TREATMENT OUTCOMES OF COMBINED LASER WITH INTRAVITREAL BEVACIZUMAB VERSUS LASER TREATMENT ALONE IN CASES OF STAGE 3+ RETINOPATHY OF PREMATURITY (ROP)

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RETINOPATHY OF PREMATURITY (ROP)

- Vasoproliferative disorder of the retina which occur in premature babies.
HISTORICAL BACKGROUND

1941 Terry: first described the disease he named AS RLF
1950 Heath: pathology of disease and its relation of oxygen
1977 Kingham: classification by indirect ophthalmoscopy and ROP replaced RLF.
1982 international classification of ROP

TREATMENT OF RETINOPATHY OF PREMATURITY

• The current standard treatment of ROP is the peripheral retinal ablation using cryo or more commonly laser photocoagulation.
EVOLUTION OF ROP TREATMENT

1986  Cryo-ROP study
1991  Shift to laser treatment
2001  ET-ROP study
2007  Anti-VEGF Therapy For ROP
2011  BEAT-ROP study

After 15 years follow-up, a statistically significant difference in unfavorable outcomes was found for treated compared with untreated eyes (30% vs. 51.9%). Treatment is indicated for threshold retinopathy.

The Early Treatment of ROP (ETROP) trial investigated whether earlier treatment with laser or cryotherapy of high-risk eyes would result in improved visual outcomes. ETROP defined high-risk prethreshold disease or type 1 ROP As:
- Any stage of ROP in zone 1 with plus
- Stage 3 ROP in zone 1 with no plus
- Stage 2, 3 in zone 2 with plus

Early treatment reduced unfavorable visual outcomes from 19.8% to 14.3% and decreased unfavorable anatomical outcomes from 15.6% to 9.0%.
The use of anti-VEGF therapy in cases of ROP could be justified by many facts:

ROP is a VEGF-mediated disease

The relative poor outcomes of standard laser treatment with more than 44% of cases had a VA of 20/200 or less.

The encouraging preliminary results of many case studies and BEAT-ROP study where anti-VEGF was used in ROP cases.

In the last five years, multiple studies, mostly case reports and case series, have demonstrated the value of the off-label use of intravitreal Avastin for ROP, either as monotherapy, in combination with laser or as rescue therapy.
ANTI-VEGF THERAPY IN ROP

BEAT-ROP Study
(Bevacizumab to Eliminate Anti-VEGF Threat in cases of ROP)

BEAT-ROP was a prospective, randomized, controlled, multicenter trial that compared intravitreal Avastin monotherapy (0.625 mg) vs conventional laser therapy for infants with stage 3 Plus ROP in zone 1 or posterior zone 2.

The study involved 150 premature babies (300 eyes) half of them received avastin as monotherapy and the other half received laser.

Results

Avastin was found to be significantly superior to laser in zone 1 stage 3+ (P = .003), but not in zone 2 (P = .27).

In addition, peripheral retinal vascularization continued as normal in the Avastin group but not the laser group.

ANTI-VEGF THERAPY IN ROP

Although the use of anti-VEGF therapy is well justified however there are still many points of concerns and controversies:

- The big concern is about the local and systemic safety of using such medication in that young age group of patients.
- The controversy exist about how to use anti-VEGF whether as monotherapy or in combination with standard laser

**Anti-VEGF monotherapy**

Monotherapy will deal with already secreted VEGF with the assumption that normal retinal vascularization will be completed later on, with potential advantage of persevering peripheral retina.

**Anti-VEGF + laser**

With combination therapy, in addition with dealing of already secreted VEGF, laser therapy will take care of the source of any new VEGF from the avascular retina by ablating it.
AIM OF THE WORK

To report the efficacy and safety of combined laser with intravitreal bevacizumab versus laser treatment alone in cases of stage 3+ retinopathy of prematurity (ROP).

PATIENTS & METHODS
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- A retrospective interventional case series of 13 premature babies (26 eyes).
- All babies were diagnosed to have stage 3 plus ROP in zone I or posterior zone II.
- All babies were selected from the NICU of Saad Specialist Hospital.
- Babies were divided into 2 groups:
  - **Group A**: 6 babies (12 eyes) received combined laser with IVB.
  - **Group B**: 7 babies (14 eyes) received laser treatment alone.
- Laser retinal treatment was done using indirect laser ophthalmoscope (IRIDEX MEDICAL) according to the guidelines of Cryo-ROP & ETROP studies.
- Intravitreal injection of bevacizumab (IVB) was done in the OR under complete aseptic technique and after finishing of laser treatment. Bevacizumab was injected in a dose of 0.625 mg in 0.025 ml (half of the adult dose) 2mm posterior to the limbus.

