Review Article:
SCREENING AND MANAGEMENT OF RETINOPATHY OF PREMATURITY

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ABSTRACT
Screening Retinopathy of Prematurity (ROP) is intended for all infants with birthweight of 1500 grams or gestational age of 28 weeks, and to infants with birthweight of more than 1500 gram with unstable condition. The procedure is carried out 4-6 weeks after delivery of 31-33 weeks after conception. Treatment is provided prior to 72 hours after the diagnosis was established as threshold disease (American Academy of Pediatrics and Strabismus, American Academy of Ophthalmology). The treatment was done with laser or cryotherapy for stage III + threshold in order to maximally suppress the production of vascular endothelial growth factor (VEGF) in ischemic retinal area. Operative procedure was carried out for vitreoretinal anatomic repair in stage IV and V.

Keywords: stage III + threshold, VEGF, on-time screening

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INTRODUCTION
Survival rate of premature infants or those with low birthweight in this country is increasing along with the improvement of capability and facilities in Neonatal Intensive Care Unit (NICU) in type A and B hospitals and maternity hospital with reliable equipment. Although the administration of high concentration oxygen is not the main cause of ROP-resulted high blindness rate, clinical significance of infant screening using high-risk low birthweight is very important in enhancing and facilitating early detection to provide immediate treatment and to maximally reduce ROP-resulted blindness rate. From observation between May and June 2006 in Neonatal Wards, Dr Soetomo Hospital, Surabaya, there was 584 birth rate, from which 15.1% received oxygen therapy. However, the incidence rate of ROP had not been well-detected. The objective of this paper was to recall the importance of ROP early diagnosis, either for pediatric-neonatologists or ophthalmologists, so that it becomes more familiar for them in order to have more competence in diagnosing and treating ROP for the cases can be immediately handled appropriately.

PATHOGENESIS

Pathogenesis of ROP

Retinal vascularization: Centrifugal from optic disc. 16 weeks gestation until 2-3 months age
Nasal retina: 35 weeks gestation
Temporal retina: 2-3 months age after full term delivery

Figure 1. Pathogenesis of ROP
CLINICAL PICTURE

Figure 2. Stages 1-3 of ROP

Figure 3. Stages 4-5 of ROP

Figure 4. Zone and clock hours

Figure 5. Plus disease

Figure 6. Threshold disease

Figure 7. Prethreshold disease
ROP SCREENING EXAMINATION IN PREMATURE INFANTS

In the treatment of ROP, it is the ultimate importance to carry out on-time early screening examination in order to provide immediate therapy after the establishment of diagnosis (Wilson et al. 2003). The signs of ROP may not be observable during delivery, as it may be visible since the age of 4 to 16 weeks. There was a report of the youngest age of 8 days and the latest age of 8 months (Crawford 1983). According to Wilson in a joint statement of The American Academy of Pediatrics, Section on Ophthalmology, The American Association for Pediatric Ophthalmology and Strabismus, there is a recommendation on screening examination that should include:

First, infants with birthweight of < 1500 grams or with gestational age of < 28 weeks, certain infants with bodyweight of 1500 grams - 2000 grams and with unstable clinical course suspected to have higher risk by pediatricians or neonatologists should undertake fundus examination with indirect ophthalmoscopy at least twice. Only one examination is regarded as sufficient if both retina demonstrate complete vascularization.

Second, ROP examination should be carried out by experienced ophthalmologist that has knowledge on premature infant examination with ROP to identify location and changes in retina with indirect ophthalmoscope. If abnormality is found, it should be recorded using international ROP classification.

Third, the first examination should be carried out within post natal/chronological age of 4-6 weeks or 31-33 weeks post conception/post menstruation (= gestational age + chronological age). The subsequent examination should be done on-time so that a sufficient time is obtained to provide therapy or reference to other facilities if needed. Therapy should be given within 72 hours after the ROP threshold is ensured to minimize the risk of retinal detachment.

Fourth, subsequent examination schedule is determined based on findings at the first examination. For example, if immature retinal vascularization is found and extended to zone II, but retinopathy is absent, the subsequent examination is scheduled 2-3 weeks thereafter until normal vascularization to zone III is observable.

