada

2 McMaster Paediatric Eye Research Group, Department of Surgery, McMaster University, Hamilton, ON, Canada

3 McMaster Pediatric Surgery Research Collaborative, Department of Surgery, McMaster University, Hamilton, ON, Canada

4 Division of Neonatology, Department of Pediatrics, McMaster University, Hamilton, ON, Canada

Table 1 National variations in ROP screening inclusion criteria

	Inclusion criteria		Timing of 1st exam		Guideline adherence	
NICU	Birth weight (g)	GA at birth (weeks)	Birth GA < 28 (weeks)	Birth GA ≥ 28 weeks	CPS	AAP/AAO
1	≤1250	<31	31	4 weeks of age	Yes	No
2	≤1250	<31	31	4 weeks of age	Yes	No
3	≤1250	<31	31	4 weeks of age	Yes	No
4	≤1250	<31	31	4 weeks of age	Yes	No
5	≤1250	<31	31	4 weeks of age	Yes	No
6	≤1250	<31	31	4 weeks of age	Yes	No
7	≤1500	<30 weeks	4 weeks after birth	4 weeks of age	No	Yes
8	<1500	<30 weeks	4 weeks after birth	4 weeks of age	No	Yes
9	≤1500	<31	31	4 weeks of age	No	No
10	<1500	<31	31	4 weeks of age	No	No
11	<1500	<31	5 weeks after birth	4 weeks of age	No	No
12	<1500	<33	31	5 weeks of age	No	No
13	<1250	<32 + 6 weeks	31 weeks	4 weeks of age	No	No
14	<1500	<33 weeks	31 weeks	4 weeks of age	No	No
15	<1250	<30	31 weeks	4 weeks of age	No	No
16	<1501	<31	31	4 weeks of age	No	No
17	<1250	<31	31 weeks (< 26 + 6)	4 weeks of age (> 27 weeks)	No	No
18	<1250	–	6 weeks after birth	6 weeks of age	No	No
19	<1500	<31	31	4 weeks of age	No	No
20	–	<32	31	4 weeks of age	No	No
21	<1500	<32[a]	4–6	4–6 weeks of age	No	No
22	<1250	–	31	4weeks of age	No	No

[a] Both criteria need to be met

(NICU)'s in Canada from September 1 to December 30, 2015. For the purposes of this study, level three NICU's were defined as care centers with the ability to provide the highest level of medical care for infants of all viable GA, including those born less than 32 weeks GA and less than 1500 g. The tool was designed to elicit information regarding screening practices for detection of ROP in tertiary NICU's. The survey also explored the screening process in terms of the person responsible for initiating the screening processes, choice of mydriatics as well as organizing follow up. The practice and use of supportive measures during ROP screening and treatment options provided were also captured.

Inclusion criteria

All 29 level three NICUs in Canada were approached for inclusion in the study via emails acquired through the Canadian Neonatal Network, which maintains a standardized NICU database, with members from 30 hospitals across Canada [4]. An invitation letter and survey link was sent electronically to the clinical director at each NICU. Implied consent by virtue of voluntary participation was assumed. The survey was kept open for a period of 8 weeks with weekly reminders sent by email. Results from the survey were entered into a database and analyzed with Microsoft Excel software. Descriptive statistics were assessed to describe adherence to CPS/COS and AAP/AAO screening ROP guidelines. Categorical variables were reported as counts and percentages.

Outcomes

The primary outcome was defined as adherence to the current CPS/COS or AAP/AAO guidelines. Specifically, guideline adherence was assessed for the following criteria: inclusion of an infant for ROP screening, age at first ROP exam, circumstances where infants outside the recommended screening criteria were deemed eligible for screening, and appropriate follow-up processes.

Secondary outcomes were defined as supportive administrative practices in use during ROP screening

Table 2 Symptoms and signs noted post ROP examination ($n = 22$)

	Frequency of symptoms/signs following eye examination (%)					
Symptom/sign	0%	1–10%	11–20%	>20%	No response	Data unavailable
Feeding intolerance	6 (27)	6 (27)	2 (9)	1 (5)	5 (23)	2 (9)
Abdominal distension	6 (27)	6 (27)	0 (0)	0 (0)	8 (37)	2 (9)
Apnea/bradycardia/desaturation	0 (0)	4 (18)	3 (14)	10 (45)	3 (14)	2 (9)
Red eye	3 (14)	7 (31)	0 (0)	4 (18)	5 (23)	3 (14)

examinations. This included type and dose of mydriatics used, and measures to reduce photophobia and discomfort after ROP-related therapeutic interventions. We also assessed availability of dedicated personnel to coordinate the exam, use of predetermined order sheets (paper or electronic) for medication and equipment required, measures in place to ensure appropriate follow up, ROP treatment options (anti-vascular endothelial growth factor [anti-VEGF] and/or laser), and treatment location. Furthermore, we assessed how many participating centers used RetCam (Clarity Medical Systems INC.) as an alternative to ophthalmoscopy.

