

# Clinical Practice Guidelines

## Screening and Management of Retinopathy of Prematurity

January 2020

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**Guideline Development Group (Alphabetical)**

Parijat Chandra	Subhadra Jalali
Deepak Chawla(Chairperson)	Praveen Kumar
Ashok K Deorari	Amanpreet Sethi
M R Dogra	Anand Vinekar

**Reviewers (Alphabetical)**

Deeksha Katoch	Rajan Shukla
Suman Rao PN	

**Editorial Board (Alphabetical)**

B D Bhatia	Praveen Kumar (Chairperson)
Deepak Chawla	Mohit Sahni
Girish Gupta	M Jeeva Sankar
Nandkishor S Kabra	Sachin Shah

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**Executive summary**

Retinopathy of prematurity (ROP) is a vasoproliferative disease of retina seen in preterm neonates. Incidence of ROP is inversely proportional to gestation and it can affect more than one-third of preterm neonates born at less than 28 weeks of gestation. Number of neonates at risk of ROP is increasing in India due to enhanced coverage of facility-based neonatal care leading to improved survival of preterm neonates. Being clinically silent in the neonatal period, ROP needs to be diagnosed by screening and treated promptly if progressing to a sight-threatening stage. Guidelines are needed about criteria to identify neonates who need screening, method of screening, indications of treatment and choice of treatment. This document presents evidence-based recommendations about screening and treatment of ROP.

The guideline has been developed using standard methods adapted by National Neonatology Forum in accordance with the process described in the GRADE Handbook and WHO Handbook for Guideline Development. The detailed methods are described elsewhere in this compilation of guidelines. Table 1 below summarizes the recommendations for practice questions prioritized by the guideline panel in consultation with a wider group of NNF members.

**Table 1: Summary of recommendations for screening and management of Retinopathy of Prematurity**

S. No.	Recommendations	Strength of recommendations	Certainty of evidence
1.	<p>Following neonates should be screened for Retinopathy of Prematurity (ROP):</p> <ul style="list-style-type: none"> <li>a. Born at less than 34 weeks of gestation, OR</li> <li>b. If gestation at birth is not known conclusively, birth weight below 2000 g, OR</li> <li>c. Born at 34-36 weeks of gestation AND having ANY of the following risk factors: need of respiratory support, oxygen therapy for more than 6 h, sepsis, episodes of apnea and need of blood transfusion, exchange transfusion or unstable clinical course as determined by pediatrician. In absence of reliable records, admission in neonatal intensive care unit (NICU) or Special Care Newborn Unit(SCNU) can be taken as a surrogate risk factor.</li> </ul>	<p>Strong</p> <p>Weak, Conditional</p>	<p>Moderate</p> <p>Very low</p>
2.	<ul style="list-style-type: none"> <li>a. First screening for Retinopathy of Prematurity (ROP) should be performed at 4 weeks postnatal age (PNA).</li> <li>b. In neonates less than 28 weeks of gestation (up to 27<sup>6</sup> weeks) or with birth weight less than 1200 g if gestation at birth is not confirmed conclusively, the first examination for ROP should be preponed to 2-3 weeks postnatal age (PNA).</li> </ul>	<p>Strong</p> <p>Strong</p>	<p>Not graded</p> <p>Very low</p>
3.	<ul style="list-style-type: none"> <li>a. A combination of topical anesthetic (TA) eye drops (0.5% proparacaine) 30 seconds prior to examination combined with oral 24% sucrose or 25% dextrose in the dose of 0.5 mL/kg just before the insertion of eye speculum should be used for prevention of pain during screening for Retinopathy of Prematurity (ROP).</li> </ul>	<p>Strong</p>	<p>Moderate</p>

	<p>b. Either non-nutritive sucking using a sterile single-use pacifier or provision of mother's smell by nearby placement of a clean cloth soaked in her breast milk may be combined with TA and 24% sucrose/25% dextrose to enhance pain relief during the screening procedure. <i>When using pacifier, the healthcare provider must explain the specific indication of its use and counsel family against using a pacifier after discharge from hospital.</i></p>	Strong, Conditional	Moderate
4.	<p>a. Wide-angle digital retinal camera may be used for screening eligible preterm neonates for presence of Retinopathy of Prematurity (ROP) needing treatment or referral <i>in settings where indirect ophthalmoscopy cannot be done due to lack of a trained ophthalmologist.</i></p> <p>b. Use of wide-angle digital retinal imaging for documentation of disease and effect of treatment in settings with ophthalmologist conducted indirect ophthalmoscopy based retinal screening program should be encouraged.</p>	Weak, Conditional	Very low
5.	<p>a. Intra-vitreous Bevacizumab may be used for treatment of type 1 Retinopathy of Prematurity (ROP) involving zone 1.</p> <p>b. Intra-vitreous Bevacizumab should NOT be used for treatment of zone 2 ROP.</p> <p>c. At present, evidence is not sufficient for use of anti-vascular endothelial growth factor (anti-VEGF) drugs other than Bevacizumab.</p> <p>Parents must be informed about benefit and risks and a written informed consent must be obtained for its use including off-label use. Follow-up retinal examinations are needed till at least 65 weeks post-menstrual age (PMA) after use of anti-VEGF drugs, with or without additional laser ablation to detect recurrence. Long term follow-up with pediatrician must be done for other developmental issues in all treated or untreated ROP cases, especially when anti-VEGF treatment is used.</p>	Weak, Conditional	Very low



## Introduction

Retinopathy of prematurity (ROP), a vasoproliferative disease of retina is observed in preterm neonates. After preterm birth, normal growth of retinal vessels from optic disc to retinal periphery is disrupted. Exposure to episodes of hypoxia and hyperoxia, poor nutrition, and systemic inflammatory response additionally cause abnormal growth of retinal vessels.(1) Unless detected by active screening and treated timely, the disease can progress to cause retinal detachment and permanent visual impairment. ROP is the leading cause of potentially avoidable childhood blindness.(2) India belongs to a group of countries with high incidence of ROP. According to an estimate, assuming that of all preterm births only 30% survived, in year 2010 about 16,000 neonates would have developed ROP and about 3000 would have gone blind in India due to ROP.(3) This number has risen over the last decade as increasing number of preterm neonates are surviving due to improved access to facility-based neonatal care and are therefore at risk of developing ROP. Other contributors to increasing incidence of ROP in India include higher incidence of prematurity, use of oxygen therapy without air-oxygen blenders, lack of use of pulse oximetry for assessing the need and monitoring the response to oxygen therapy, higher incidence of systemic sepsis, and poor compliance with screening and treatment guidelines for ROP.(4) Most of these risk factors (except prematurity) are modifiable and following standard evidence-based guidelines and having facility-specific standard operating procedures (SOPs) may reduce the incidence of ROP.

During the neonatal period, ROP is a silent disease and active screening by retinal examination is needed for detecting its presence, severity and need of treatment. Different studies from India have reported varying incidence of ROP depending on baseline characteristics of enrolled subjects, type of ROP reported, year of publication and type of neonatal unit.(3,5–8) Well-established tertiary care units have shown gradual decline in the incidence of ROP over the years with improvement in quality of neonatal care and establishment of robust screening and treatment programs.(9) More recent reports of incidence of ROP in India are from newer or more 'peripheral' hospitals and about neonates referred from district hospitals to tertiary care centers.(10,11)

## Scope of the guideline and Target audience

### Aim

Aim of these guidelines is to provide evidence-based guidance for prevention of blindness due to ROP. Specific issues addressed in these guidelines include identification of neonates who need screening eye examination (screening criteria), comparison of different approaches to screening, different treatment options and pain relief during screening or treatment. Primary prevention of ROP by reducing exposure to risk factors like oxygen, blood products, poor nutrition and systemic infection is addressed by different set of guidelines.

### Target audience

These guidelines are for intended to be used by pediatricians, neonatologists, ophthalmologists, nurses, ophthalmic technicians, social workers, community health workers (including ASHA) and other healthcare providers involved in care of preterm neonates. In addition, the guidelines can be used by state and national health administrators, program managers and policy makers to improve efforts to prevent blindness due to ROP.

### Population of interest

These guidelines are applicable to preterm neonates being cared for in both secondary (special neonatal care units at district hospitals) and tertiary care (neonatal intensive care units) neonatal health facilities in public and private sectors. These guidelines are also meant for standalone or integrated ophthalmic clinics, departments or hospitals.

### How to use these guidelines

This systematic review on screening and management of retinopathy of prematurity led to the development of a group of 6 recommendations. Each recommendation was graded as **strong** when there was confidence that the benefits clearly outweigh the harms, or **weak** when the benefits probably outweigh the harms, but there was uncertainty about the trade-offs. A strong or weak recommendation was further classified as **conditional** if the benefits outweigh the harms in some situations but not in others. For example, some recommendations were relevant only to settings in low and middle-income countries where resources are very limited while others were considered relevant only to settings where certain types of facilities are available. To ensure that each recommendation is correctly understood and applied in practice, the context of all context-specific recommendations is clearly stated within each recommendation, and additional remarks are provided where needed. Users of the guideline should refer to these remarks, which are presented along with the evidence summaries within the guideline.

### Questions relevant to clinical practice

The guideline author panel included neonatologists and ophthalmologists. Initially a set of questions and outcome of interest were framed by the panel (list in the detailed online document). These sets of questions and outcomes were circulated by email for scoring on a scale of 1 to 9 (7-9 of critical importance, 4-6 important and 1-3 not important). Final rating of the guideline questions and outcomes was done by the guideline panel based on response received from 30 subject experts (26 neonatologists and 4 ophthalmologists).

