Review

A protocol for the treatment of retinopathy of prematurity in Spain∗

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ABSTRACT

Objective: To prepare a protocol for the treatment of retinopathy of prematurity (ROP) agreed by the majority of Spanish ophthalmologists dedicated to this topic.

Material and method: A draft of the protocol was produced taking into account the experience of the participants and up to date publications. This draft was corrected by all the ophthalmologists participating in the project, and the final document was agreed by all of them.

Results: We present general guidelines as an aid for the treatment of ROP, including treatment criteria, treatment methods, a calendar of action, and follow-up.

Conclusions: It is important to have a common working protocol for the treatment of ROP to improve care and to avoid mistakes. Although individual Hospitals may adapt the protocol to their daily activity, it is recommended that there is a minimal working protocol agreed by most of professionals dedicated to pediatric ophthalmology in Spain.

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Protocolo de tratamiento de la retinopatía del prematuro en España

RESUMEN

Objetivo: Realizar un protocolo de tratamiento de la retinopatía del prematuro (ROP) consensuado por la mayor parte de oftalmólogos españoles dedicados al tema.

Material y método: Se realizó un borrador del protocolo según la experiencia de los participantes y las publicaciones actualizadas. Este borrador fue corregido por los participantes en el protocolo y se llegó al documento final consensuado por todos los participantes.

Resultados: Se presentan las directrices generales para realizar el tratamiento de la ROP, incluyendo criterios de tratamiento, metodología de actuación, calendario de actuación y seguimiento.

Conclusiones: Es importante disponer de un protocolo de actuación común en el tratamiento de la ROP para mejorar la actuación y evitar errores. Aunque cada centro hospitalario deba adaptar el protocolo a su actividad clínica, es recomendable que existan un mínimo de procedimientos consensuados por todos los oftalmólogos dedicados a la ROP.

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Introduction

Retinopathy of prematurity (ROP) is a peripheral proliferative vitreoretinopathy that expresses in immature premature infants of as yet unknown etiopathogeny. Premature babies are born with an immature retina in what concerns vascularization. Through a mechanism which to date is unknown even though there is an increasing amount of information, a number of metabolic events occur at the limits of the mature–immature retina which restricts the normal growth and development of vessels and causes the secondary appearance of neovessels and fibrovascular tissue that could evolve toward traction with retina detachment.

ROP has a very important social and economic impact. About 5% of survivors weighing less than 1000 g are legally blind. A higher percentage exhibits significant visual alterations. Severe ROP is directly associated to severe neurological development disorders and, in the presence of visual problems, the functional evolution of these patients is worse, as 77% are unable to take care of themselves. The severity of ROP is taken as a long-term neurological dysfunction marker1 and currently it is considered an important health problem.

It is essential to have a diagnostic and follow-up protocol in order to ensure adequate management of ROP.

Classification of retinopathy of prematurity

In order to establish a treatment protocol for ROP it is essential to determine its classification. In 1984 the International ROP Classification was published and modified in 1997 to include the classification of DR, cicatricial changes and sequels. In 2005 it was reviewed to include standards for each parameter by means of photographs2 (Fig. 1).

Each ROP case is defined according to 3 areas.

Localization

The retina is divided in 3 concentric zones:

- Zone I is the innermost area centered in the papilla from which the vessels progress. Its radius is twice the distance between the papilla and the macula.
- Zone II is concentric to zone I and its diameter reaches the nasal ora serrata. Recent studies have differentiated
and anterior and posterior zone II because the involvement in posterior zone I or zone II is more severe. Accordingly, the ROP developed in this “posterior zone” (posterior zone I + zone II) is defined as posterior ROP. Clinically, the limit of said posterior zone is established when looking through the lens of 2.2 or 25D, with the papilla being at the opposite limit of the lens.

- Zone III is the temporal half moon which goes from zone II to the limits of the temporal ora serrata.

**Circumferential/clock extension**

The involvement must be specified in circumferential clock hours.

**Evolutionary stage**

Five stages have been differentiated:

- Stage 1 corresponds to the line separating the vascular and avascular retina.
- Stage 2 corresponds to the munticular crest, with thickened separation line which becomes prominent. Possibility of arteriovenous shunts and thickening of vessels posteriorly to the crest.
- Stage 3 corresponds to extra-retinal vascularization, with crest reddening and posterior growth of continuous or discontinuous anomalous vessels. This neovascularization is derived from the posterior edge of the crest and is usually accompanied by gylal proliferation.
- Stage 4 corresponds to subtotal, exudative or tractional retina detachment without or with involvement of the fovea (4a, 4b respectively).
- Stage 5 corresponds to total RD, subdivided in open or closed anterior and posterior tunnel.

