The ETROP Study

Design

- Findings
- Recent findings

Objective

To determine whether earlier treatment using ablation of avascular retina in high risk prethreshold ROP results in improved grating visual acuity and retinal structural outcomes compared with conventional treatment

High-Risk ROP: RM-ROP 2

- A model based on the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity natural history cohort
- Risk factors analyzed to compute risk of blindness
- Risk ≥ 0.15, randomization offered Risk < 0.15, observed
- http://www.sph.uth.tmc.edu/rmrop/Riskcalc/
- disclaimer.aspx

Design

- Bilateral, high risk prethreshold: one eye treated early, fellow eye managed conventionally
- Asymmetric ROP: high risk eye randomized to treatment or conventional management
- Primary outcome: grating acuity at 9 months (unfavorable ≤1.85 cycles/deg); masked testers
 Secondary outcome: structure of retina at 6 and 9 months (unfavorable = 4B, 5, or fold through macula)

Table 2: Baseline Characteristics of Rand (N=401)	omized Patients
Patients with bilateral high-risk prethreshold. %	79.1
Birth weight, g (mean ± SD)	703 ± 148
Gestational age, wk (mean ± SD)	25.3 ± 1.4
Male, %	54.4
Singleton birthy, %	71.1
Born in the study hospital, %	80.3
Race. %	
Caucasian	63.8
African American	18.0
Hispanic	14.7
Other	3.5

Results

- Grating Acuity Results: Reduction in unfavorable visual acuity outcomes from 19.8% to 14.3% (P< .005)
- Unfavorable structural outcomes reduced from 15.6% to 9.0% (P< .001)

Application of Type 1 and Type 2 Criteria for ROP Management

Treatment Type 1 Eyes:

Plus disease in the ETROP study required two quadrants (usually 6 clock hours) Clinical judgment advised

<u>Observing Type 2 Eyes</u>: Some Type 2 eyes are high risk by RM-ROP2, but if these eyes progress to Type 1 or to threshold, they can be treated

RecentETROP Research

- Outcome after stage 4 and 5 surgery:poor
- Myopia: better with laser? No
- Impoved Snellen acuity at 6 yrs for Type 1 ROP
- Visual fields only slightly affected even for Zone I cases

Retinal Detachment Outcome

- 88 eyes with RD
- Aprox 1/3 had macular attachment
- Most of these were 4A
- A few eyes had favorable visual acuity outcome (5 eyes with 4A) none with stage 5



Astigmatism at 6 years

- 50% had 1.00 D or more
- 25% had 2.00 D or more
- Astigmatism was progressive
- Advise follow up for refractive errors and amblyopia

Grating Acuity

- Improved with early treatment but only in type 1 eyes
- Type 2 eyes a tendency to worse acuity

Visual Fields

- Essentially no or minimal effect of early treatment for type 1 eyes c/w conventionally managed eyes
- For type 2 eyes, visual fields worse with erlier treatment

ROP <500 grams BWT

- Approx 50% develop high-risk prethreshold (63 infants of 401 randomized were <500 gms)
- Outcomes similar to the entire cohort
- Strabismus, refractive error common

Final Acuity (Snellen) at 6 years

- For the entire group, no significant difference in acuity outcome with 20/200 cutoff
- But for the entire group, favorable structural outcome
- Significant benefit for eyes with type 1 disease
 No benefit for eyes with type 2: trend to worse acuity outcomes