Questions chosen to be addressed by the guideline panel included the following:

1. Which preterm neonates should be screened for presence of ROP?
2. When should the first screening examination for ROP be done?
3. What interventions must be used prevention of pain during ROP screening?
4. Can digital retinal imaging be used for screening for ROP?
5. Can anti-VEGF agents be used for treatment of severe ROP?
6. Can topical anesthesia with and without oral sucrose be used for pain relief during laser therapy for ROP?

## Outcomes of interest

Benefits and harms in critical outcomes formed the basis of the recommendations for each question. Following outcomes of interest were proposed to be used by the guideline panel.

### *Critical*

1. Mortality
2. Severe neurodevelopmental disability
3. Severe visual impairment
4. Retinal detachment (unfavorable retinal structure)
5. Recurrence of ROP
6. Premature infant pain profile

### *Important*

1. Visual acuity
2. Cataract
3. Refractive errors
4. Crying time
5. Hypoxia, hypotension or apnea

### *Neither critical nor important*

6. Feed intolerance
7. Duration of hospital stay
8. Local minor adverse effects

A systematic review of literature was done, and a standardized form was used to extract relevant information from studies. Systematically extracted data included: study identifiers, setting, design, participants, sample size, intervention or exposure, control or comparison group, outcome measures and results.

## Interpretation of recommendations

We used GRADE approach for assessing the quality of evidence and the recommendations. The quality of the set of included studies reporting results for an outcome was graded as: *high*, *moderate*, *low* or *very low*. The strength of a recommendation reflects the degree of confidence that the desirable effects of adherence to a recommendation outweigh the undesirable effects. The decisions were made on the basis of evidence of benefits and harms, quality of evidence, values and preferences of policymakers, health-care providers and parents and whether costs are qualitatively justifiable relative to benefits in low- and middle-income countries.

## **Evidence review and Formulation of recommendations**

### **Methodology**

Using the assembled list of priority questions and critical outcomes from the scoping exercise, the GDG identified systematic reviews that were either relevant or potentially relevant and assessed whether they needed to be updated. A systematic review was considered to be out of date if the last search date was two years or more prior to the date of assessment. If any relevant review was found to be out of date, it was updated.

### **Search strategy**

Cochrane systematic reviews were the primary source of evidence for the recommendations included in this guideline. In addition, key databases searched included the Cochrane database of systematic reviews of RCTs, the Cochrane controlled trials register and MEDLINE (1966 to August 2019). The reference lists of relevant articles and a number of key journals were hand searched. Details of search strategy are provided in the online annexure.

### **Data abstraction and summary tables of individual studies**

A standardized form was used to extract information from relevant studies. Systematically extracted data included: study identifiers, setting, design, participants, sample size, intervention or exposure, control or comparison group, outcome measures and results. The following quality characteristics were recorded for RCTs: allocation concealment, blinding of intervention or observers, loss to follow up, intention to treat analysis, analysis adjusted for cluster randomization (the latter only for cluster RCTs). The quality characteristics recorded for observational studies were likelihood of reverse causality, selection bias and measurement bias, loss to follow-up and analysis adjusted for confounding. The studies were stratified according to the type of intervention or exposure, study design, birth weight and gestational age, where possible. Effects were expressed as relative risks (RR) or odds ratios (OR) for categorical data, and as mean differences (MD) or weighted mean differences (WMD) for continuous data where possible. All studies reporting on a critical outcome were summarized in a table of individual studies.

### **Pooled effects**

Pooled effects for developing recommendations were considered, wherever feasible. If results of three or more RCTs were available for an outcome, and the overall quality of evidence using the GRADE approach was at least "low", observational studies were not considered. Pooled effects from published systematic reviews were used if the meta-analysis was appropriately done, and the reviews were up to date. However, if any relevant published study not included in the systematic review or a methodological problem with the meta-analysis was identified, the results were pooled in RevMan 5. For pooling, the author-reported adjusted effect sizes and confidence intervals (CIs) were used as far as possible. Random effects models for meta-analysis were used if there was an important inconsistency in effects, and the random effects model was not unduly affected by small studies. Where pooling of results was not possible, the range of effect sizes observed in the individual studies was used in the development of recommendations.

## Quality assessment

Quality assessment of the body of evidence for each outcome was performed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. The GRADE approach was used for all the critical outcomes identified in the PICOs, and a GRADE profile was prepared for each quantitative outcome within each PICO. Accordingly, the quality of evidence for each outcome was rated as “high,” “moderate,” “low,” or “very low” based on a set of criteria. As a baseline, RCTs provided “high-quality” evidence, while non-randomized trials and observational studies provided “low-quality” evidence. This baseline quality rating was then downgraded based on consideration of risk of bias, inconsistency, imprecision, indirectness and publication bias. For observational studies, other considerations, such as magnitude of effect, could lead to upgrading of the rating if there were no limitations that indicated a need for downgrading.

### Risk of bias

**Inconsistency of the results:** The similarity in the results for a given outcome was assessed by exploring the magnitude of differences in the direction and size of effects observed from different studies. The quality of evidence was not downgraded when the directions of the findings were similar and confidence limits overlapped, whereas quality was downgraded when the results were in different directions and confidence limits showed minimal overlap.

**Indirectness:** Rating of the quality of evidence were downgraded where there were serious or very serious concerns regarding the directness of the evidence, i.e. where there were important differences between the research reported and the context for which the recommendations are being prepared. Such differences were related, for instance, to populations, interventions, comparisons or outcomes.

**Imprecision:** The degree of uncertainty around the estimate of effect was assessed. As this was often a function of sample size and number of events, studies with relatively few participants or events (and thus wide confidence intervals around effect estimates) were downgraded for imprecision.

**Publication bias:** Quality rating could also be affected by perceived or statistical evidence of bias that may have led to underestimation or overestimation of the effect of an intervention as a result of selective publication based on study results. Where publication bias was strongly suspected, evidence was downgraded by one level.

GRADE profile software was used to construct “Summary of Findings” tables for each priority question; these tables include the assessments and judgements relating to the elements described above and the illustrative comparative risks for each outcome. Relevant information and data were extracted in a consistent manner from the systematic reviews relating to each priority question by applying the following procedures. First, up-to-date review documents and/or data (e.g. RevMan file) were obtained from the Cochrane Library. Secondly, analyses relevant to the critical outcomes were identified and selected. The data were then imported from the RevMan file (for Cochrane reviews) or manually entered into the GRADE profilers (for non-Cochrane reviews). For each outcome, GRADE assessment criteria (as described above) were applied to evaluate the quality of the evidence. In the final step of the assessment process, GRADE evidence profiles were generated for each priority question.

**Document review**

The GDG met face to face on two occasions and prepared a draft of the full guideline document with revisions to accurately reflect the deliberations and decisions of the GDG participants. The draft guideline was then shared electronically between the GDG members for further comments. The inputs of the peer reviewers were included in the guideline document and further revisions were made to the guideline draft as needed. After the peer review process, the revised version was prepared.

## Classification of ROP

Guideline panel recommends use of International Classification of ROP (ICROP) for classifying ROP. ICROP describes vascularization of the retina and characterizes ROP by its position (zone), severity (stage), and extent (clock hours).(14,15)

Location	Zone 1	Circle with optic nerve at its centre and a radius of twice the distance from optic nerve to macula
	Zone 2	Concentric circle from edge of zone 1 to ora serrata nasally and equator temporally
	Zone 3	Lateral crescent from zone 2 to ora serrata temporally
Severity	Stage 1	Presence of thin white demarcation line separating vascular from avascular retina
	Stage 2	Addition of depth and width to the demarcation line of stage 1, so as the line becomes ridge
	Stage 3	Presence of extra retinal fibrovascular proliferation with abnormal vessels and fibrous tissue extending from ridge to vitreous
	Stage 4	Partial retinal detachment not involving macula (4A) and involving macula (4B)
	Stage 5	Complete retinal detachment
Plus disease	Presence of dilatation and tortuosity of at least two retinal vessels at posterior pole of eye. Also associated with pupillary rigidity and vitreous haze in advanced cases. Dilatation and tortuosity less than of plus severity is termed pre-plus. Both plus and pre-plus diseases denote active disease.	
Extent	Extent of ROP described in 30 <sup>o</sup> clock hours (a total of 12 clock hours of 30 <sup>o</sup> each)	

**Aggressive posterior ROP (AP-ROP)** is a rapidly progressing, severe form of ROP, if untreated, usually progresses rapidly to stage 5 ROP. The characteristic features of this type of ROP include its posterior location, prominence of plus disease, and the ill-defined nature of the retinopathy. This may not have classical ridge or extraretinal fibrovascular proliferation, but rather have innocuous looking retina and tortuous vessels forming arcades. This type of ROP is likely to get missed by inexperienced examiners. Observed most commonly in Zone I, it may also occur in posterior Zone II. It occurs in extremely preterm and extremely low birth babies but is reported from India in heavier and less preterm babies also. APROP may also start earlier than type 1 ROP (vide infra).

## Screening for ROP

The aim of a ROP screening program is to detect ROP early, follow it up closely during its evolution, and treat if it assumes potentially serious severity level.

The onus of identifying eligible baby and providing written and verbal information about exact date, time, place and person who will conduct the first screening and also counseling the

family regarding the immense importance of this timely eye examination rests with the child care provider, usually the pediatrician or neonatologist.

For screening examination, pupils should be dilated with 2.5% phenylephrine and 0.5-1% tropicamide. Various protocols of pupillary dilation are followed. Combination drops of 0.5% tropicamide and 2.5% phenylephrine have become available now obviating the need for dilution. One drop of the combination formulation can be instilled twice at 30 minutes interval prior to the examination. Alternatively, one drop of 0.5 % tropicamide is instilled every 10-15 minutes up to 4 times starting 1 hour before the scheduled time for examination. This is followed by one drop of 2.5 % phenylephrine just before examination. Repeated instillation of phenylephrine should be avoided due to its systemic side - effects.