Fifth, if in the first examination the risk of ROP is found, it is recommended to follow the schedule below:

1. Infants with ROP that possibly develop into threshold ROP should be examined minimally every week, including:
   a. Any infants with a few threshold ROP in zone I.
   b. Infants with ROP in zone II, including:
      1. Stage 3 ROP without plus disease.
      2. Stage 2 ROP with plus disease.
      3. Stage 3 ROP with plus disease, but remains less extensive for ablative operation.

2. Infants with less severe ROP in zone II should be examined every 2 weeks. In infants without ROP but with incomplete vascularization in zone I, examination should be carried out every 1-2 weeks until retinal vascularization reaches zone 3 or the occurrence of threshold.

3. If vascularization in zone II is incomplete, while the ROP is absent, the subsequent examination should be carried out in an interval of 2-3 weeks, until vascularization reaches zone III.

4. Retina with incomplete vascularization only in zone III generally may experience maturation. ROP in zone III generally may experience regression without advanced symptoms. However, normal vascularization in zone III during the first examination is very premature infants is rarely found. If normal vascularization in zone III among infants with very low birthweight, it should be verified in a re-examination that should be carried out minimally 2-3 weeks later.

Sixth, infants with threshold accompanied with plus disease should receive ablation therapy minimally 1 eye in 72 hours after diagnosis, generally before the occurrence of retinal detachment. Stage 3 ROP with vascularization in zone I or the border of zone I-II may appear different from stage 3 in zone II where the occurring proliferation looks flat. Elevation may be
observable only if the disease becomes worse. If it is difficult to differentiate stage 2 and 3 in posterior are, the infant suspected at stage 3 zone I or the border of zone I-II with plus disease should be examined carefully to determine whether he/she belongs to threshold group or not.

Seventh, parents of infants with ROP should be given with explanation on the course of the disease and the possibilities that may occur in this disease during treatment, starting from the beginning of diagnosis and continued along with the progressiveness of the disease.

Eighth, the responsibility of examination and follow-up for infants with ROP risks should be decided carefully by each Neonatal Intensive Care Unit (NICU). Special criteria for ROP examination should be established by each NICU through consultation and agreement between neonatologists and ophthalmologists. If hospital decides to refer the patient before vascular maturation reaching zone III, the availability of treatment in referral place should be provided. The physician who gives reference is responsible to mention, either orally or written, needed eye examination and other requirements needed in referred place. Physician in referred place should ensure the condition of the patient's eye and communicate with physician who gives reference, so that the subsequent examination can be adjusted to the patient's condition. If the follow-up responsibility is given to the parents, they should understand that blindness may occur and subsequent examination is important for the success of treatment. This information should be given to parents both orally or written.

MANAGEMENT

CRYOTHERAPY

To prepare the parents is not an easy way since they are stressful with their baby's condition, augmented with information that their baby has potential to become blind, which requires an urgent therapy. This situation can be helped by explaining the information on ROP screening and severity. Generally, regression occurs in stage 1 and 2 ROP, but there is no particular therapy until it reaches stage 3. In 1986, multicenter trial for stage 3 ROP was commenced and the results were unexpected, such as posterior retinal detachment, macula-affecting retinal fold, or significant reduction of retrolental tissue in eyes treated with cryotherapy compared to those receiving no cryotherapy. Therese is in serious complications and Taylor D et al. recommended therapy for at least one eye if threshold disease is present. The current therapy indication is for threshold ROP, particularly in zone 1. Time of therapy is highly important, because if cicatrics is found or vitreous is affecting, retinal ablation either with cryotherapy or laser become ineffective. Therapy is given as soon as possible, ideally 2-3 days after threshold ROP is identified (Wilson ME et al 2003). However, cryotherapy is aimed to avascular retina by damaging cells, including spindle cells, so that the active ROP can be halted (McPherson AR 1986).

