Effectiveness and future implications of COVID-19-related risk stratification for managing retinopathy of prematurity: The Indian twin cities retinopathy of prematurity study report number 10

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Purpose: To evaluate the effectiveness and future implications of COVID-related risk stratification for managing retinopathy of prematurity (ROP). Methods: A prospective study was conducted at a tertiary eye care center from the beginning of the lockdown in India from 23 March 2020 till the end of the first phase of lockdown on 29 May 2020. We evaluated 200 prematurely born infants (<34 weeks of gestational age) using the new safety guideline protocols for low-risk babies developed in conjunction with the Indian ROP Society for care during the COVID-19 pandemic. Low risk included babies born at more than 30 weeks of gestational age, post menstrual age 34 weeks or above at presentation, more than 1000 grams of birth weight, and stable systemically with good weight gain. Results: New guidelines were implemented in 106 (53%) infants who were low risk while 94 (47%) infants with high risk were followed up as per the old guidelines. Out of the 106 infants (212 eyes) managed by the new guidelines, good outcome (group 1) was seen in 102 (96.2%) infants. Twenty-seven of the 102 infants had some form of ROP and 5 of these infants needed treatment. None of the low-risk babies with no detachment at presentation managed by new guidelines required surgery later (group 2). Two (1.9%) infants came with retinal detachment at presentation and underwent successful surgery (group 3) and two infants (1.9%) were lost to follow up. Conclusion: New risk stratification during the COVID-19 pandemic was an efficient and safe strategy in managing low-risk ROP babies.

Key words: COVID-related risk stratification for ROP, effectiveness of ROP COVID-safety guidelines, ROP care during COVID-19 pandemic

The COVID-19 pandemic reached our city of Hyderabad on 2 March 2020 with the testing of an international traveler who reported positive. On 18 March, our eye care network pyramid of primary, secondary and tertiary care center of excellence at Hyderabad city decided to close down all non-essential services, and India went into a complete, strict national “lockdown” from 23 March. With no previous experience of a pandemic, preparations for strategic planning of dealing with the pandemic in our eye hospital evolved,[1] and retinopathy of prematurity (ROP) was one amongst the few conditions that was identified as a disease requiring essential services, the care of which would be carried out rigorously even during the devastating and life-threatening pandemic. In order to take care of premature babies at risk of blindness during the pandemic, the vitreoretinal faculty involved with ROP care drafted preliminary, modified guidelines that would provide effective care, reduce visits and consider safety measures for the staff, ROP babies and parents during the processes of ROP screening and treatment. Subsequently, in collaboration with the executive board members of the Indian Retinopathy of Prematurity (IROP) Society, modified guidelines were drafted that were then published and circulated on the society website and also included in the publication of the All-India Ophthalmological Society (AIOS) response to COVID.[2]

Purpose: To evaluate the effectiveness and safety of the new IROP Society’s COVID-19-related risk stratification guidelines at the center of excellence at Hyderabad in prevention of ROP-related vision loss.

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Methods

This was a prospective study conducted at a tertiary eye care center at Hyderabad from the beginning of the national lockdown in India from 23 March 2020 till the end of the first phase of lockdown on 29 May 2020 as imposed by the Telangana state and the central government of India. We included all prematurely born infants (< 34 weeks of gestational age) who were evaluated by our ROP team under the ongoing IRB approved (Ethics number LEC 08088) Indian Twin Cities ROP Screening (ITCROPS) program. This included infants who visited the institute directly and also those who were examined at the outreach hospitals/Neonatal Intensive Care Unit (NICU’s) that the team visited for screening. During this time period, we screened 200 babies after taking informed consent from caregivers. The study was conducted in accordance with the declaration of Helsinki.

We collected the demographic data, gestational age (GA), post menstrual age (PMA) at presentation, birth weight (BW) and clinical severity of the zone and stage of ROP at presentation. Subsequent treatment given, follow up visits and outcomes were also recorded. First screening was done as per the day-30 and day-20 strategy and was unchanged from our previous protocols and followed protocols of the national ROP guidelines of the Government of India. Briefly, the protocol requires the first ROP screening to be done within 30 days of birth for babies born at less than 34 weeks of gestational age and/or less than 2000 grams birth weight; and for babies less than 30 weeks of gestational age and less than 1500 grams birth weight, earlier screening is done before 20 days of birth to detect severe cases of aggressive posterior retinopathy of prematurity (APROP).