Ophthalmological notes should be made after each ROP examination, detailing zone, stage and extent in terms of clock hours of any ROP and the presence of any pre-plus or plus disease. These notes should include a recommendation for the timing of the next examination (if any) and be kept with the baby's medical record (Figure 1).

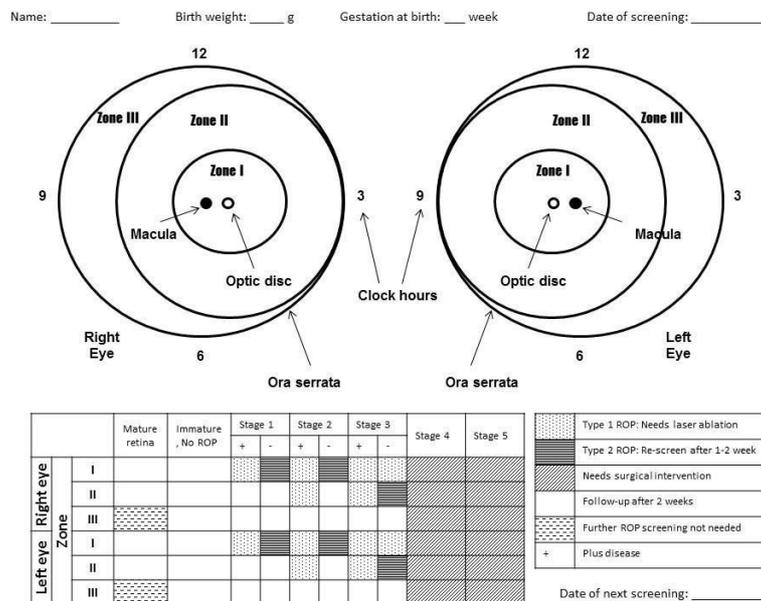


Figure 1: Suggested format to record ROP screening

## Questions, Evidence summaries and Recommendations

### Practice Question 1: Which preterm neonates should be screened for presence of ROP?

*PICO question:* In preterm neonates born at different gestation ages (population) will eye screening examination (intervention) versus no eye screening examination (control) lead to decreased incidence of severe visual impairment (outcome)?

Retinopathy of prematurity (ROP) is leading cause of potentially avoidable childhood blindness.(2) Blindness due to ROP can be prevented by screening eye examination and if needed treatment of severe stages of ROP. Screening guidelines are important in two contexts: Firstly, India with largest number of preterm births, increasing coverage of facility-based neonatal care and thereby, improving survival of preterm neonates has increasing number of babies at risk of developing blindness due to unrecognized and untreated ROP.(4) Secondly, there is a need to recognize which group of preterm babies are at risk of developing ROP and therefore need screening examination. Very preterm babies born at less than 32 weeks of gestation are at highest risk but constitute only about 15% of preterm births.(17) Most (85%) preterm neonates are born at 32-36 weeks of gestation and evidence-based screening guidelines are needed for this group of neonates.

### Summary of evidence

Critical outcomes relevant to this question were severe visual impairment or blindness and unfavorable retinal structure. Latter was included as a critical outcome as severe visual impairment can be recorded only with long-term follow-up. Unfavorable retinal structure can be recorded during initial patient follow-up and is a predictor of severe visual impairment. Important outcomes included refractive errors. Side effects of screening examination like transient feed intolerance, episodes of apnea or bradycardia and conjunctivitis were not considered critical or important.

Screening for a health condition is application of a sensitive diagnostic test on a population to detect the condition in early or asymptomatic stage. Screening can improve individual and population health if followed by adequate follow-up and appropriate treatment. We could not find any study comparing screening (and treatment) with no screening. Therefore, we searched for indirect evidence to answer the following questions:

1. What is risk of blindness or severe visual impairment due to ROP if no treatment is offered despite presence of severe ROP? This is equivalent to not screening at all. For answering this question, we extracted data from the control group of the CRYOROP study.(18) In this study neonates with bilateral threshold ROP were randomized to receive cryotherapy for one eye and no cryotherapy for the contralateral eye. Neonates with threshold ROP in only one eye were randomly assigned to receive cryotherapy or no cryotherapy for the affected eye.
2. What is risk of blindness or severe visual impairment due to ROP is screening is followed by best evidence-based treatment? This is equivalent to having an ideal ROP screening program. For answering this question, we extracted data about type 1 ROP babies in the 'early treatment' arm of the ETROP study.(19) In this randomized controlled trial,

one of eyes (if bilateral symmetrical eye disease) or neonates (if asymmetrical eye disease) were randomized to early or later treatment of high-risk pre-threshold disease.

Data thus derived was used to calculate relative risk of the critical outcome of blindness or severe visual impairment comparing screening and no screening approach.

Moderate quality evidence (Table 2 and see evidence profile in the detailed online annexure) suggests that screening (followed by early treatment of severe ROP) as compared to 'no screening' was associated with 60% relative reduction (RR: 0.40; 95% CI: 31% to 52%) in the incidence of blindness or severe visual impairment. There was also 72% relative reduction (RR: 0.28; 95% CI: 19% to 42%) in incidence of unfavorable retinal structure (moderate quality evidence). Data about incidence of refractive errors in the two studies is available with different definitions and without clear information about denominators. Therefore, effect of screening on this outcome was not entered in the evidence profile. Incidence of high myopia reported in the control group of CRYOROP study (defined as >6D, 42.3%, 58/137) and in 'early treated' type 1 ROP (defined as >5 D, 37.2%, numbers not reported) is similar. (18,19)

Preterm neonates being a heterogenous group, baseline risk of ROP was divided into two categories based on incidence of ROP at different gestations reported in Indian studies: those at high risk (about one-third of screened need treatment. e.g. neonates born at <32 weeks of gestation) and those at low risk of ROP (about 10% of screened need treatment e.g. neonates born at 32-36 weeks of gestation but are sick and are admitted in NICU/SNCU). (5,8–11,20) For every 1000 neonates screened (and treated if found eligible) versus not screened (and therefore not treated) there would be 219 fewer (95% CI: from 252 fewer to 175 fewer) cases of severe visual impairment in high-risk group neonates and 63 fewer (95% CI: from 72 fewer to 50 fewer) cases of severe visual impairment in low-risk group neonates.

A large subgroup of preterm neonates especially those born at 34-36 weeks of gestation are not admitted in neonatal intensive care unit (NICU) or Special Care Newborn Unit (SCNU) but are provided care while roomed-in with mother. Even if needing admission, due to unfavorable demand-supply ratio of beds in the NICU/SNCU, many public hospitals in India are forced to provide care to these neonates on ward beds or cots. There is absence of evidence about risk of ROP or blindness due to ROP in this subgroup of neonates and on beneficial effects of screening this largest subgroup of preterm neonates. The guideline panel in absence of evidence assumes that if risk factors of ROP are present (even if not admitted in NICU/SNCU), these babies should be screened for presence of ROP.

### *Values and preferences*

As guidelines authors, we are of the viewpoint that 'blindness or severe visual impairment', the critical outcome of this guideline is valued highly by all the stakeholders including patients, families, clinicians, policymakers and legal system. Therefore, we do not consider that there is any important uncertainty about importance of this outcome. Other outcomes like refraction errors may be rated differently by patients, families, clinicians or policymakers; however, we believe that these are not as critical as blindness or severe visual impairment.

**Table 2 : Eye screening compared to no eye screening for reducing blindness due to retinopathy of prematurity in preterm neonates**

Patient or population: reducing blindness due to retinopathy of prematurity in preterm neonates

Setting: Healthcare facilities in India (Neonatal intensive care unit, special neonatal care units, neonatal follow-up clinics and ophthalmology outdoor units or follow-up clinics)

Intervention: eye screening

Comparison: no eye screening

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with no eye screening	Risk with eye screening			
Blindness or severe visual impairment (Blindness) assessed with: Visual acuity follow up: mean 5 years	Study population		RR 0.40 (0.31 to 0.52)	433 (1 observational study)	⊕⊕⊕○ MODERATE <sup>a,b</sup>
	630 per 1,000	252 per 1,000 (195 to 328)			
	32-36 weeks GA				
	105 per 1,000	42 per 1,000 (33 to 55)			
	<32 weeks GA				
	365 per 1,000	146 per 1,000 (113 to 190)			
Unfavorable retinal structure assessed with: Fundus examination follow up: mean 5 years	443 per 1,000	124 per 1,000 (84 to 186)	RR 0.28 (0.19 to 0.42)	403 (1 observational study)	⊕⊕⊕○ MODERATE <sup>a,b</sup>

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

#### Explanations

a. Data derived from two treatment groups of two different RCTs. Certainty of evidence is downgraded as this is classified as an observational comparison. No further downgrading was done by authors for within study risk of bias.

b. Control group event rate derived from CRYOTHERAPY study and treatment group event rate derived from the outcome of early treatment in type 1 ROP in the ETROP study. However, patients, intervention (screening), control (no treatment=no screening) and the outcomes are relevant to and directly related to the question.

**RECOMMENDATION 1**

Gestational age and/or birth weight are two important parameters taken into consideration while deciding which babies to screen for Retinopathy of Prematurity (ROP).