Results

Of the 29 tertiary nurseries surveyed, 22 (76%) centers completed the questionnaire. Table 1 shows ROP screening inclusion criteria currently used by each center. In order to be considered compliant with current guidelines, centers had to adhere to both weight and GA screening cutoffs provided by CPS or AAP. Ten different screening criteria were found to be in use across Canada, with only six centers following the CPS guidelines and two centers following the AAP guidelines. Reasons for screening babies outside any given unit's inclusion criteria included unstable clinical course or high oxygen demand as decided by the attending neonatologist.

Use of RetCam for eye examinations

Both the AAP/AAO and CPS/COS acknowledge the use of RetCam for screening purposes as an adjunct to indirect ophthalmoscopy, recognizing that skilled personnel and equipment may be a limitation. It was interesting to note that RetCam was used in 36% (8/22) of centers.

Variations in supportive NICU practices during ROP screening

As per both the AAP and the CPS recommendations, follow up of infants screened for ROP should be conducted by the treating ophthalmologist. Clear timelines based on the examination findings have been defined [1, 3]. A pre-specified medication order form, whether paper or electronic, facilitates standardization of practice, reduction of error and effective screening. In this survey, five centers (23%) did not use any pre-specified, standardized medication order forms [5].

There were also variations regarding topical drug regimens used for pupil dilation prior to screening. The most commonly used dilating regimens were: Cyclopentolate 0.5% + Phenylephrine 2.5% in 15 (68%) centers and Cyclopentolate 0.2% + Phenylephrine 1% in four (18%) centers. Most centers report the use of supportive healthcare practices aimed at reducing discomfort during the eye examination. These included dimming overhead lights in six (27%) centers, altered respiratory support in five (22%) centers and feeding changes in two (9%) centers.

Morbidity due to eye examination

Table 2 highlights the reported perceived morbidity caused by ROP examinations in neonates. Apnea, bradycardia and desaturation events were the most common complications of the screening process, reported to occur by 17 (77%) NICUs at least some of the time, and more than 20% of the time following ROP examinations by nearly half of the NICUs (ten centers, 45%).

The majority of centers surveyed use both anti-VEGF and laser as treatment options for ROP, with 12/17 responding centers using anti-VEGF and laser therapy as the treatment of choice. Three centers (14%) reported only using laser treatment, one center (4.5%) reported only anti-VEGF, one center (4.5%) reported "other" without specification as to which treatment was used, and five centers provided no response. The most common location for administration of anti-VEGF was at the infant's bedside, reported at 50% (11/22) centers. Conversely, the most common location for laser therapy administration was the operating room, indicated in 50% (11/22) of centers.

Discussion

This is the first national study to evaluate neonatal intensive care practices for not only ROP screening inclusion criteria but also ROP screening and treatment from a practice,

process and organizational perspective. Given the response rate of 76%, we believe these results are an accurate representation of current existing practices in Canadian tertiary NICU's.

Despite published recommendations from the AAP/AAO and the CPS/COS, the results of our study show variation in screening inclusion criteria practices. Possible rationale for variations include the fear of missing babies with severe ROP [6]. Variations in practice may also be a reflection of differences in regional perinatal care. Bain et al. [7] reviewed factors associated with failure to screen newborns for ROP and found that infants with higher birth weights and higher GAs were missed most frequently. The resources available and costs involved may be a limiting factor for smaller, more rural centers [8]. Unstable clinical status of the babies at the recommended screening times may also contribute to inconsistent screening.

In recent years, telemedicine has emerged as the means to ensure screening for ROP in centers where technical expertise and resources are limited. Results from longitudinal prospective cohort studies have reported excellent sensitivity and specificity for this screening modality [9, 10]. Vinekar et al. [11], through their KIDROP model developed a specific tool to facilitate disease classification by trained technicians. In a further study that included 1257 infants with birth weights <1251 g in 13 North American centers, Quinn et al. reported strong support for the validity of digital retinal images taken by trained non-physician imagers [12]. Despite the evidence that exists in its favor, there is limited use of RetCam for ROP screening in Canadian NICU's. Increased use of RetCam may reduce the number of dangerous and expensive transfers of premature babies between hospitals due to limited availability of ophthalmological expertise. In addition, images captured can be used for benchmarking and quality improvement initiatives, which may facilitate increased adherence to guidelines and objectivity among ophthalmologists.

