Newest guidelines in ROP

Neonatus 2017

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Data Monitoring Committee Novartis Rainbow studies

RA nibizumab compared with laser therapy for the treatment of INfants BO rn prematurely With retinopathy of prematurity
Outline

• Background on ROP
• Pathophysiology
  • 2 phase theory
• Classification
• Screening
  • International guidelines
  • Neonatal period - Follow up
• Treatment guidelines
  • ETROP
  • Anti-VEGF

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Normal vascularisation of retina

- In utero
- Regulation angiogenesis: intra-uterine + maternal factors
- Starts at week 16
- Completed: nasal border week 36, temporal border week 40
- Balanced concentrations of growth factors obligatory for normal vessel development: Insuline-like Growth Factor 1 (IGF) and Vascular Endothelial Growth Factor (VEGF)

http://iovs.arvojournals.org/article.aspx articleid=2185859

Developing retina
Normal retina
Partially developed retina
Premature birth

Disconnection placenta
• Relative hyperoxia
• Extra uterine environment (roomair)
• AV or extra $O_2$
• Vascular endothelial growth factor (VEGF)
• Insulin-like growth factor (IGF) 1
• Angiogenesis

Vaso-obliterative phase
ROP phase II

- Relative hypoxia
  - Metabolic activity retina > capacity retinal vessels
- > 32 weeks GA
- VEGF ↑
- Angiogenesis ↑↑
- Neovascularisations on verge vascular/avascular retina
- Risk for retinal detachment

Vaso-proliferative phase
Retinopathy of prematurity / ROP

The younger the infant

The larger the avascular area

The more ischaemia

The higher the VEGF production

The higher the risk for (severe) ROP
ICROP (2005)

- Outgrowth of vessels (Zone I - III)
- Stage 1 - 5 and Aggressive Posterior (AP) - ROP
- Pre-plus en Plus disease
Zone (area of retinal vascularization)

Zone I
• Posterior pole

Zone II
• Posterior Zone II
• Full vascularization nasal part of retina

Zone III
• Residual temporal crescent

The lower the Zone, the larger the avascular area, the higher the chance of ROP
Avascular retina

GA 26 weeks
* Posterior zone II
** Border zone I – zone II

Distance optic disc – center of macula:
Revised-ICROP stages

ROP 1

ROP 2

ROP 3

ROP 4

ROP 5

AP ROP

Arch Ophthalmol 2005

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Plus disease (+)

- Increased arterial tortuosity and venous dilatation in Zone I
- Caused by retinal hypoxia resulting in release of vascular growth factors (VEGF)
- Major criterion for treatment
Treatment criteria

Treatment with laser in expert center

<table>
<thead>
<tr>
<th>Type 1</th>
<th>Zone</th>
<th>Plus</th>
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</thead>
<tbody>
<tr>
<td>ROP 1 or 2 or 3</td>
<td>I</td>
<td>+</td>
</tr>
<tr>
<td>ROP 3</td>
<td>I</td>
<td>-</td>
</tr>
<tr>
<td>ROP 1 (or 2)</td>
<td>II</td>
<td>+</td>
</tr>
</tbody>
</table>

Careful observation

<table>
<thead>
<tr>
<th>Type 2</th>
<th>Zone</th>
<th>Plus</th>
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<tbody>
<tr>
<td>ROP 3</td>
<td>I</td>
<td>-</td>
</tr>
<tr>
<td>ROP 1 or 2</td>
<td>II</td>
<td>+</td>
</tr>
</tbody>
</table>
Why do we screen?

• Potentially sight threatening disease
• 20-50% develop any form of ROP
• Most resolve spontaneously
• Small proportion (5-8%) progresses to severe ROP with subsequent blindness

Visual disability is largely preventable when detected and treated in time
Who do we screen?

- Different screening criteria are used

- Burden of screening for patient (discomfort), doctor (time consuming), health care insurance and governmental costs

- Large inventories always find an exception with high GA / BW

- Worldwide attempts to find uniform guidelines
  - Easy: GA – BW
  - Cost effective (high vs low limits)
    - Expert opinion / GCP
    - More complex: risk factor guided
IPOSC worldwide survey of ROP

Figure 1  Countries with and without screening for ROP and those with ROP screening guidelines. ROP, retinopathy of prematurity.

Mora JS. A worldwide survey of ROP. BJO online first aug 30, 2017
## Published screening criteria