Conclusion

Treat type 1 eyes promptly
But even more caution for type 2 eyes

RETING RUID FORMER. RETING 309=7. DID NOT CALL THE. DID NOT CALL THE. ROP. WELL. PED 07H 40F5 Page 1 Page 1 **Disclosures & Acknowledgments Plus Disease Diagnosis** MFC is an unpaid member of the Scientific Advisory Board of Clarity Medical Systems (Pleasanton, CA) · Determines need for treatment - CRYO-ROP, ETROP **ROP Diagnosis: Potential** Grant support: NIH EY19474 and EY13972, RPB · Dilation of venules & tortuosity Areas of Subjectivity of arterioles Collaborators: - Standard photo: minimum amount <u>Ophthalmology</u>: John Flynn, Rony Gelman, Susan Koreen, Tom Lee, David Kim, Steve Williams, Preeti Thyparampil, Paul Chan - Newer "pre-plus" category Biomedical Informatics & Computer Science: Justin Starren, Leanne Currie, Elena Martinez-Perez STOP-ROP & ETROP: >2 Both adequate dilation and tortuosity needed?

- Neonatology: Osode Coki, David Bateman, Karen Scott

LISER 30 MIN PER EYE

Most critical elements of ICROP: Plus disease & Zone I

- Public Health: Evelyn Du, Joshua Graff Zivin





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October 24, 2011

Michael F. Chiang, MD

quadrants. Same 2 quadrants?

CRYO-ROP Group, Arch Oc

Does peripheral retina matter? Other things?

106:471-9

Which are the "key" vessels? Few severe vessels enough?







50% LESS OPH WARTS TO SCREEN LEAST NUMED 26,000 GREAT 3750000 MEDIAN 8000 000 Causation and Prevention -**Financial Disclosures** of ROP Malpractice Claims · Denise Chamblee, M.D. · No financial disclosures - OMIC Committee member - Pediatric Ophthalmologist - Newport News, Virginia · Anne M. Menke, R.N., PhD - OMIC Risk Management









	OMIC's	Top Te	n	1	
Amount	Description	Specialty	State	Year	1
\$3,3~5,000	ROP	Rean .		2007	1
\$2,000,000	Ghoma in 10 mo old haby	Pediatric		2009	1
\$1,200,000	Glucoma in 8 yr old	Pediatric		2001	1
\$1,000,000	Tx of corneal alcer in 2vr old	General		1999	1
\$1,000,000	Misda sareoid/Pred overdose	General		302	1
\$1,000,000	ROP	Pediatric		2009	1
\$1,000,000	ROP	Pediatric		2010	1
\$309,933	Starke post stab surgery	General		:999	1
\$983,771	LASIK ectasu	Retitetive		2006	1
\$r500	Parente of Chalance and a	General	1	345	1





Analysis

· What went wrong?

- · Could it have been prevented?
- · How could it have been prevented?

(C)

Clinical	Systems	Physician	Patient/Parent
Dispute over what to do Which babies to screen When to begin treatment What to do if treatment fails	•Follow-up •Error cannot be attributed solely to individual	*Standard of care (SOC) concerns •Attitude •Records incomplete or altered	 Poor compliance with follow up, medication instructions, refusal of recommended care



Risk Is:	sues in	ROP	Cases	
	CLINICAL	SYSTEM	PHYSICIAN	PARENTS
PRIMARY	2	12	5	0
SECONDARY	1	0	1	6
TERTIARY	1	0	1	0
TOTAL	5	11	7	6

Systems issues- 12 Preventable?

· Examples - Discharge/follow up appointments - Hospital transfers

6

- Referral to retina/treating ophthalmologist
- All Preventable?

Systems issues Primary cause 12/19 infants

- Eye exam ordered but eye MD never contacted
- Infant transferred to feed and grow hospital before initial exam with instructions for 2 week f/u. Admitting RN thought was for 2 weeks after discharge.