**Following neonates should be screened for Retinopathy of Prematurity (ROP) :**

- a. Born at less than 34 weeks of gestation, OR**
- b. If gestation at birth is not known conclusively, birth weight below 2000 g, OR**
- c. Born at 34-36 weeks of gestation, AND having ANY of the following risk factors:** need of respiratory support, oxygen therapy for more than 6 h, sepsis, episodes of apnea and need of blood transfusion, exchange transfusion or unstable clinical course as determined by pediatrician. In absence of reliable records, admission in neonatal intensive care unit(NICU) or Special Care Newborn Unit(SCNU) can be taken as a surrogate risk factor.

*Strong recommendation, Moderate quality evidence for recommendations 1a and 1b*

*Conditional recommendation, Very low quality evidence for recommendation 1c*

*Interactive visual guide available at:*

**Resources required**

Two different models of ROP screening have been tested and implemented in India -1) retinal examination by a trained ophthalmologist using an indirect ophthalmoscope and 2) retinal image capturing using a wide-angle retinal camera by an ophthalmic technician or an ophthalmologist with onsite or remote assessment for presence and severity of disease.(21) Of these, former strategy has been used most commonly (a separate statement in these guidelines compares these two approaches). Blencowe et al have provided a conservative estimate of need of 300,000 screening sessions per year in India based on neonatal mortality rate prevalent in year 2010.(3) Further, for treatment of severe ROP detected by screening, 2500 working days of eye care providers skilled in laser ablation are needed annually. With improvement in coverage of facility based neonatal care and declining neonatal mortality rate these numbers are likely to be significantly higher. Presently, sporadic data is available

about coverage of ROP screening in India. A recent situational analysis conducted at major academic hospitals indicates need of upscaling. This guideline group believes the although implementing ROP screening program needs moderate resources, in long-term it is likely to be more cost-effective than caring for children and adults blinded by severe ROP. As an ophthalmologist is present in many district-level public hospitals, most areas of the country can be covered by this already available human resource. However, training for retinal examination and indirect ophthalmoscope need to be provided. Alternative strategies of public-private partnership, use of wide-angle retinal camera with tele-screening or training of neonatal care providers for ROP screening need to be tested and implemented to improve coverage in areas where ophthalmologists are not available.

#### *Monitoring and evaluation*

Quality of ROP screening program needs to be monitored. The guideline panel recommends following quality measures:

Proportion of eligible neonates screened timely (within 4 weeks if born at >28 weeks of gestation and within 3 weeks if born at 28 weeks or lower gestation)

These quality measures should be viewed and implemented in conjunction with other measures suggested in these guidelines.

#### *Research gaps*

1. Implementation research is needed to improve the certainty of evidence of desirable and undesirable effects of screening in neonates born at 32-36 weeks of gestation, including those who are provided treatment outside NICU or SNCU.(22)
2. Development and validation of ROP prediction models (e.g. based on presence of IUGR, respiratory support, sepsis, post-natal weight gain, and other risk factors) may decrease the number of neonates who need screening (especially among those born at >32 weeks of gestation).
3. Accuracy of screening by non-ophthalmologist health care providers like pediatricians or nurses using wide-angle retinal camera.
4. Implementation research to improve coverage of screening and completion of screening especially in neonates discharged before 4 weeks of PNA.

**Practice Question 2: When should the first screening examination for retinopathy of prematurity (ROP) be done?****Summary of evidence**

Progression of ROP follows a distinct timeline as per postmenstrual age (PMA) rather than postnatal age (PNA) of the infant. In addition, ROP usually does not develop before 2-3 weeks of PNA. The median age at detection of stage 1 ROP is 34 weeks. If it progresses in severity, ROP needing treatment appears at 34 to 38 weeks. Therefore, according to American Academy of Pediatrics, critical time for screening is 34 to 38 weeks PMA when the neonate is likely to reach the treatment worthy stage of disease.

However, based on higher incidence of APROP which is not only aggressive but also presents earlier than type 1 ROP (vide infra) and large incidence of inaccurate pregnancy dating especially in rural areas, we recommend that first screening examination should be carried out at 4 weeks of postnatal age (PNA).<sup>(14,16)</sup> For neonates born at less than 28 weeks of gestation (up to 27<sup>6/7</sup> weeks) or with birth weight less than 1200 g if gestation at birth is not confirmed reliably, first screening examination should be performed at 2-3 weeks of PNA, especially to detect APROP. After first screening examination, follow-up examinations are normally required every 1-2 weeks depending upon ROP staging and should be recommended by the examining ophthalmologist (Figure 1). ROP screening can be terminated once there is complete vascularization of retina without any ROP, or if the ROP has shown complete regression. This normally happens at around 40 to 44 weeks of PMA.

**RECOMMENDATION 2**

- In India, the **first screening for Retinopathy of Prematurity (ROP) should be performed at 4 weeks postnatal age (PNA).**
- **In neonates less than 28 weeks of gestation (up to 27<sup>6/7</sup> weeks) or with birth weight less than 1200g if gestation at birth is not confirmed conclusively, the first examination for ROP should be preponed to 2-3 weeks postnatal age (PNA).**
- Follow-up examinations are normally required every 1-2 weeks depending upon ROP staging and as recommended by the examining ophthalmologist.
- ROP screening can be terminated once there is complete vascularization of retina without any ROP, or if the ROP has shown complete regression. This normally happens at around 40 to 44 weeks of post-menstrual age (PMA).

*Strong recommendation, Not graded/Very low*

**Practice Question 3: What interventions must be used prevention of pain during ROP screening?**

*PICO question:* In preterm infants undergoing screening for retinopathy of prematurity (population) should oral sucrose or glucose (interventions) versus placebo (control) be used for prevention of pain (outcome)?

*PICO question:* In preterm infants undergoing screening for retinopathy of prematurity (population) should systemic paracetamol (interventions) versus placebo (control) be used for prevention of pain (outcome)?

ROP screening is a painful procedure. Neonates undergoing indirect ophthalmoscopy for ROP screening exhibit significant changes in behavior indicating pain during and immediately after the examination. These behavioral responses may persist beyond first few hours after screening and may be accompanied by other physiological and local alteration like increased spitting or vomiting, apneic episodes and eye swelling. Inability to control pain can also lead to long-term consequences in the form of altered pain processing, attention deficit disorder, impaired visual perceptual ability and executive functions at school age.(23) There is a need for proper analgesia regime that is both effective and safe during the brief procedure of ROP screening.

**Summary of evidence**

Critical outcome relevant to this question included pain score measured by premature infant pain profile. Important outcomes included crying time and physiological changes in heart rate, blood pressure and oxygen saturation.

There is moderate quality evidence (Table 3) that combining oral sucrose administration with non-nutritive sucking decreased PIPP score during ROP screening examinations. In a systematic review of 3 studies involving 134 preterm infants undergoing ROP screening, sucrose in varying concentrations of 24%-33% along with non-nutritive sucking decreased premature infant pain profile (PIPP) score as compared to water along with non-nutritive sucking (mean difference: -2.12; 95% CI: -2.86 to -1.43).(24) In another systematic review of 2 studies involving 114 infants, sucrose given by pacifier decreased PIPP score as compared to sterile water given by pacifier (mean difference: -2.47; -3.66 to -1.66) along with decreased crying time (mean difference: -21.1 sec; 95% CI: -33.1 to -9.1).(24) There is low quality evidence that combining sucrose with swaddling with pacifier have no effect on PIPP score as compared to water with swaddling with pacifier based on only one randomized controlled study with a total of 32 preterm infants. There was no significant effect on heart rate, blood pressure and respiratory rate. In one study, there was significant difference in the percentage oxygen saturation (%) between the comparison groups with a lower oxygen saturation in the sucrose group (mean difference: -3.00; -5.86 to -0.14). In all the studies, local anesthetic (LA) eye drops were used in both the groups.

The evidence regarding use of oral paracetamol compared to placebo is conflicting (Table 4) with two trials showing no effect on PIPP score.(25) In the trial by Seifi et al, 2013 the dose of 15 mg/kg was used 30 minutes prior to the procedure along with topical anesthetic drops.(26) One trial by Kabata et al. 2016 the dose of 15 mg/kg was used 60 minutes prior to the procedure along with topical anesthetic drops.(27) in this trial mean PIPP score was lower as compared to placebo (11.3 vs 14). Though PIPP score was lower in the paracetamol group still preterm infants suffered considerable amount of pain. When oral paracetamol (dose of 15 mg/kg 30 minutes prior to the procedure) was compared with oral 24% sucrose (0.2 ml just prior

to the procedure), the PIPP score was significantly less in the sucrose group (12.9 vs 9) in the first 45 seconds during the ROP screening examination.