<table>
<thead>
<tr>
<th>Country</th>
<th>Criterion GA (weeks)</th>
<th>Criterion BW (grams)</th>
<th>Extra criteria</th>
<th>Revision</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>≤ 30</td>
<td>≤ 1500</td>
<td>GA &gt; 30 or BW 1500-2000 with unstable clinical course</td>
<td>2013</td>
</tr>
<tr>
<td>Canada</td>
<td>≤ 30</td>
<td>≤ 1250</td>
<td>GA&gt;30 or BW&gt;1250 with unstable clinical course</td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>&lt; 30</td>
<td>&lt; 1250</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Netherlands</td>
<td>&lt;30</td>
<td>&lt;1250</td>
<td>30-32 and 1250-1500 with ≥1 risk factor: AV, sepsis, NEC, cardiotonica, postnatal steroids*</td>
<td>2013</td>
</tr>
<tr>
<td>Sweden</td>
<td>&lt; 31</td>
<td></td>
<td>high risk</td>
<td>2012</td>
</tr>
<tr>
<td>UK</td>
<td>&lt;31</td>
<td>&lt;1251</td>
<td>GCP: &lt;32 and &lt; 1501</td>
<td>2008</td>
</tr>
<tr>
<td>Germany</td>
<td>&lt; 32</td>
<td>&lt;1500</td>
<td>32-36 if &gt;3 days O2</td>
<td>2008</td>
</tr>
<tr>
<td>Spain</td>
<td>&lt;32</td>
<td>&lt;1500</td>
<td></td>
<td>2012</td>
</tr>
<tr>
<td>Denmark</td>
<td>&lt;32</td>
<td>&lt;1750</td>
<td></td>
<td>2011</td>
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<tr>
<td>Poland</td>
<td>&lt;33</td>
<td>&lt;1800</td>
<td>high risk</td>
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</tbody>
</table>

*Reduction screening: 31.9% less infants, 23.7% less fundus examinations*
ROP-screening algorithms

- ROP-score
  - BW
  - GA
  - Transfusions
  - AV yes/no
  - weight at 6 wks PNA

- Table:
  | BW (birth weight) in grams | 1000 | Use the birth weight in grams
  | GA (gestational age) in weeks | 28   | Use the gestational age in weeks
  | BLOOD TRANSFUSION (up to 8th week of life) | 1 | Use 0 for none or 1 for yes if the baby underwent any blood transfusion
  | OXYGEN IN MECHANICAL VENTILATION (up to 8th week of life) | 1 | Use 0 for none or 1 for yes if the baby underwent oxygen-therapy
  | WEIGHT AT COMPLETED 6 WEEKS OF LIFE | 1400 | Use the weight in grams measured at completed the 6th week of life

- ROPScore
  - Proportional Weight Gain: 0.40
  - ROPScore: 16.9

- Higher the ROPScore = Higher the risk for developing ROP
- Cutoff point for any stage ROP = 11 and for severe ROP = 14.5
- NPV (Negative predictive values) = 93% of not developing any stage of ROP and 99% of not developing severe ROP

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WINROP: weekly weight gain

Weight-IGF-Neonatal ROP Algorithm

• Web based

• GA, BW and weekly postnatal weight

• Estimation of the differences between expected safe weekly weight gain and actual weight gain

• Alarm

National study (PlosOne Sep 2013):

• Identify extremely premature infants with type 1 ROP

• Sensitivity 95.7%

Effective screening

• Screen as less as possible but
  • identify infants with ROP in time to be able to adjust ROP-related parameters (cooperation ophthalmologist – neonatology dpt)
  • do not miss the window of opportunity for treatment

• Universal screening guideline difficult to establish
  • Socioeconomic factors
  • Local level of neonatal care
1\textsuperscript{st} screening PMA - PNA

Something we do agree on:

1\textsuperscript{st} screening: 4-5 weeks PNA but not before 31 weeks PMA

<table>
<thead>
<tr>
<th></th>
<th>PMA</th>
<th>PNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{st} screening</td>
<td>31 (27.4-38.1)</td>
<td>6 (4-13.6)</td>
</tr>
<tr>
<td>1\textsuperscript{st} detection ROP</td>
<td>34 2/7 (29-44)</td>
<td>6.8 (2-18)</td>
</tr>
<tr>
<td>Detection severe ROP</td>
<td>36 6/7 (31.4-42.1)</td>
<td>10.3 (6.9-14.7)</td>
</tr>
</tbody>
</table>

Follow up screening

• Depends on stage, plus, zone and general condition of the infant
Pitfalls in screening

No screening / unintended loss

• Transfer / discharge: up to 30% loss
• Ophthalmologist not notified

More drop outs

• Transferral before 1st screening examination
• More transferrals
• Inadequate information in transfer letter
• Instructions for follow up not clear (define week or date !)
• No appointment for follow up
• No show or change of appointment
• Parents not informed about purpose or necessity of screening
NEDROP app (iOS and Android): screening and treatment guidelines

Info folder parents
National guideline

www.nedrop.nl
E-mail: nedrop@lumc.nl
NEDROP phone number

Siilo app for telemedicine

(ROP-check: cloud based - AAP criteria)
Follow up ex-prematures

- Refractive errors (26-31%)
- Strabismus (18-33%)
- Amblyopia (10-22%)
- Cerebral visual impairment (30-50%)
- Structural retinal changes
- Optic atrophy
- Ischaemic disease

No universal screening program.
Most screen < 32 weeks +/- ROP at ± 18 months and before school age.
Bevacizumab – late recurrences

BEATROP study: Treatment type 1 ROP in zone 1

> 1 year after treatment
  • Larger vessels progress but..
  • No capillary meshwork
  • Peripheral ischaemia

Screening advise: monthly until the age of 1 ½ years of age

Fluoresceine angiogram?
Closing remarks

• ROP is a significant threat to vision

• Timely detection and appropriate timing of treatment is essential for successful outcome

• Adherence to screening programs is crucial

• Additional measures
  • Communication ophthalmologist – neonatologist
  • Realise that changes in care may have far-reaching consequences
  • Monitor outcomes
  • Involve the parents
Q U E S T I O N S?

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