New safety protocol: A detailed history regarding fever, cold, cough, recent travel and quarantine stamp among the caregivers or the baby was asked before entry into hospital and again before any examination. All precautions of proper technique of scrubbing with necessary personal protective equipment (PPE), proper social distancing between the parents, doctors and medical staff, and strict hand hygiene and cleaning protocols were maintained during the process of screening [Fig. 1]. Individual autoclaved speculum and indenter for each baby was used and appropriate sanitization of indirect ophthalmoscope and lenses besides the chairs/computer key boards etc., used was done. An ROP safety virus containment box was designed [Fig. 2] and used to protect the examiner from aerosols generated from a crying baby. Detailed ROP history and fundus findings were recorded as per the international classification and were unchanged from previous protocols.

New Follow-up and management protocol [Table 1]: Based on history, general physical status and the retinal findings, babies were then divided into two groups, namely high-risk babies and low-risk babies. High-risk babies included those where the GA was less than 30 weeks, PMA less than 34 weeks at presentation, birth weight less than 1000 grams, poor weight gain or “failure to thrive” babies. In such babies, there was no change in our follow-up or treatment protocols and was based on the Early Treatment for Retinopathy Of Prematurity (ETROP) guidelines and the Rashtriya Bal Swasthya Karyakram (RBSK) guidelines. Low risk included babies born at >30 weeks of gestational age, ≥34 weeks of post menstrual age at presentation, weighing more than 1000 grams (birth weight), and babies born systemically stable with good weight gain. Good weight gain was defined as weight gain of at least 15 grams/kg bodyweight per day (roughly 100 grams per week in a 1 kg neonate). Table 1 describes the differences in protocol for management and follow-up of these infants. In such babies with no ROP or low-risk staged (stage 1 or 2) ROP in zone 2 anterior and beyond, the subsequent follow-up was conducted in 3 to
Table 1: New revised protocol of follow up for the low-risk infants with ROP

| ROP status                                                                 | Current international guidelines for follow-up and intervention for all babies (both high-risk and low-risk babies) | New COVID era revised protocol (only in low-risk babies) |
|----------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|---------------------------------------------------------|
| 1) Zone 2 anterior, stage 1 or 2                                           | 2 weeks follow-up                                                                                 | 3-4 weeks follow-up                                     |
| 2) Zone 2 posterior, stage 1 or 2                                           | 1 week follow-up                                                                                  | 2 weeks follow-up                                       |
| 3) Zone 2 or 3, stage 3, pre-plus                                           | Follow-up                                                                                         | Same day laser                                          |
| Treatment during first visit                                               | Observe                                                                                          | Same day laser                                          |
| Follow-up                                                                  | 1 week follow-up post laser                                                                      | 2 weeks follow-up post laser                            |
| 4.) Zone 1 ROP with vascularized fovea                                     | Same day laser                                                                                    | Same day laser                                          |
| Treatment during first visit                                               | 1 week follow-up post laser                                                                      | 2 weeks follow-up post laser                            |
| Follow-up post treatment                                                   | Same day intravitreal anti-VEGF                                                                  | Same day intravitreal anti-VEGF                        |
| 5.) Zone 1 ROP with non-vascularized fovea/APROP not amenable to laser      | Next day hospital follow-up post injection and 1 week hospital follow-up                        | Next day hospital follow-up post injection and 1 week hospital follow-up |
| Treatment during first visit                                               |                                                                                                  |                                                         |
| Follow-up post treatment                                                   |                                                                                                  |                                                         |
| 6) Stage 4A and 4B ROP                                                     | Immediate surgery, admission same day; discharge after following up day one.                     | Immediate surgery, evening check, same day discharge.  |
| Treatment during first visit                                               | Next follow-up at hospital at 1 week and 1 month.                                                | 1-week teleconsultation and 1-month hospital follow-up  |
| Follow-up post treatment                                                   |                                                                                                  |                                                         |
| 7) Stage 5 ROP                                                            | After surgery, admission same day; discharge after following up on day one.                       | Deferred till the COVID-19 pandemic was under control in the city up to 4 weeks or scheduled as per availability of surgery dates. |
| Treatment during first visit                                               | Next follow up at hospital at 1 week and 1 month.                                                | Post-surgery 1-week teleconsultation and 1 month hospital follow-up |
| Follow-up post treatment                                                   |                                                                                                  |                                                         |