Current existing guidelines do not make recommendations surrounding the initiation of supportive administrative and healthcare practices for ROP screening. Survey results report apnea/bradycardia and desaturation events followed by red eye as the most common adverse clinical signs and symptoms following ROP examinations. These results are consistent with previous studies that have investigated potential adverse physiological effects of ROP screening on premature infants [13, 14]. Possible explanations for these outcomes could be that these events are a physiological response to the pain associated with the procedure. The results of our study report the use of Cyclopentolate 0.5% and Phenylephrine 2.5% as the most commonly used mydriatic combination for the screening process. This is consistent with reported literature on the safety and efficacy of this combination for screening [15].

Recognizing that the ROP screening procedure is associated with potential adverse consequences, some centers have adopted specific supportive practices; the most common being dimming of the overhead lights. These examinations are stressful on the patient, and cause strain to infants who may already suffer from significant morbidity. Current guidelines do not provide recommendations on the minimization of potential adverse consequences of screening, even though they are fairly common, as evidenced by the results in Table 2.

When examining reported data from the 2014 Canadian Neonatal Network Annual Report [16], 1614 infants were born between 31 and 32 weeks GA, of whom 226 underwent confirmed ROP screening. Of the infants screened, 76% ($n = 172$) were found not to have ROP, and no infants were found to have ROP stages 3–5. When examining birthweight data from the same report, 922 infants with a birth weight of 1250–1499 g were delivered in 2014, with 380 undergoing completed ROP screening exams. Of these, 71% ($n = 269$) did not have ROP, only one infant was diagnosed with stage three ROP, and none were diagnosed with stage 4 or 5 ROP. This means that in 2014, as many as 441 infants were unnecessarily screened for ROP, as they fell outside current CPS screening criteria. When multiplied over the course of years, this "small" deviation in guideline adherence can potentially lead to thousands of infants who may be undergoing unnecessary ROP screening.

While we are unable to determine how many infants fell under one category of screening but not the other (e.g., <1250 g but 33 weeks GA) we can still see that the majority of infants undergoing screening outside of guideline criteria do not develop significant ROP, and are put at higher risk of bradycardia or desaturation. Current evidence for these supportive practices is anecdotal, and therefore further studies need to be conducted to develop evidence based best practice models surrounding ROP examination.

The Cryotherapy for Retinopathy of Prematurity Study (CRYO-ROP) study [17] established cryotherapy as a successful treatment modality for the treatment of ROP. Furthermore, over the last several decades laser photocoagulation has replaced cryotherapy as the gold standard for ROP treatment. Possible but rare adverse effects of laser photocoagulation include cataracts, unintended laser burns and retinal detachment [18–21].

The role of VEGF in the pathogenesis of ROP has been well established [22]. The recent study by and bevacizumab for stage 3+ retinopathy of prematurity (BEAT-ROP) Cooperative Group was the first randomized controlled study that looked at the efficacy of Bevacizumab as a treatment modality for ROP in comparison to laser [23]. Recurrence rates of Zone I and posterior Zone II ROP were decreased with use of Bevacizumab when compared to traditional laser therapy, though the results were not statistically significant. In a literature review spanning the last

7 years, Klufas and Chan reported a trend towards robust scientific evidence guiding the use of intravitreal anti-VEGF for the treatment of ROP. However, given reported adverse events and limited follow up, the current use of anti-VEGF for the treatment of ROP is still deemed as "off label" [24]. Results from a recent Canadian study reporting neurodevelopmental outcomes in infants <29 weeks who were treated with anti-VEGF versus laser photocoagulation report higher odds of neurodevelopmental disabilities in infants who received anti-VEGF [25].

The primary limitation of this study is the lack of 100% response rate. This can be problematic due to potential intrinsic management differences between the level three NICU's that responded and those that did not. While we did not survey level two nurseries in the country, the greatest amount of ROP screening and treatment occurs in the level three NICUs and so we feel this survey is representative of current practice patterns.