**Table 3: Sucrose or glucose[intervention] compared to placebo for prevention of pain in preterm infants undergoing screening for retinopathy of prematurity**

Patient or population: prevention of pain in preterm infants undergoing screening for retinopathy of prematurity

Setting: in neonatal follow up care setting

Intervention: Sucrose or glucose[intervention]

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with Sucrose or glucose[intervention]			
PIPP during examination (Sucrose by syringe + Swaddle+ Pacifier) vs (Water by syringe + Swaddle + Pacifier) Scale from: 0 to 21	The mean PIPP during examination (Sucrose by syringe + Swaddle+ Pacifier) vs (Water by syringe + Swaddle + Pacifier) was 0	MD 0 (2.08 lower to 2.08 higher)	-	32 (1 RCT)	⊕⊕○○ LOW a,b
Crying time (%) (Sucrose by syringe + Swaddle+ Pacifier) vs (Water by syringe + Swaddle + Pacifier)	The mean crying time (%) (Sucrose by syringe + Swaddle+ Pacifier) vs (Water by syringe + Swaddle + Pacifier) was 0	MD 10 lower (32.91 lower to 12.91 higher)	-	32 (1 RCT)	⊕⊕○○ LOW a,c
Heart rate (beats/min)	The mean heart rate (beats/min) was 0	MD 6 lower (19.33 lower to 7.33 higher)	-	32 (1 RCT)	⊕○○○ VERY LOW a,d
Mean blood pressure (mmHg)	The mean blood pressure (mmHg) was 0	MD 7 lower (18.48 lower to 4.48 higher)	-	32 (1 RCT)	⊕⊕○○ LOW a,b

**Table 3: Sucrose or glucose[intervention] compared to placebo for prevention of pain in preterm infants undergoing screening for retinopathy of prematurity**

Patient or population: prevention of pain in preterm infants undergoing screening for retinopathy of prematurity

Setting: in neonatal follow up care setting

Intervention: Sucrose or glucose[intervention]

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with Sucrose or glucose[intervention]			
Respiratory rate (breaths/min)	The mean respiratory rate (breaths/min) was 0	MD 2 higher (5.07 lower to 9.07 higher)	-	32 (1 RCT)	⊕⊕○○ LOW <sup>a,b</sup>
Oxygen saturation (%)	The mean oxygen saturation (%) was 0	MD 3 lower (5.86 lower to 0.14 lower)	-	32 (1 RCT)	⊕⊕○○ LOW <sup>a,b</sup>
Total crying time	The mean total crying time was 0	MD 33.9 lower (76.22 lower to 8.42 higher)	-	30 (1 RCT)	⊕⊕○○ LOW <sup>a,b</sup>
Oxygen saturation (%) during examination	The mean oxygen saturation (%) during examination was 0	MD 1.71 lower (5.85 lower to 2.43 higher)	-	30 (1 RCT)	⊕⊕○○ LOW <sup>a,b</sup>
PIPP score during eye examination (24%-33% Sucrose+ Non-nutritive sucking) vs (Water+ Non-nutritive sucking)	The mean PIPP score during eye examination (24%-33% Sucrose+ Non-nutritive sucking) vs (Water+ Non-nutritive sucking) was 0	MD 2.15 lower (2.86 lower to 1.43 lower)	-	134 (3 RCTs)	⊕⊕⊕○ MODERATE <sup>b,e</sup>

**Table 3: Sucrose or glucose[intervention] compared to placebo for prevention of pain in preterm infants undergoing screening for retinopathy of prematurity**

Patient or population: prevention of pain in preterm infants undergoing screening for retinopathy of prematurity

Setting: in neonatal follow up care setting

Intervention: Sucrose or glucose[intervention]

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with Sucrose or glucose[intervention]			
PIPP score during eye examination - Sucrose via syringe versus control (sterile water via syringe)	The mean PIPP score during eye examination - Sucrose via syringe versus control (sterile water via syringe) was 0	MD 1 lower (2.54 lower to 0.54 higher)	-	20 (1 RCT)	⊕⊕○○ LOW <sup>b,e</sup>
PIPP score during eye examination - Sucrose + pacifier versus control (sterile water + pacifier)	The mean PIPP score during eye examination - Sucrose + pacifier versus control (sterile water + pacifier) was 0	MD 2.47 lower (3.27 lower to 1.66 lower)	-	114 (3 RCTs)	⊕⊕⊕⊕ HIGH
Crying time (s) during eye examination	The mean crying time (s) during eye examination was 0	MD 21.1 lower (33.1 lower to 9.1 lower)	-	64 (1 RCT)	⊕⊕⊕○ MODERATE <sup>b</sup>

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).  
CI: Confidence interval; MD: Mean difference

#### Explanations

a. No explanation on random sequence and allocation concealment in the study text ; b. Wide Confidence interval c. Wide CI d. Wide CI e. there was increased risk of selection bias on random sequence generation and allocation concealment in one study

**Table 4: Oral paracetamol compared to placebo for prevention of pain in preterm infants undergoing screening for retinopathy of prematurity**

Patient or population: prevention of pain in preterm infants undergoing screening for retinopathy of prematurity

Setting: in neonatal follow up care setting

Intervention: oral paracetamol

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with oral paracetamol			
PIPP score in first 45 seconds of eye exam (Oral paracetamol versus placebo)	The mean PIPP score in first 45 seconds of eye exam (Oral paracetamol versus placebo) was 0	MD 0.8 lower (1.69 lower to 0.09 higher)	-	80 (1 RCT)	⊕⊕⊕○ MODERATE <sup>a</sup>
PIPP score in last 45 seconds of eye exam (Oral paracetamol versus placebo)	The mean PIPP score in last 45 seconds of eye exam (Oral paracetamol versus placebo) was 0	MD 0.2 higher (0.9 lower to 1.3 higher)	-	80 (1 RCT)	⊕⊕⊕○ MODERATE <sup>b</sup>
PIPP score 5 minutes after eye exam (Oral paracetamol versus placebo)	The mean PIPP score 5 minutes after eye exam (Oral paracetamol versus placebo) was 0	MD 1.57 lower (3.79 lower to 0.66 higher)	-	11 (1 RCT)	⊕⊕○○ LOW <sup>c</sup>
PIPP score during eye examination	The mean PIPP score during eye examination was 0	MD 2.7 lower (3.55 lower to 1.85 lower)	-	114 (1 RCT)	⊕⊕⊕⊕ HIGH
Crying time (s) during eye examination	The mean crying time (s) during eye examination was 0	MD 4.8 higher (1.69 lower to 11.29 higher)	-	114 (1 RCT)	⊕⊕⊕○ MODERATE <sup>d</sup>
PIPP score in first 45 seconds of eye exam (Oral Paracetamol versus sucrose)	The mean PIPP score in first 45 seconds of eye exam (Oral Paracetamol versus sucrose) was 0	MD 3.9 higher (2.92 higher to 4.88 higher)	-	81 (1 RCT)	⊕⊕⊕○ MODERATE <sup>g,h</sup>

**Table 4: Oral paracetamol compared to placebo for prevention of pain in preterm infants undergoing screening for retinopathy of prematurity**

Patient or population: prevention of pain in preterm infants undergoing screening for retinopathy of prematurity  
 Setting: in neonatal follow up care setting  
 Intervention: oral paracetamol  
 Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with oral paracetamol			
PIPP score in last 45 seconds of eye exam	The mean PIPP score in last 45 seconds of eye exam was 0	MD 1.1 higher (0.08 lower to 2.28 higher)	-	81 (1 RCT)	⊕⊕⊕○ MODERATE <sup>a,i</sup>
PIPP score 5 minutes after eye exam ( Oral paracetamol versus morphine)	The mean PIPP score 5 minutes after eye exam ( Oral paracetamol versus morphine) was 0	MD 1.1 higher (0.7 lower to 2.9 higher)	-	11 (1 RCT)	⊕⊕○○ LOW <sup>i</sup>

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; MD: Mean difference

#### Explanations

a. Wide Confidence interval b. Wide CI c. Wide CI d. wide CI e. Wide CI f. Wide CI h. only one study with small sample size i. Wide CI j. Small sample size with wide CI

A systematic review and network meta-analysis by Disher et al published in 2018 and including literature up to February 2017 compared effect of different pain relief interventions singly or in combination.(28) Most effective modality to decrease the PIPP was sweet taste (sucrose or glucose) combined and topical anesthetic with or without multi-sensory stimulation (non-nutritive sucking or familiar odor). This multimodal intervention also improved important outcomes like oxygen saturation reactivity and cry time. However, even with this significant intervention a large proportion of neonates (>60%) continued to experience significant pain. There is low quality evidence suggesting that not using speculum during screening examination is associated with low pain score and reduced or absent crying. However, effect of this in causing inability to examine peripheral retina and therefore possibly missing diagnosis of ROP has not been investigated.

**RECOMMENDATION 3**

**A combination of topical anesthetic (TA) eye drops (0.5% proparacaine) 30 seconds prior to examination combined with oral 24% sucrose or 25% dextrose in the dose of 0.5 mL/kg just before the insertion of eye speculum should be used for prevention of pain during screening for Retinopathy of Prematurity (ROP).**

*Strong recommendation, Moderate quality evidence*

Either **non-nutritive sucking using a sterile single-use pacifier or provision of mother's smell by nearby placement of a clean cloth soaked in her breast milk may be combined with TA and 24% sucrose/25% dextrose to enhance pain relief** during the screening procedure.

When using pacifier, the healthcare provider must explain the specific indication of its use and counsel family against using a pacifier after discharge from hospital.

*Strong, Conditional recommendation, Moderate quality evidence*

*Interactive visual guides available at:*



### *Values and preferences*

As guidelines authors, we are of the viewpoint that pain during and after ROP screening examination is valued highly by all the stakeholders including families and clinicians. Neurological, cognitive and executive functioning, valued highly at a later age, are influenced by many neonatal morbidities and interventions and role of exposure to repetitive intense pain in causing dysfunction is supported by evidence. Therefore, we do not consider that there is any important uncertainty about importance of pain relief.

There is apprehension among neonatal and pediatric physicians about using pacifier in front of family as latter may pick the practice of using unclean pacifiers at home after discharge

leading to increased risk of gastrointestinal infections. Although, there is no evidence supporting this outcome, guideline authors have made conditional recommendation about use of pacifier for pain relief.

#### *Resources required*

Oral single use sucrose preparation, intravenous 25% glucose preparation to be used orally, pacifier and topical anesthetic eye drops are available in Indian market and can be used for pain relief. No additional human resources are required for administering these agents.

#### *Monitoring and evaluation*

Practice of pain relief during ROP screening program needs to be monitored. The guideline panel recommends following quality measures:

Proportion of neonates who were given the recommended pain prevention intervention during ROP screening

This quality measures should be viewed and implemented in conjunction with other measures suggested in these guidelines.