The technique of cryotherapy is as follows:
1. Pupil is widened as in fundus examination.
2. Aesthetic topical eyedrop is administered, and palpebral speculum is installed.
3. Retinal cryoprobe is put under the palpebra.
4. Retinal cryoprobe position is monitored with indirect ophthalmoscope.
5. Freezing is carried out on the area of avascular retina.
6. Ice ball is formed until the area of avascular retina, not beyond fibrovascular proliferation area.
7. If abnormality lies on posterior area, conjunctival incision is done nearby the limbus.

Cryotherapy effects observation:
1. Signs of plus disease may disappear in 12-24 hours.
2. Palpebral edema may disappear in 2-3 days.
3. Ridge will be involuted and vascularity may be seen between cryoscars in 1 week.
4. Cryoscar will be well-pigmented in 2 weeks.

Cryotherapy complications:
1. Systemic complications, including bradycardia, cyanosis, and respiratory depression.
2. Ocular complications, including palpebral edema, laceration, and conjunctival bleeding, pre retinal bleeding and vitreous bleeding.

LASER THERAPY

a. Argon Laser

Photocoagulation in peripheral retina is considered as the main therapy in ROP. Argon-green and diode-red wavelength can be transmitted through indirect ophthalmoscope. The benefit of laser therapy as compared to cryotherapy are as follows: it is more easily reach the posterior segment, damage all retinal later evenly, from outer plexiform layer until pigment epithelium, it has higher precision, easier to approach the ridge, not damaging sclera, and reduces the risk of vitreous bleeding. Argon laser technique is as follows: The patient is under general anesthesia in sedative condition. By using indirect ophthalmoscope with 20 D or 28 D aspheric lens, non-contiguous burn is made on avascular retina. The 20D lens makes 480 mm spot size,
ad the 28D lens makes 363 mm spot size. About 200-2000 shots are needed to cover the area. Power used is 150-450 mW. Laser is beamed approximating the ridge as careful as possible not to touch the ridge. Laser therapy complications are burn in cornea, iris, and cataract. Retinal and vitreous bleeding may occur. In the study of McNamara et al, it was found that argon laser therapy was more effective than cryotherapy. Another study using larger samples concluded that both laser therapy and cryotherapy are the same effective for ROP therapy in zone II and laser therapy tends to be more effective than cryotherapy in zone I ROP cases. Laser therapy is, however, difficult for anterior segment of the retina, so that the combination of both therapies is safer and more effective (Andrew et al 1999).

b. Diode Laser

Diode laser therapy is different from the transmission system of argon laser. Using an indirect ophthalmoscope diode laser with 200 mm fiber optic for photocoagulation, avascular retina is theraped with 28 D aspheric lens, spot size 600 mm, early intensity 320 mW, duration 300 msec, until the formation of creamy white lesion with a distance of 150-300 mm and the number of shots 200-1000, depending on the disease's location. In a protocol study comparing 814/815 nm diode laser with cryotherapy, it was found that cryotherapy produced more unfavorable anatomical outcomes compared to diode laser. Another study concluded that diode laser therapy produces less complications and as the same effective as cryotherapy. Furthermore, compared to cryotherapy, diode laser therapy made pigment epithelial cells less dispersed and no damage in blood-retinal barrier. Diode laser semiconductor radiates coherent light in a distance nearby the infra red, rendering the main absorption and cicatrix of photocoagulation histopathologically different from that in argon laser therapy.

SURGICAL THERAPY IN STAGE 4 ROP

Stage 4 ROP is an indication for surgery with scleral buckling technique. The technique is as follows:

1. First, a 360° is carried out, if there is active retinopathy, cryotherapy or laser therapy is given to avascular retina, and encircling-band is provided beneath the rectal muscle.
2. Buckling is installed to support areas with higher ridge, then, subretinal fluid drainage is done. The band is fixed tight in temporal area and caution should be taken not to give too tight fixation since it may result in increased intraocular pressure and disturb retinal circulation and choroid, resulting in pale retinal appearance.
3. Using indirect ophthalmoscopy, it can be assured that retinal perfusion and choroid is sufficiently adequate and buckle's position is ensured.