The results of this study capture the variation in screening practices that exist despite established guidelines. In addition, there is variation in process measures surrounding ROP screening where current evidence is anecdotal. There is an urgent need for standardization given the morbidity burden associated with the disease and screening process. Further studies are required to elucidate areas of concern outlined in this paper.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Jeffries AL. Retinopathy of prematurity recommendations for screening. Paediatr Child Health. 2010;15:667–74.
2. Wilkinson AR, Haines L, Head K, Fielder AR. UK retinopathy of prematurity guideline. Early Hum Dev. 2008;84:71–74.
3. Fierson WM, American Academy of Pediatrics, Section on Ophthalmology, American Academy of Ophthalmology, American Association for Pediatric Ophthalmology and Strabismus, American Association of Certified Orthoptists. Screening examination of premature infants for retinopathy of prematurity. Pediatrics. 2013;131:189–95.
4. The Canadian Neonatal Network. Abstractors manual, (v 1.3.4). http://www.canadianneonatalnetwork.org/Portal/LinkClick.aspx?fileticket=U4anCYsSN20%3D&tabid=69.
5. Ehringer G, Duffy B. Promoting best practice and safety through pre-printed Physician orders. In: Henriksen K, Battles JB, Keyes MA, et al., editors. Advances in patient safety: new directions and alternative approaches (Vol. 2: Culture and Redesign). Rockville, MD: Agency for Healthcare Research and Quality; 2008. https://www.ncbi.nlm.nih.gov/books/NBK43696/.
6. Amer M, Jafri WH, Nizami AM, Shomrani AI, Al-Dabaan AA, Rashid K. Retinopathy of prematurity: are we missing any infant with retinopathy of prematurity? Br J Ophthalmol. 2012;96:1052–5.
7. Bain LC, Dudley A, Gould JB, Lee HC. Factors associated with failure to screen newborns for retinopathy of prematurity. J Pediatr. 2012;161:819–23.
8. Black L, Hulsey T, Lee K, Parks DC, Ebeling MD. Incremental hospital costs associated with comorbidities of prematurity. Manag Care. 2015;24:54–60.
9. Abdul Aziz AA, Isaac M, Tehrani NN. Using telemedicine to screen for retinopathy of prematurity. CMAJ. 2014;186:1012–4.
10. Wang SK, Callaway NF, Wallenstein MB, Henderson MT, Leng T, Moshfeghi DM. SUNDROP: six years of screening for retinopathy of prematurity with telemedicine. Can J Ophthalmol. 2015;50:101–6.
11. Vinekar A, Gilbert C, Dogra M, Kurian M, Shainesh G, Shetty B, et al. The KIDROP model of combining strategies for providing retinopathy of prematurity screening in underserved areas in India using wide-field imaging, tele-medicine, non-physician graders and smart phone reporting. Indian J Ophthalmol. 2014;62:41–49.
12. Quinn GE, Ying GS, Daniel E, Hildebrand PL, Ells A, Baumritter A, et al. Validity of a telemedicine system for the evaluation of acute-phase retinopathy of prematurity. JAMA Ophthalmol. 2014;132:1178–84.
13. Mitchell AJ, Green A, Jeffs DA, Roberson PK. Physiologic effects of retinopathy of prematurity screening examinations. Adv Neonatal Care. 2011;11:291–7.
14. Sun X, Lemyre B, Barrowman N, O'Connor M. Pain management during eye examinations for retinopathy of prematurity in preterm infants: a systematic review. Acta Paediatr. 2010;99:329–34.
15. Neffendorf JE, Mota MP, Xue K, Hildebrand GD. Efficacy and safety of phenylephrine 2.5% with cyclopentolate 0.5% for retinopathy of prematurity screening in 1246 eye examinations. Eur J Ophthalmol. 2015;25:249–53.
16. Shah P, Yoon EW, Chan P, Members of the Annual Report Review Committee. The Canadian neonatal network annual report 2014. http://www.canadianneonatalnetwork.org/Portal/LinkClick.aspx?fileticket = eGgxmMubxjk%3d&tabid = 39. Accessed 2 Oct 2016.
17. Palmer EA, Hardy RJ, Dobson V, Phelps DL, Quinn GE, Summers CG, et al. 15-year outcomes following threshold retinopathy of prematurity: final results from the multicenter trial of cryotherapy for retinopathy of prematurity. Arch Ophthalmol. 2005;123:311–8.
18. Trigler L, Weaver RG Jr, O'Neil JW. Case series of angle-closure glaucoma after laser treatment for retinopathy of prematurity. J AAPOS. 2005;9:17–21.
19. Simons BD, Wilson MC, Hertle RW, Schaefer DB. Bilateral hyphemas and cataracts after diode laser retinal photoablation for retinopathy of prematurity. J Pediatr Ophthalmol Strabismus. 1998;35:185–7.
20. Lambert SR, Capone A Jr, Cingle KA, Drack AV. Cataract and phthisis bulbi after laser photoablation for threshold retinopathy of prematurity. Am J Ophthalmol. 2000;129:585–91.
21. Gordon RA, Donzis PA. Myopia associated with retinopathy of prematurity. Ophthalmol. 1986;93:1593–8.
22. Travassos A, Teixeira S, Ferreira P, Regadas I, Travassos AS, Esperancinha FE, et al. Intravitreal bevacizumab in aggressive posterior retinopathy of prematurity. Ophthal Surg Lasers Imaging. 2007;38:233–7.
23. Mintz-Hittner HA, Kennedy KA, Chuang AZ, BEAT-ROP Cooperative Group. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. New Engl J Med. 2011;364:603–15.
24. Klufas MA, Chan RV. Intravitreal anti-VEGF therapy as a treatment for retinopathy of prematurity: what we know after 7 years. J Pediatr Ophthalmol Strabismus. 2015;52:77–84.
25. Morin J, Luu TM, Superstein R, Ospina LH, Befebvre F, Simard MN, et al. Neurodevelopmental outcomes following bevacizumab injections for retinopathy of prematurity. Pediatrics. 2016;137:e20153218.