#### *Research gaps*

1. Use of stronger but safe analgesic agents for pain relief during ROP screening.
2. Speculum and indenter free screening and its effect on pain and accurate diagnosis of ROP.

### **Practice Question 4: Can digital retinal imaging be used for screening for ROP?**

*PICO Question* : In preterm infants needing screening retinal examination (population) should digital retinal photography (interventions) versus indirect ophthalmoscopy (control) be used for diagnosis of ROP (outcome)?

Use of broader criteria for eligibility for ROP screening as outlined in the national guidelines and in the current guidelines combined with improved survival of preterm neonates has resulted in increase in number of neonates who need ROP screening. In addition, in many districts of the country ophthalmologists trained in indirect ophthalmoscopy are not available. Reference method for ROP screening worldwide and in most screening and treatment clinical trials is indirect ophthalmoscopy with retinal drawings. However, it requires in-person examination by a trained ophthalmologist. Wide-angle digital camera provides an opportunity for retinal imaging by an ophthalmic technician or other healthcare persons caring for neonates (e.g. pediatrician or nurse) and remote or later review of the collected images by an ophthalmologist. This is especially relevant for a country like India with high number of preterm births in large number of health facilities and insufficient number of trained ophthalmologists. In addition, digital retinal imaging also allows for documentation of retinal findings which can be used for teaching, quality control and medico-legal issues.

## Summary of evidence

Critical outcomes relevant to this question were severe visual impairment or blindness and unfavorable retinal structure. Latter was included as a critical outcome as severe visual impairment can be recorded only with long-term follow-up. Unfavorable retinal structure can be recorded during initial patient follow-up and is a predictor of severe visual impairment. Important outcomes included refractive errors. Side effects of screening examination like transient feed intolerance, episodes of apnea or bradycardia and conjunctivitis were not considered critical or important.

No evidence is available comparing the effect of digital retinal imaging and indirect ophthalmoscopy-based approach on the outcomes identified by the guideline authors. A systematic review by Athikarisamy et al assessed accuracy of wide-angle retinal imaging in diagnosing ROP needing treatment or referral.(29) Sensitivities reported in the included studies varied from 46% to 100%, with the majority being >90%; specificity ranged from 62% to 100% with the majority being >90%. PPV was 62–97%, and NPV was 77–100% for diagnosing clinically significant ROP (Table 5). Low sensitivity was reported from two studies which used previous version of retinal camera which was not able to take images of the peripheral retina in small eyes. Studies conducted with more recent version of the camera have reported higher sensitivity. The systematic review did not report pooled sensitivity and specificity due to heterogeneity in individual study's results. However, most of the studies have reported greater than 90% sensitivity. Guideline authors graded the evidence for test accuracy as of very low quality due to serious risk of bias in use of reference standard, inconsistent results across studies and imprecision.

Experience is available from India about feasibility and effectiveness of telemedicine based ROP screening in areas where trained ophthalmologists are not available.(30,31) Evidence is also emerging about use of newer lower cost retinal cameras.(32)

**Table 5: Should Wide-angle digital retinal photography be used to diagnose retinopathy of prematurity in preterm neonates?**

Patient or population: preterm neonates | Setting: neonatal units and ophthalmic centers  
 New test: [comparator test] | Reference test: Indirect ophthalmoscopy |  
 Range of sensitivities: 0.46 to 1.00 | Range of specificities: 0.62 to 1.00

Test result	Number of results per 1,000 patients tested (95% CI)			Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence 5% Typically seen in low-risk >32 weeks	Prevalence 30% Typically seen in 28-32 weeks	Prevalence 45% Typically seen in <28 weeks		
True positives	23 to 50	137 to 300	205 to 450	679 (6)	⊕○○○ VERY LOW <sup>a,b</sup>
False negatives	0 to 27	0 to 163	0 to 245		
True negatives	589 to 950	434 to 700	341 to 550	679 (6)	⊕○○○ VERY LOW <sup>a,b</sup>
False positives	0 to 361	0 to 266	0 to 209		

CI: Confidence interval

Explanations a. Two of six studies did not use reference standard and all 6 studies had unclear or high risk of flow and timing of test b. Due to heterogeneity in results not possible to combine outcomes

### Values and preferences

As guidelines authors, we are of the viewpoint that 'blindness or severe visual impairment', the critical outcome of this guideline is valued highly by all the stakeholders including patients, families, clinicians, policymakers and legal system. Therefore, we do not consider that there is any important uncertainty about importance of this outcome.

#### RECOMMENDATION 4

- Wide-angle digital retinal camera may be used for screening eligible preterm neonates for presence of Retinopathy of Prematurity (ROP) needing treatment or referral in settings where indirect ophthalmoscopy cannot be done due to lack of a trained ophthalmologist.

*Weak, Conditional recommendation, Very low-quality evidence*

- In a program following tele-screening approach, appropriate provisions must be made for timely evaluation of the captured retinal images by a trained ophthalmologist. Timing of image acquisition and remote evaluation should be such that there is no delay in administration of treatment or counseling of family, if needed. Backup camera, transport and human resources must be part of the tele-screening program. As retinal images may not be satisfactory in a small proportion of those screened, a backup arrangement for indirect ophthalmoscopy by a trained ophthalmologist should also be part of such a tele-screening program.
- Use of wide-angle digital retinal imaging for documentation of disease and effect of treatment in settings with ophthalmologist conducted indirect ophthalmoscopy based retinal screening program should be encouraged.

### Resources required

No studies are available comparing cost of different approaches to ROP screening. Cost incurred in purchase and maintenance of wide-field retinal image camera is high. However, a single camera can provide coverage to a large geographical area. On the other hand, ophthalmologist led ROP screening program also has cost associated with initial training and salary. Lower cost retinal cameras are now available which however need validation in sufficiently large studies.

### *Monitoring and evaluation*

The guideline panel recommends following quality measures about treatment of ROP:

1. Proportion of neonates in whom indirect ophthalmoscopy was needed due to failure of retinal imaging
2. Mean duration from image acquisition to image evaluation
3. Mean duration from suspicion of treatment worthy ROP by image evaluation to treatment

This quality measures should be viewed and implemented in conjunction with other measures suggested in these guidelines.

### *Research gaps*

1. Effectiveness of tele-screening program in preventing severe visual impairment due to ROP
2. Accuracy of use of retinal imaging by neonatal care providers

## **Treatment of ROP**

Most neonates with early stages of ROP show spontaneous regression. However, severe ROP involving the posterior retina or causing fibrovascular proliferation if not detected timely and if untreated can cause permanent loss of vision. Although the reported incidence of severe ROP varies with degree of prematurity and level of neonatal care, about one-third of extremely preterm neonates can develop severe ROP. Severe ROP is treated with laser ablation of the peripheral avascular retina. Laser ablation destroys the avascular retina producing VEGF resulting in regression of abnormal vessels.

In literature search, the guideline group identified ROP treatment guidelines published in December 2018 by American Academy of Pediatrics. (14) These guidelines are based on updated literature review and the guideline authors feel that the recommendations about indication of treatment can be applied without any change for Indian neonates.

**Box 1 : Treatment criteria for Retinopathy of Prematurity**

For deciding about need of treatment of ROP, it is divided into type 1 and 2 is based on results of Early Treatment for Retinopathy of Prematurity Randomized Trial (ETROP).(19)

Type 1 ROP (needs treatment):

- Zone I, any stage ROP with plus disease
  - Zone I, stage 3 ROP without plus disease
  - Zone II, stage 2 or 3 ROP with plus disease
- APROP in any zone is also included in treatment needing ROP

Type 2 ROP (needs close follow-up):

- Zone I, stage 1 or 2 ROP without plus disease (excluding APROP)
- Zone II, stage 3 ROP without plus disease (excluding APROP)

Before ETROP study laser ablation was performed in neonates with threshold ROP, a classification based on location and stage of ROP. ETROP study demonstrated improved visual outcome if laser ablation is performed in eyes with 'high-risk' pre-threshold ROP. Type 1 ROP includes threshold ROP and subset of pre-threshold ROP likely to benefit from early treatment. Early treatment of proliferative ROP with laser ablation leads to improved functional and structural outcomes as compared to late treatment. Facilities for laser therapy in the form of laser equipment, anesthetist, trained ophthalmologist, a pediatrician or neonatologist to monitor the baby during and after the procedure and post-procedure inpatient care if needed should be available at set-ups providing treatment of ROP.

**Practice Question 5 : Can anti-VEGF agents be used for treatment of severe ROP?**

*PICO question:* In preterm infants needing treatment for presence of type 1 retinopathy of prematurity (population) should intraocular administration of anti-VEGF antibody (interventions) versus laser ablation (control) be used for prevention of severe visual impairment (outcome)?

Laser ablation, the standard of treatment for type 1 ROP and APROP, may not be able to preserve the peripheral field of vision. An alternative modality of treatment of severe ROP has emerged in the form of antibodies to VEGF. Injected into the vitreous chamber, anti-VEGF antibodies can cause regression of abnormal vessels without destroying the peripheral retina. APROP is emerging as a common variant due to suboptimal neonatal care and improved survival of very small babies. With the emergence of anti-VEGF drugs as a treatment option besides the time-tested laser treatment, there is a need to evaluate its efficacy and compare it to laser treatment. In addition, apart from its role in normal retinal vascular development,

VEGF is needed for development of glomeruli, alveoli and parts of brain. This raises concern about possible adverse effects of suppression of normal ocular and systemic VEGF levels after intraocular administration of anti-VEGF antibodies.