Topical antibiotic, steroid, and cycloplegia are given post-operatively. After 1 year post-operation, scleral buckle is removed so that the eyeball and the orbita can grow. However, if there is a risk of detachment due to high elevation of the ridge, the removal of scleral buckle is delayed. A study had been undertaken to assess the anatomical effectiveness of scleral buckling in ROP stages 4A, 4B and 5, and it was concluded that scleral buckling may reduce ROP progressiveness from stage 4A to 4B to stage 5, reduce vitreous traction and facilitate retinal reattachment.

SURGICAL THERAPY IN STAGE 5 ROP

Closed vitrectomy technique

The management of stage 5 ROP is the most complicated one and is a challenging problem. Several authors approved closed vitrectomy technique using gauge 20-22 and cutter which mechanically cuts the vitreous through sclera. The portal side is done posteriorly from iris root, ± 2-3 mm from limbus to prevent ciliary body. The presence of vitreous traction can be minimized with vitreous cutter. If a dense retrolental membrane is found, incision is made on proliferative tissue behind the lens. The tissue is separated from the retina by using scissor and forceps. Extraretinal fibrovascular membrane removal is done by excising the membrane on the surface of ciliary body to prevent the occurrence of synechiae. Hyaloid arterial system, which is commonly attached to nasal shunt and nasal retina, is removed. Finally, hyaluronic acid is injected, so that retina is moved backward. Andrew et al. concluded that the appropriate time of operation, retinal configuration, subretinal fluid composition, and RPE appearance is closely related with the outcome of visual acuity. Studies with ERG revealed severe and fixed retinal dysfunction in stage 5 ROP after retinal reattachment was carried out with scleral buckling or vitrectomy (Andrew 1999).

REHABILITATION

Rehabilitation was carried out for infants with prematurity or lower birthweight without ROP. The incidence of strabismus is increased in ROP cases, which is due to asymmetric maturation of extraocular muscles resulting from less normal neurological growth.
of premature children (strabismus rate ranging between 7 and 31%). Treatment with observation, training or operation may restore binocular vision optimally. In infants with premature history and regressive ROP, the incidence of myopia is between 8-20%, and even astigmatism and anisometropia may occur in 17-20%. Early examination is done periodically with refractive cycloplegia until the condition is stable after the age of 3 years. The management of amblyopia, if found, is important to prevent fixed low vision, while training glasses is given for special visual rehabilitation among those with permanent visual handicap.

CONCLUSION
Retinopathy in prematurity is proliferative retinopathy in premature infants and those with low birthweight. Nasal retina generally is vascularized completely in gestational age of 36 weeks, while vascularization in temporal retina is delayed until gestational age of 40 weeks, and even 1 month after delivery. Hypoxia and hypoxia results in the cessation of spindle cell migration and induces neovascularization. Kanski suggested that avascular retina releases vascular endothelial growth factor (VEGF), which, during intrauterine age, it stimulates the migration of retinal vascularization. After delivery, VEGF production is reduced due to relative hypoxia and the cessation of vascular migration. It is followed with the increase of metabolic need and then excessive VEGF production occurs, resulting in neovascularization complications. Although it was previously thought that oxygen delivery to premature infants is the primary cause of this disease, today a plenty of factors are suggested as the cause of retinopathy in prematurity, which include low birthweight, gestational age, vitamin E deficiency, transfusion, and other factors supposedly related with prematurity retinopathy, gestational complications, intraventricular bleeding, repeated apnea, respiratory distress syndrome and information during prematurity treatment. Clinical picture comprises acute/active retinopathy in prematurity according to international classification 1987 and cicatrix prematurity retinopathy. Diagnosis is established based on complete anamnesis, careful clinical examination, and on-time early screening examination. In stage I and II, spontaneous regulation can be expected to occur. The most effective action is by preventing premature delivery. Therapies for stage III + threshold are laser therapy or cryotherapy, while stage IV and V is operation. Rehabilitation is carried out regularly to all infants with history of prematurity with or without ROP in order to overcome the possibility of myopia, amblyopia or strabismus that may occur.

REFERENCES
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