PATIENTS & METHODS

- All babies were examined at 1, 2, 4 weeks after treatment and then every 4 weeks for at least 6 months.
- RetCam photography (Clarity Medical Systems, Pleasanton, CA) was done to document pre-treatment and post-treatment fundus pictures.
- Patients’ demographic and clinical data (including gender, birth age, weight, time of surgery) were retrieved and analyzed.
- Treatment outcomes:
  - primary outcomes: regression of the active ROP
  - secondary outcomes: recurrence of the disease, development of complications such as vitreous hemorrhage and/or fibrotic complications including tractional detachment.
RESULTS

Gender
- Female: 38%
- Male: 62%

Birth age
- 22-27 W: 8%
- 28-31 W: 31%
- > 32 W: 61%
RESULTS

Birth weight

- < 1000 GM: 15%
- 1000-1500 GM: 39%
- > 1500 GM: 46%

RESULTS

Regression of the active ROP
(disappearance of extra retinal NVES and plus disease)

Group A: 100%
Group B: 78.50%
RESULTS
Regression of the active ROP
Group A
Regression of the active ROP

**RESULTS**

Group A

[Images of eye scans for Group A]

Regression of the active ROP

**RESULTS**

Group B

[Images of eye scans for Group B]
RESULTS Regression of the active ROP
Group B

RESULTS
Treatment complications

Cataract: Two eyes (16.6%) in group A and no eyes (0%) in group B developed cataract.

Hemorrhage: Two eyes (16.6%) in group A and 4 eyes (28.6%) in group B developed vitreous and/or preretinal hemorrhage.

Fibrotic complications: Five eyes (41.6%) of cases in group A developed fibrous vitreoretinal bands along the major vascular arcade 2-4 months after treatment, which progressed to tractional detachment in 2 eyes (16.6%).
RESULTS
POST- TREATMENT HEMORRHAGE

RESULTS
POST-TREATMENT FIBROTIC COMPLICATIONS
SUMMARY & CONCLUSIONS

- Combined laser with intravitreal bevacizumab injection is more effective than laser treatment alone in inducing a rapid and complete regression of the active disease in cases of stage 3+ ROP.

- The rate of complications such as complicated cataract, and fibrotic complications including tractional retinal detachment are relatively high in cases received combination therapy.

- The use of combination therapy have the advantage of tackling the already secreted VEGF by the intravitreally injected Avastin and at the same time laser treatment will ablate the peripheral ischemic retina which is the source of VEGF.

SUMMARY & CONCLUSIONS

- The encouraging results of BEAT-ROP study, will likely convince treating physicians to shift from laser photoablation to intraocular Avastin, however we have be very careful about this shift as there are many concerns and criticisms about the study as:

  - The rate of recurrence in laser treated patients in that study was exceptionally high (42%) in zone 1 cases which is not the case of the most published studies that report a success rate between 70-97.5%.

  - In the BEAT-ROP study the total number of death are 7 babies (5 of them are in the Avastin group while only 2 babies in laser group).

  - The very late recurrence of the disease (mean 16.0 ± 4.6 weeks) seen in the Avastin group(compared to almost one week in laser group) raising the concern that frequent and relatively long-term follow-up will be required.

BEAT-ROP study open the green light of using Avastin as monotherapy in ROP cases , however the results are not strong enough to support the use of Avastin as an alternative to the standard laser treatment.
SUMMARY & CONCLUSIONS

• There is no doubt that anti-VEGF therapy will have a major role in the treatment of ROP cases in the next few years, however there are still many questions need to be answered:
  
  When to use?? Early VS Late
  How to use?? Monotherapy VS combination with laser VS rescue therapy
  What is the optimal dose?? The size of neonatal eye is 1/3 of the adult eye.
  What about the local safety?? Ocular complications and ocular toxicity??
  What about systemic safety?? especially long-term impacts on development???

These are very vital questions that need unbiased answers so that our decision-making will be based on science and not just populism.
Thorough investigation, using well-designed scientific protocols, and monitoring of the long-term ocular, systemic, and developmental outcomes, will be needed to reach definite conclusions.

THANK YOU