### Summary of evidence

Critical outcomes relevant to this question were severe visual impairment or blindness and unfavorable retinal structure. Latter was included as a critical outcome as severe visual impairment can be recorded only with long-term follow-up. Unfavorable retinal structure can be recorded during initial patient follow-up and is a predictor of severe visual impairment. Important outcomes included failure of treatment leading to need of back-up treatment modality (e.g. laser therapy after failure of anti-VEGF agent or vice versa), recurrence of ROP, refractive errors and deep ophthalmic infections. Some side effects of treatment procedure like transient feed intolerance, episodes of apnea or bradycardia and conjunctivitis were not considered critical or important.

Most of evidence on use of anti-VEGF agents is from trials using bevacizumab. Very low-quality evidence pooled from three RCTs suggests that there is no significant difference in incidence of complete or partial retinal detachment (RR: 1.04; 95%CI: 0.21 to 5.13) between bevacizumab and laser therapy.(33) The quality of evidence from the three RCTs included in the pooled estimate was lowered because of unclear risk of selection bias, outcome assessment not being masked, serious risk of bias in analysis due to unit of analysis error, presence of significant heterogeneity and imprecision.

None of the RCTs have reported the outcome of severe visual impairment. One observational study which reported this outcome at 18-24 months of age, showed no significant change in this outcome (OR: 1.51, 95% CI: 0.59 to 3.90, low-quality evidence).

For the outcome of recurrence of ROP, pooled results from two RCTs (Table 6) with eye being the unit of analysis, there was increased risk with bevacizumab therapy (RR: 5.36, 95% CI: 1.22 to 23.50, very low-quality evidence). On subgroup analysis, the risk of recurrence of ROP needing retreatment was increased in patients with zone 2 ROP while decreased in zone 1 ROP. This has an important bearing in low- and middle-income countries where ensuring timely and complete follow-up remains challenging.

Low quality evidence from a single RCT suggests lower risk of very high myopia at or after 12 months of age in the anti-VEGF group (RR: 0.06; 95% CI: 0.02 to 0.20). Other outcomes like neonatal mortality, cataract and risk of recurrence of ROP after treatment were not found to be significantly different in the RCTs which reported these outcomes. Neurodevelopmental disability, a critical outcome has not been reported by any RCT. Observational study data has not shown any significant difference in risk of severe disability.

It is important to note that for all the critical and important outcomes noted above, the risk estimates are imprecise with 95%CI around the pooled estimate including both 1) no effect and 2) appreciable benefit or appreciable harm. Therefore, it is very likely that actual risk estimate may be substantially different from the one pooled from existing literature.

In a three-arm, parallel group, superiority trial (RAINBOW study), Stahl et al compared single bilateral intravitreal dose of ranibizumab 0.2 mg, ranibizumab 0.1 mg, and laser therapy.(34) The primary outcome of treatment success (defined by survival without active ROP, unfavorable structural outcome, or need for treatment switch up to 24 weeks after starting investigational treatment) occurred in 80%, 75% and 66% infants respectively. The guideline

group did not pool the RAINBOW trial data with the current Cochrane review because of following reasons: use of a different shorter acting drug-ranibizumab and heterogeneity in effect on the outcome depending on the zone of ROP, gestation at birth and regions of world. In absence of the data on long-term effect including on neurodevelopmental outcome and lack of effect in region 2 (includes India) in the subgroup analysis, the guideline panel does not recommend the use of ranibizumab for treatment of ROP.

Overall, the evidence indicates possible beneficial effect of anti-VEGF treatment in the form of lower incidence of severe refractive errors. This advantage of anti-VEGF drug may be due to like rapid control of neovascularization, rapid neovascular regression and pupillary dilation and revascularization of retina with better visual fields. These beneficial effects are important in zone 1 ROP where laser treatment irreversibly ablates the central retina leading to poor functional outcomes.

**Table 6: Anti-vascular endothelial growth factor therapy compared to cryo/laser therapy for treatment of retinopathy of prematurity**

Patient or population: treatment of retinopathy of prematurity

Setting:

Intervention: Anti-vascular endothelial growth factor therapy

Comparison: cryo/laser therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with cryo/laser therapy	Risk with Anti-vascular endothelial growth factor therapy			
	Non APROP				
Structural outcome - partial or complete retinal detachment	90 per 1,000	94 per 1,000 (19 to 462)	RR 1.04 (0.21 to 5.13)	272 (3 RCTs)	⊕○○○ VERY LOW a,b,c,d,e,f
	APROP				
	370 per 1,000	385 per 1,000 (78 to 1,000)			
Blindness or severe visual impairment (Blindness) assessed with: Visual assessment follow up: range 18 months to 24 months	53 per 1,000	78 per 1,000 (32 to 179)	OR 1.51 (0.59 to 3.90)	362 (1 observational study)	⊕⊕○○ LOW e,g,h
Recurrence of ROP (unit of analysis: eyes)	23 per 1,000	123 per 1,000 (28 to 540)	RR 5.36 (1.22 to 23.50)	188 (2 RCTs)	⊕○○○ VERY LOW a,c,f
Severe disability (Disability) assessed with: CP/Low PDI MDI/Blindness	400 per 1,000	432 per 1,000 (336 to 531)	OR 1.14 (0.76 to 1.70)	365 (1 observational study)	⊕○○○ VERY LOW e,g,h
Structural outcome - partial or complete retinal detachment - Zone I	61 per 1,000	13 per 1,000 (1 to 258)	RR 0.21 (0.01 to 4.26)	64 (1 RCT)	⊕○○○ VERY LOW a,b,c,d,e,f
Structural outcome - partial or complete retinal detachment - Zone II	0 per 1,000	0 per 1,000 (0 to 0)	RR 5.13 (0.25 to 103.45)	208 (3 RCTs)	⊕○○○ VERY LOW a,b,c,d,e,f

**Table 6: Anti-vascular endothelial growth factor therapy compared to cryo/laser therapy for treatment of retinopathy of prematurity**

Patient or population: treatment of retinopathy of prematurity

Setting:

Intervention: Anti-vascular endothelial growth factor therapy

Comparison: cryo/laser therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with cryo/laser therapy	Risk with Anti-vascular endothelial growth factor therapy			
Structural outcome - complete retinal detachment (unit of analysis: eyes)	77 per 1,000	25 per 1,000 (1 to 577)	RR 0.33 (0.01 to 7.50)	26 (1 RCT)	⊕○○○ VERY LOW <sup>b,e,f,i</sup>
Refractive error - very high myopia - at or after 12 months of age (unit of analysis: eyes)	416 per 1,000	25 per 1,000 (8 to 83)	RR 0.06 (0.02 to 0.20)	211 (1 RCT)	⊕⊕○○ LOW <sup>a,b</sup>
Mortality before discharge from primary hospital	18 per 1,000	27 per 1,000 (5 to 158)	RR 1.50 (0.26 to 8.75)	229 (2 RCTs)	⊕⊕○○ LOW <sup>e,f,i</sup>
Mortality at 30 months of age	93 per 1,000	80 per 1,000 (28 to 229)	RR 0.86 (0.30 to 2.45)	150 (1 RCT)	⊕⊕○○ LOW <sup>e,f,i</sup>
Local adverse effects - corneal opacity requiring corneal transplant (unit of analysis: eyes)	7 per 1,000	2 per 1,000 (0 to 57)	RR 0.34 (0.01 to 8.26)	286 (1 RCT)	⊕○○○ VERY LOW <sup>a,b,e,f</sup>
Local adverse effects - lens opacity requiring cataract removal (unit of analysis: eyes)	11 per 1,000	2 per 1,000 (0 to 31)	RR 0.15 (0.01 to 2.79)	544 (3 RCTs)	⊕○○○ VERY LOW <sup>a,b,e,f</sup>
Recurrence of ROP	204 per 1,000	180 per 1,000 (96 to 333)	RR 0.88 (0.47 to 1.63)	193 (2 RCTs)	⊕○○○ VERY LOW <sup>a,e,j</sup>
Recurrence of ROP - Zone I	424 per 1,000	64 per 1,000 (17 to 263)	RR 0.15 (0.04 to 0.62)	64 (1 RCT)	⊕⊕○○ LOW <sup>a,b</sup>
Recurrence of ROP - Zone II	92 per 1,000	234 per 1,000 (93 to 583)	RR 2.53 (1.01 to 6.32)	129 (2 RCTs)	⊕⊕○○ LOW <sup>a,b</sup>

**Table 6: Anti-vascular endothelial growth factor therapy compared to cryo/laser therapy for treatment of retinopathy of prematurity**

Patient or population: treatment of retinopathy of prematurity  
 Setting:  
 Intervention: Anti-vascular endothelial growth factor therapy  
 Comparison: cryo/laser therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)
	Risk with cryo/laser therapy	Risk with Anti-vascular endothelial growth factor therapy			

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).  
 CI: Confidence interval; RR: Risk ratio; OR: Odds ratio

#### Explanations

- a. Outcome assessment not masked.
- b. Serious risk of bias in analysis (unit of analysis error) in one or more of the included studies.
- c. Unclear risk of selection bias (details of allocation concealment not provided in the individual studies).
- d. Heterogeneity is present on visual inspection of the forest plot and high I<sup>2</sup> value
- e. 95%CI around the pooled estimate includes both 1) no effect and 2) appreciable benefit or appreciable harm.
- f. Number of events too small.
- g. Possibility of selection bias. Smaller and sicker babies in the bevacizumab group
- h. Much smaller babies with mean GA 25 weeks and mean BW 640 g
- i. Outcome assessment not masked, but outcome is objective.
- j. Evidence of large heterogeneity (I<sup>2</sup> = 86%).