When it was a zone 2 posterior with low-risk ROP, then the follow-up was done in 2 weeks rather than the earlier protocol of 1 week. Any zone 2 ROP with pre-plus or stage 3 in either of the high-risk or low-risk group babies was treated on the same day and was called after 2 to 3 weeks for follow-up as against our earlier protocol of not treating some of the babies with pre-plus disease. Zone 1 ROP with vascularized fovea underwent laser on the same day and was called after 2 weeks for follow-up instead of our routine of one week follow-up for all zone 1 diseases. APROP not amenable to laser or half zone ROP (fovea not vascularized) underwent off-label intravitreal at 1/3rd of the adult dosage (0.4 mg/0.015) Avastin (Bevacizumab) on the same day and follow-up was done after 1 week instead of the earlier protocol of one day. The care givers were given the email address and WhatsApp number of the treating doctor to which they were asked to send the images of the babies’ eye on day 1 post injection, so that any redness or lid swelling could alarm the treating doctor regarding the possibility of endophthalmitis. Subsequent management would be either as a monotherapy (rarely) or more often as a combined therapy with additional laser therapy as per our published protocol. Stage 4A and 4B ROP at presentation were immediately scheduled for surgery and usually discharged the same evening after opening the eye patch, as opposed to mandatory admissions and opening patch only the next day in our earlier protocols. Parents were asked to send the images of eyes to the treating doctor at week 1 via teleconsultation and follow up in the institute after 3 to 4 weeks. In case a local ROP or retina doctor was available, they could check locally and the two doctors would communicate with each other over teleconsultation or WhatsApp. Surgery for stage 5 ROP with retrolental fibroplasia and poor prognosis at presentation was deferred till the COVID-19 pandemic was under control in the city, for up to 4 weeks or scheduled as per availability of surgery dates.

The above new screening and treatment protocols were based on the IROP society consensus statement with the aim of reducing the number of screening visits in high-risk babies by providing early laser treatment of stage 3 and pre-plus ROP to prevent the probable chances of missing follow-up in the present pandemic crisis that had severe curtailment of transport and accessibility for the public. The delay and reduction in the frequency of follow up in low-risk babies was a calculated risk taken to significantly reduce the risk of transmission of COVID-19 in the infants, parents and health care providers while at the same time preventing ROP from advancing to a level where blindness would ensue.

All infants were followed till the retina was mature or disease regressed completely with or without treatment, after which the follow-up was advised in 3–4 months for refraction, squint and vision assessment as per earlier protocol. The outcome measures were divided into three groups. Group 1 was good outcome with mature retina or regressed ROP and no retinal detachment after following the new COVID-19 ROP guidelines; group 2 was poor outcome defined as eyes with no retinal detachment at presentation progressing to retinal detachment requiring surgery; group 3 was satisfactory anatomical outcome of retinal detachment at presentation that underwent surgery and was assessed as successful if the retinal status stabilized and ROP entered a quiescent state. Descriptive statistics was used to analyze the proportion of infants in each group of the outcome measure.
Results

During the 66-day lockdown due to COVID-19 pandemic, we managed 200 premature infants. Out of these, 133 were infants screened for the first time and 77 were infants who were on follow up. Out of these 200 infants, 132 were screened in outreach hospitals in the city of Hyderabad, 11 babies were screened in outreach hospitals outside Hyderabad city but within Telangana state and 57 babies were screened in the institute campus, Hyderabad. Out of the 57 babies screened in the campus, 15 were from Hyderabad, 29 were from outside Hyderabad but within Telangana state and 13 were from outside states [Fig. 3]. Altogether, out of 200 babies, 147 were from urban areas of Hyderabad and 40 were from rural Telangana and 13 babies from other states.

In the included cohort, 95 (47.5%) infants were males and 105 (52.5%) were females. One hundred six (53%) infants qualified under the low-risk category and 94 (47%) under the high-risk category. Eighty-five out of 200 babies (42.5%) (27 of low risk and 58 of high risk) had some form of ROP. Out of this, 42 required treatment (5 of low risk and 37 of high-risk). Thirty-one infants (61 eyes) underwent laser retinopathy, 15 (30 eyes) underwent intravitreal bevacizumab injection, and 8 (16 eyes) underwent surgery.

The new guidelines of follow-up criteria were implemented in 106 (53%) infants who were low risk while 94 (47%) infants with high risk were followed up as per the old guidelines. Out of the 106 infants screened according to new guidelines, good outcome to mature retina was seen in 87 (92.5%) infants (group 1), 1 baby expired due to respiratory distress syndrome, 6 (6.4%) infants came with detachment at presentation and underwent successful surgery (group 3), and none of the infants with no detachment at presentation progressed to require surgery (group 2) [Flow chart 2]. None of the parents, infants, doctors and other staff involved in care developed any symptoms of COVID-19.

Group 1: Good outcome; mature retina or regressed ROP and no retinal detachment
Group 2: Poor outcome; no retinal detachment at presentation progressing to retinal detachment
Group 3: Satisfactory after surgery for eyes presenting with ROP-related retinal detachment

Discussion

Retinopathy of prematurity is a cause for preventable blindness when appropriately screened and treated timely. The COVID-19 pandemic posed as an unprecedented challenge for the ROP care across the country because of the likelihood of late and severe presentation. This was anticipated either due to the lack of screening services during the lockdown when many medical facilities across the country went into closure, especially in remote areas, lack of transport facilities or apprehension of parents regarding COVID-19 affecting the child and the family per se halting their approaching the services.