In addition, the classification establishes the “plus disease”, a sign of severity which may appear at any stage. It indicates a high flow vascular short-circuit due to active arteriovenous shunts and is characterized by tortuosity and dilatation of the posterior pole vessels in at least 2 quadrants, and/or pupil rigidity. The presence of disease plus is indicated adding a plus sign to the stage.

There are additional concepts which must be known in ROP, such as the “pre-threshold disease” and the “threshold disease”, which appeared with the development of the Multi-center Trial of Cryotherapy for Retinopathy of Prematurity (ETROP) and the ETROP Study (Early Treatment for ROP Randomized Trial). The “type I prethreshold disease” is defined as: zone I, any stage with disease plus; zone I, stage 3 without disease plus and zone II, stage 2+ and 3+, and “prethreshold disease type 2” as: zone I, stage 1 or 2 without disease plus, and zone II, stage 3 without disease plus. “Threshold disease” is defined as the presence in zone I or II of stage 3+ in 5 consecutive hours or 8 overall hours.

Finally, “posterior ROP” is defined as any degree of retinopathy in the posterior zone (posterior zone I and zone II) in the presence of plus signs.

**Retinopathy of prematurity treatment**

**Treatment criteria**

Treatment is considered to be necessary in the presence of:

1. Threshold disease: 5 consecutive hours or 8 overall hours in stage 3 plus.
2. Prethreshold disease type 1:
   - Zone I, any stage with disease plus.
   - Zone I, stage 3 without disease plus.
   - Zone II, stage 2+ and 3+.

**Treatment methodology**

**Diode laser photoacoagulation**

At this time, diode laser photoacoagulation is the treatment of choice. In what concerns methodology, the following is applicable.
Pre-treatment guidelines.

1. The treatment must be applied within 48–72 hours after diagnosis.
2. The ophthalmologist and the anesthetist must present an informed consent to the parents or legal custodians.
3. Pre-surgery midriasis must be achieved applying the minimum dosage to avoid the side effects of midriatics, achieving at the same time efficient and lasting midriasis enabling the application of laser. Ideally, parasympathetic blockers should be associated (1% tropicamide or 0.5 or 1% cyclopentolate) with sympathomimetics (phenylephrine at 2.5 or 1%). Guidelines for midriasis may be established in each center on the basis of studies demonstrating efficacy and safety.

Treatment guidelines.

- Anesthesia can be topical, sedation with gases, IV sedation, general anesthesia with intubation or laryngeal mask according to the criteria of each center on the basis of its experience and results.
- Anesthesia can be applied in the neonatal unit or operating theater at the choice of each hospital.
- It is recommended to maintain adequate environmental temperature and apply thermal protection to the infant.
- It can be applied through indirect ophthalmoscopy, the most widely used method, or transscleral by means of a retinopexy probe. In the case of indirect ophthalmoscopy, it is essential to be extremely careful to avoid accidental application on the macular area.
- The initial energy is of about 350 mW (depending on the equipment and the time of use: with longer time more powerful energies are required), with an application time of 200 ms and repetition time of 400 ms, which enables focusing on the different zones maintaining the foot on the pedal. A whitish-creamy lesion must be obtained and it should be applied in nearly confluent manner throughout the avascular retina. The final scars are broader than the impacts and this must be taken into account in posterior retinopathy to avoid scars close to the paramacular zone. The entire avascular retina must be treated in a single session. Partial treatment is not recommended.
- The 360° of avascular retina must be treated, although the meridians of II and IX may be left untreated.

Post-treatment guidelines

- Topical anti-inflammatories can be prescribed after treatment.
- After the treatment, the patient must be checked within 7–10 days from the first application. If signs of activity and untreated areas persist, these must be completed.

Cryotherapy

At present, cryotherapy is not the first choice of treatment and is applied in the following circumstances:
- Poor midriasis or opacities making laser application impossible.
- As coadjuvant to laser treatment in case of persistent neovascularizations that could benefit from application of cryotherapy. These cases involve high risk of bleeding and therefore application must be carried out with extreme caution.
- Urgent cases of aggressive ROP requiring urgent treatment and laser is not available.

Pretreatment guidelines. These are the same as the diode laser application guidelines. An informed consent must be given to parents and pre-surgery midriasis must follow said indications.

Treatment guidelines.