#### Values and preferences

As guidelines authors, we are of the viewpoint that 'blindness or severe visual impairment', the critical outcome of this guideline is valued highly by all the stakeholders including patients, families, clinicians, policymakers and legal system. Therefore, we do not consider that there is any important uncertainty about importance of this outcome. Other outcomes like refraction errors may be rated differently by patients, families, clinicians or policymakers; however, we believe that these are not as critical as blindness or severe visual impairment. Regarding choice of intervention, while laser therapy would entail possible loss of peripheral vision, use of anti-VEGF drug would need more frequent and longer follow-up visits. We could not find evidence about the value assigned to alternative course of action by families. Due to wide variation in socio-economic strata and ease of access to treatment services in India, inter- and intra-stakeholder variation in values and preferences cannot be ruled out.

**RECOMMENDATION 5**

- a. Intra-vitreous Bevacizumab may be used for treatment of type 1 Retinopathy of Prematurity (ROP) involving zone 1.
- b. Intra-vitreous Bevacizumab should NOT be used for treatment of zone 2 ROP, due to higher incidence of need of retreatment and lack of evidence on possible harmful effects.
- c. At present, evidence is not sufficient for use of anti-vascular endothelial growth factor (anti-VEGF) drugs other than Bevacizumab.

*Weak, Conditional recommendation, very low quality evidence*

- Long term follow-up retinal examinations including retinal periphery are needed till at least 65 weeks post-menstrual age (PMA) after use of anti-VEGF drugs as there is definite risk of recurrence with or without additional laser ablation. Any persisting avascular retina can lead to recurrence at later date and supplemental therapy with laser ablation after significant revascularization may be needed. Long term follow-up is also required for assessment of refractive errors, squint and delayed onset retinal detachment in all treated or untreated ROP cases, especially when anti-VEGF treatment is used.
- Long term follow-up with pediatrician must be done for developmental issues related to brain, lungs and other organ systems in all treated or untreated ROP cases, especially when anti-VEGF treatment is used.

Due to lack of evidence about long-term effects including neurological outcome, parents must be informed about the benefit and risks, and a written informed consent must be obtained for use of anti-VEGF drugs, including off-label use.

The guideline panel suggests establishment of a national registry of cases who receive treatment with anti-VEGF treatment to monitor serious side effects.

*Interactive visual guide available at:*



### *Resources required*

No evidence is available regarding certainty of evidence of the required resources. Anti-VEGF drugs are costly and considering that both eyes often need to be injected, or multiple injections may be needed - the cost can be considerable. Further, intraocular administration needs to be done in an operation theatre where sterility can be assured, and injections can be given safely under operative microscope magnification under proper anesthetic supervision. This may further add to costs of the procedures. The cost of laser treatment is much lesser as only laser machine availability is needed. The laser machine has significant cost but is a one-time purchase and can be used for multiple procedures for other eyes diseases in adults as well. Lastly, due to increased risk of recurrence, more frequent retinal examination sessions and longer follow-up is required with anti-VEGF treatment.

### *Monitoring and evaluation*

The guideline panel recommends following quality measures about treatment of ROP:

1. Proportion of neonates who were given the recommended treatment (laser or anti-VEGF) within 24, 24-48 and >48 h of qualifying for treatment
2. Proportion of neonates who were administered anti-VEGF agent and completed follow-up till at least 65 weeks PMA
3. Proportion of neonates who were administered anti-VEGF agent and developed deep ophthalmic infection

This quality measures should be viewed and implemented in conjunction with other measures suggested in these guidelines.

### *Research gaps*

1. Long-term follow-up including visual, neurological, pulmonary and renal outcomes in studies comparing laser and anti-VEGF therapies.
2. Alternative anti-VEGF agents with shorter half-life and less propensity to suppress physiological systemic VEGF levels.

**Practice Question 6 : Can topical anesthesia with and without oral sucrose be used for pain relief during laser therapy for ROP?**

*PICO Question:* In preterm infants undergoing laser ablation treatment for retinopathy of prematurity (population) can topical anesthesia with and without oral sucrose (interventions) versus general anesthesia (alternate intervention) versus no analgesia (control) be used for prevention of pain during and after treatment (outcome)?

Laser photocoagulation of peripheral retina, the standard treatment for severe ROP, is a painful procedure. The standard of care for pain relief in infants undergoing laser photocoagulation for ROP in most neonatal units across the world is general anesthesia (GA) or a combination of sedation, analgesia and paralysis (SAP). On the other hand, in India, neither GA nor SAP is used during laser therapy for ROP presumably because of lack of awareness about need and/or lack of anesthetists trained for neonatal anesthesia. Preterm infants suffer considerable amount of pain during the procedure. Pain in preterm infants can lead to apnea, increased hemodynamic instability, raised intracranial pressures and permanent brain damage. Long-term consequences include altered pain processing, attention deficit disorder, impaired visual perceptual ability and executive functions at school age in very preterm infants. Hence, it is important to mitigate pain and resultant physiological dysfunction during laser ablation therapy. Oral sucrose or dextrose are the most frequently used analgesics in neonates and their use has been associated with reduction of pain-induced behavioral changes in preterm and term infants during various painful procedures.

**Summary of evidence**

Critical outcome relevant to this question included pain score measured by premature infant pain profile. Important outcomes included crying time and physiological changes in heart rate, blood pressure and oxygen saturation.

Guideline authors could not identify any trial comparing GA/SAP with no pain relief or any other pain prevention strategy.

There is low-quality evidence (Table 7) from one RCT about role of oral dextrose in prevention of pain during the laser therapy for ROP. In this study single dose of 2ml of oral 25% dextrose administered just before the start of procedure with topical anesthesia was compared with only topical anesthesia.(35) For the critical outcome of PIPP no significant difference was observed in the two groups and PIPP values indicated significant residual pain in both the groups. There was also no difference for important outcomes including change in the heart rate and oxygen desaturation.

Significantly, even for retinal screening examination, pain prevention is not adequate with oral administration of a sweet agent (sucrose or dextrose) combined with topical anesthesia and multisensory stimulation with a pacifier. Laser ablation is a significantly longer and more painful procedure and guideline authors are of the viewpoint that administration of GA or SAP as is the standard practice should be promoted for this procedure.

**Table 7: Sucrose analgesia along with local anesthetic eye drops compared to local anaesthetic eye drops alone for pain management during ROP laser therapy**

Patient or population: pain management during ROP laser therapy

Setting: in the neonatal intensive care unit

Intervention: sucrose analgesia along with local anesthetic eye drops

Comparison: local anaesthetic eye drops alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with local anaesthetic eye drops alone	Risk with sucrose analgesia along with local anesthetic eye drops			
PIPP score 30 seconds after the start of procedure (PIPP score )	The mean PIPP score 30 seconds after the start of procedure was 0	MD 0.18 lower (3.51 lower to 3.15 higher)	-	24 (1 RCT)	⊕○○○ VERY LOW a,b,c
Increase in heart rate (> 24 beats/min)	333 per 1,000	-1167 per 1,000 (-13,300 to 10,967)	Risk difference - 3.5 (-39.9 to 32.9)	24 (1 RCT)	⊕○○○ VERY LOW a,b,c
Oxygen desaturation (<90%)	250 per 1,000	-2083 per 1,000 (-6,888 to 11,138)	Risk difference - 8.33 (-27.55 to 44.55)	24 (1 RCT)	⊕○○○ VERY LOW a,b,c

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).  
CI: Confidence interval; MD: Mean difference

#### Explanations

- a. No blinding was done
- b. Wide Confidence interval
- c. Small sample size

#### Values and preferences

We feel that subjecting preterm neonates to significant pain for 30-40 minutes of laser therapy will not be acceptable to any of the key stakeholders including the families. However, this needs to be weighed against the possible delay or lack of treatment increasing the risk of severe visual impairment.

**RECOMMENDATION 6**

- a. General anesthesia (GA) or sedation, analgesia and paralysis (SAP) for management of pain are recommended during laser treatment for Retinopathy of Prematurity (ROP).

*Strong recommendation, Very low quality evidence*

- b. Alternatively, orally administered sweet agents (24% sucrose or 25% dextrose) with topical anesthesia and multisensory stimulation may be used, if GA or SAP cannot be administered safely and referring the patient to another facility will cause delay in the treatment of severe ROP. In this situation, a written informed consent should be obtained from the parents.

*Weak, Conditional recommendation, Very low quality evidence*

*Interactive visual guide available at:*

*Resources required*

GA/SAP require presence of anesthesia team trained and/or experienced in providing neonatal anesthesia, neonatal bed and trained nurse for post-operative monitoring. Policy makers, hospital administrators, and anesthesia and ophthalmology departments should make active efforts to ensure availability of these resources. Providing these resources should not be difficult as laser ablation is done at healthcare facilities where various ophthalmic surgical procedures needing GA/SAP are already being practiced.

*Monitoring and evaluation*

The guideline panel recommends following quality measures about treatment of ROP:

Proportion of neonates who received GA/SAP during laser therapy

This quality measures should be viewed and implemented in conjunction with other measures suggested in these guidelines.

*Research gaps*

1. Use of stronger but safe analgesic agents for pain relief during laser therapy when GA/SAP are not available.
2. Tools for measurement of pain during and after laser ablation therapy

**Abbreviations**

ASHA	Accredited Social Health Activist	CI	Confidence interval	GA	General anesthesia
ICROP	International Classification of ROP	MD	Mean difference	NICU	Neonatal intensive care unit
OR	Odds ratio	PIPP	Premature infant pain profile	PMA	Postmenstrual age
PNA	Postnatal age	RCT	Randomized controlled trial	ROP	Retinopathy of prematurity
RR	Risk ratio	SAP	Sedation, analgesia and paralysis	SCNU	Special care newborn unit
TA	Topical anesthesia	VEGF	Vascular endothelial growth factor		

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