Managing ROP effectively is a race against time. The inhouse ROP care faculty in conjunction with the executive board members of the IROP society came up with a set of guidelines to manage ROP safely and effectively during the life-threatening pandemic. The main strategy employed was triaging babies into low- and high-risk categories after the first examination followed by reduction in number of follow-ups in the low-risk babies. Numerous safety measures were also implemented to ensure the safety of infants, parents and health care workers during the pandemic. The implementation and outcomes of these guidelines that take a calculated risk in low-risk infants with ROP, needs to be analyzed. We formulated and strengthened our in-house and outreach screening facilities across the urban and rural Telangana state to provide effective screening services while implementing the new guidelines. By delaying the follow-up of low-risk staged
ROP by 1 or 2 weeks and laser treated zone 1 ROP by 1 week more than the old guidelines in low-risk babies, we were able to decrease the frequency of follow-up by at least 2 visits per baby. Similarly, by treating the pre-plus disease on the same day, we not only decreased the frequency of follow-up visits but also the likelihood of presentation with threshold ROP due to missing the follow-up visits. One follow-up at Day one post-injection in APROP babies receiving intravitreal injection and two follow-up visits in surgically managed stage 4A, 4B at postoperative days 1 and 7 were reduced due to online teleconsultation. The prompt approval and release of teleconsultation protocols by the government of India for the first time, during the pandemic-lockdown, proved to be of immense help.

Out of the 106 low-risk babies screened with new guidelines, only 5 needed treatments. Hence if one considers two visits per non-treatment requiring baby and one visit per treatment requiring baby being reduced as per our new guidelines, then we were able to reduce around 207 visits (202 visits in no treatment requiring and 5 in treatment requiring) when considering the entire total of low-risk babies. The calculated risk that was taken by following the new guidelines in low-risk babies which accounted for 53% (106/200 babies) of total babies screened showed very good outcomes with none of the babies with no detachment at presentation progressing to detachment during the follow-up course. The close planning with parents ensured a remarkable compliance to follow-up with only 2 babies of the 200 lost to follow-up. Hence delaying the follow-up visits in low-risk staged ROP, early treatment of pre-plus disease by laser and online teleconsultation in babies receiving intravitreal injection or surgically managed stage 4A/4B was an efficient strategy to reduce the contact and chance of transmission of COVID-19 among babies, parents and health care providers. All the babies with no detachment at presentation reached mature retina during the course of follow up by new guidelines. Once the retina was mature or the disease regressed completely with or without treatment, the babies were then called after 3–4 months for refraction, squint evaluation and vision assessment.

Due to the strict scientific protocols of safety measures followed during screening none of the babies, parents or health care providers developed symptoms of COVID-19 during the follow-up care. While many health care facilities including practitioners doing ROP screening and treatment were shut down due to the pandemic, our facility was open and continued managing babies with no shutdown of care. Data shows that new guidelines in no way caused any suboptimal outcomes even in the unprecedented challenging situation of the pandemic. The new follow-up screening stratification into low-risk and high-risk could become the new normal although the small sample size was a limitation in this study. Treating at pre-plus would be only a temporary measure and not the norm. Data also showed that most of the babies screened were in outreach hospitals where our ROP screening team approached the neonatal care units in urban and rural Telangana. As was expected, this improved the compliance to timely and effective screening and management of ROP. Lesser number of infants were able to travel directly to the apex center in Hyderabad. Only a few of those infants who were referred either within or from outside the state were able to manage expensive transport, police blockades across travel routes and take on the fear of a genuine risk of COVID infection. What our data cannot reflect is the amazing individual efforts of civil society, social media, doctors, hospital administrators, police and politicians in helping vulnerable babies reach us on time during the strict lockdown with the highest fear of death and of the unknown across the country.

**Conclusion**

The new risk stratification in COVID-related ROP guidelines were an efficient and a safe strategy in managing low-risk ROP babies in the situation of a global pandemic crisis with a
very favorable outcome. The risk of COVID-19 transmission among the baby, caregivers and health care providers was mitigated. High-risk ROP was managed as efficiently and effectively with no change during the COVID-19 pandemic, except for additional safety measures. Proper, planned scientific strategy, team work and innovative thinking with the support of enabling legislation by the central government, each played a critical role in saving newborns from going blind due to ROP during the pandemic. Efficient, effective and compassionate care provided by doctors and other frontline health workers (nurses, technicians, drivers, housekeeping, and security staff) even at the risk of getting infected, overcame the challenge posed by the unknown and potentially lethal COVID-19 pandemic.

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Conflicts of interest
There are no conflicts of interest.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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