Terms and Conditions

Springer Nature journal content, brought to you courtesy of Springer Nature Customer Service Center GmbH (“Springer Nature”).
Springer Nature supports a reasonable amount of sharing of research papers by authors, subscribers and authorised users (“Users”), for small-scale personal, non-commercial use provided that all copyright, trade and service marks and other proprietary notices are maintained. By accessing, sharing, receiving or otherwise using the Springer Nature journal content you agree to these terms of use (“Terms”). For these purposes, Springer Nature considers academic use (by researchers and students) to be non-commercial.
These Terms are supplementary and will apply in addition to any applicable website terms and conditions, a relevant site licence or a personal subscription. These Terms will prevail over any conflict or ambiguity with regards to the relevant terms, a site licence or a personal subscription (to the extent of the conflict or ambiguity only). For Creative Commons-licensed articles, the terms of the Creative Commons license used will apply.
We collect and use personal data to provide access to the Springer Nature journal content. We may also use these personal data internally within ResearchGate and Springer Nature and as agreed share it, in an anonymised way, for purposes of tracking, analysis and reporting. We will not otherwise disclose your personal data outside the ResearchGate or the Springer Nature group of companies unless we have your permission as detailed in the Privacy Policy.
While Users may use the Springer Nature journal content for small scale, personal non-commercial use, it is important to note that Users may not:

1. use such content for the purpose of providing other users with access on a regular or large scale basis or as a means to circumvent access control;
2. use such content where to do so would be considered a criminal or statutory offence in any jurisdiction, or gives rise to civil liability, or is otherwise unlawful;
3. falsely or misleadingly imply or suggest endorsement, approval , sponsorship, or association unless explicitly agreed to by Springer Nature in writing;
4. use bots or other automated methods to access the content or redirect messages
5. override any security feature or exclusionary protocol; or
6. share the content in order to create substitute for Springer Nature products or services or a systematic database of Springer Nature journal content.

In line with the restriction against commercial use, Springer Nature does not permit the creation of a product or service that creates revenue, royalties, rent or income from our content or its inclusion as part of a paid for service or for other commercial gain. Springer Nature journal content cannot be used for inter-library loans and librarians may not upload Springer Nature journal content on a large scale into their, or any other, institutional repository.
These terms of use are reviewed regularly and may be amended at any time. Springer Nature is not obligated to publish any information or content on this website and may remove it or features or functionality at our sole discretion, at any time with or without notice. Springer Nature may revoke this licence to you at any time and remove access to any copies of the Springer Nature journal content which have been saved.
To the fullest extent permitted by law, Springer Nature makes no warranties, representations or guarantees to Users, either express or implied with respect to the Springer nature journal content and all parties disclaim and waive any implied warranties or warranties imposed by law, including merchantability or fitness for any particular purpose.
Please note that these rights do not automatically extend to content, data or other material published by Springer Nature that may be licensed from third parties.
If you would like to use or distribute our Springer Nature journal content to a wider audience or on a regular basis or in any other manner not expressly permitted by these Terms, please contact Springer Nature at

onlineservice@springernature.com