- Treatment must be carried out in the operating room.
- It is recommended to maintain adequate temperature in the environment and apply thermal protection to the premature.
- Pediatric probes must be used. The use of adult probes is contraindicated.
- General anesthesia is recommended as this is a more painful treatment and causes more cardiorespiratory instability conditions in the patient.
- It is applied with ophthalmoscopy coagulation control.
- The probe is maintained until a whitish scar is obtained.
- Defreezing must be awaited before separating the probe with great care because the sclera of prematures is very fragile.
- Care must be taken to avoid very anterior applications which could damage the ciliary body, with the risk of phthisis bulbi.
- A palpebral opening could be necessary in extremely posterior applications.
- Action on extracocular muscles must be avoided.
- Intra-surgical general anti-inflammatories can be applied to diminish inflammatory reactions.

Post-treatment guidelines.

1. Post-surgery chemosis is practically the rule in the case of cryotherapy and therefore topical treatment with anti-inflammatories must be prescribed. General anti-inflammatories can also be utilized according to the criterion of the ophthalmologist.
2. Due to increased conjunctival manipulation, it is recommended to utilize post-surgery topical antibiotic therapy as well.
3. The first examination is recommended to be carried out at 24–48 hours to assess the degree of inflammation and the presence of possible complications such as vitreous hemorrhage, conjunctival tears, hypotony, cataracts, etc. and prescribe the corresponding treatment. Subsequently, the ocular fundus must be examined within 7–10 days.

Treatment in advanced stages of the disease

If conventional laser photocoagulation treatment fails and the disease progresses to stage IV or more, the patient must be referred to the national reference Center for treating the advanced stages of the disease.
At present, treatment alternatives comprise:

- Cerclage for stage 4.
- Vitrectomy with lens preservation for stage 4.
- Vitrectomy + lensectomy via pars plana.
- Open vitrectomy.

**Use of anti-vascular endothelial growth factor**

The use of anti-VEGF is justified in ROP for the following reasons:

- VEGF is directly involved in the pathogenicity of ROP.13-15
- Anti-VEGF has demonstrated its efficacy in ophthalmological pathologies involving neovascularization in adults with a similar physiopathological basis (ARMD with neovascular proliferation, ischemic retinal venous thrombosis, etc.).16,17
- In contrast with ARMD or diabetic retinopathy where the production stimuli is sustained in time, in ROP there is a single VEGF release pulsation.
- The eye is an immunologically and anatomically privileged area for the application of these therapies.18
- Reports have been published on animal experiments.19
- Reports have been published on isolated cases.20-28
- Clinical trials are in progress for use in prematures.29-31

**Indications for use**

Treatment with anti-VEGF is indicated in the following cases:

- ROP laser treated over 360° with risk of progression and threatening loss of vision, if no fibrous membranes are marked.
- ROP in which laser treatments cannot be performed as first choice due to poor midriasis, opacity of media or other causes.
- ROP requiring vitrectomy due to association.

As anti-VEGF is an off-label treatment, the appearance of new indications could be evaluated in due course, provided there is sufficient clinical experience and positive references.32

**Drug and dosage**

Even though several anti-VEGF agents have been approved (pegaptanib [Macugen®, Pfizer], partial VEGF blocker; ranibizumab [Lucentis®, Novartis], total blocker with monoclonal antibody fraction and bevacizumab [Avastin®, Roche], total blocker with full monoclonal antibody), bevacizumab is the most widely used and experienced drug in prematures. As this is an off-label treatment, special consent must be obtained for its use together with bibliographic support.

The dosage can vary between 0.65 and 0.70 mg in 0.03 ml.

**Methodology**

- It can be applied in the operating room or in the neonatology unit, in the latter case taking extreme care in what concerns sterilization.
- It can be applied with anesthetic sedation or general anesthesia.
- Prior to surgery, betadine eyedrops must be applied in 3 administrations at 10 min intervals, antibiotic eye drops (latest generation quinolone) and 0.5% thimolole eyedrops, as well as periocular and eyelid skin cleaning with betadine solution.
- The injection must be applied at 2–3 mm of the sclerocorneal limbus in the inferior temporal or nasal quadrant toward the location of the optic nerve. After applying the injection, antibiotic eye drops must be administered.
- Antibiotic and mydriatic eyedrops shall be prescribed for the post surgery period.
- 24 hours after the treatment the patient must be examined for early identification of complications, with special attention to the possibility of endophthalmitis.
- The ocular fundus must be examined within 7–10 days from the treatment. If laser photoacoagulation is not available and the visualization conditions improve laser can be applied in the avascular zone.

**Conflict of interests**

No conflict of interests has been declared by the authors.

**REFERENCES**