100

- · Hospital staff wrote wrong follow-up date in chart.
- Screening ophthalmologist told mother to take baby to retina in 1-2 weeks. Mother scheduled outpatient appointment under new name. Staff did not ask if infant premature or seen in hospital. Rescheduled twice due to hospitalization



"System" issues documents

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- Hospital protocol
- · Office protocol
- ROP Coordinator job description
- · Outpatient screener protocol
- Office scheduling ROP guidelines



Physician issues Primary cause 5/19 infants	大学	
Follow-up recommendations		n med
 – 27 week baby seen at 31 weeks – 6 recommended (2003) 	3 wk f/u	1,000,00
 26 week baby seen at 32 weeks – 6 recommended (2004) 	6 month f/u	3.750,001
- 24 week baby seen at 33 weeks - 4 recommended (2008)	4 week f/u	

Knowledge issues Prevention

- · Examiner error occurs
- · Keep in mind your own falliability
- · Re-examine if confirmation warranted
- Consider "elements" of case in addition to your findings

CME specific to ROP

New Educational Resources

- FOCUS ROP
- Online
- Clinical/practical
- Case examples/photos





- "ROP: Materials for Creating a Hospital Safety Net"
- "ROP: Materials for Creating an Office Safety Net"
- Step-by-step protocols, clinical guidelines, education for parents, ROPC job description

New	Resources	
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 Materials available to all at <u>www.omic.com</u> in the "Risk Management Recommendations" section

Cart

- Questions or suggestions
- amenke@omic.com
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- denisechamblee@cox.net



Normal fetal vascularization Full term PaO_2 is 90 mm hg-What is normal PaO_2 of the fetus? requires hypoxic environment **Retinopathy of Prematurity** Immature Retina Physiclogic VESF Fetal PaO2 Fetal PaO2 =22-24 mm hg Baby PaO2 = 80-90 mm hg 1. 90mm hg 戊 Kenneth W. Wright, MD 2. 80mm hg Ŀ Fetal hypoxia is "good" it stimulates VEGF and normal vessel growth Director, Wright Foundation for Pediatric Ophthalmology and Strahismus 3. 70 mm hg K W. 4. 25 mm hg Clinical Professor of Ophthalmology USC Keck School of Medicine Los Angeles, California Vascular Endothelial Growth Factor









Critical Period From birth until vessels vascularize the retina . .









	ROP Laser Therapy Inborn Birth Weight <1500g
	Cedars-Sinai & VON 1998 - 02 sats 83% - 93%
8 3	
and SP (D)	
	Pediatrics 200





Prevent Severe ROP BW <1,000 grams

Keep O₂ sats 83% - 93% from birth - first 6 to 8 weeks are critical!

Keep oxygen saturations stable – avoid fluxuations

MOST COMMON NEERS OF SKIPPER RETAINS. IZ-6 %. IZ-6 %. IF SPACE > 1 /2 DISAMENEN OF LASER SPOTS. 10/24/11 CONSIDERED SKIPPED AREA.







ONLY 20% OF STACE & ROP HAVE GOOD ANATOMICAL RESPONSE.

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10/24/11







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							20/20
1	0.64	0.65	0.66	0.67	0.68	0.69	Ó
2	0.86	4.8	6.5	9.8	13.00	20/60	20/60
	LV 19	LV 9	Lv 9	Lv	Lv 9	LV 9	
3	cm	cm	cm	9cm	cm	cm	HM
	LV 9	LV 9					
4	cm	cm	LP	LP	LP	LP	LP
Grou							
p 2							
						20/20	20/20
5	0.43	0.64	0.8	1.6	6.5	0	0
6	0.86	1.3	13	65	9.8	20/80	120/80

		Refrac	tion		
	12	24	36	48	60
Group 1	months	months	months	months	months
1	-3.00	-3.00	-3.00	-3.75	-3 50
2	-1.50	-1.75	-1.75	-1.75	-2.00
3	+5.50	+5.00	+5.50	+6.50	+7.00
4	+10.50	+10.50	+10.50	+12.50	+11.00
Group 2					
5	-3.50	-4.00	-4.00	-4.75	-5.00
6	-5.00	-4.75	-6.00	-6.75	-7.00
7	+0.12	+0.12	+0.12	+0.12	-0.25
8	-2.00	-2.50	-2.50	-2.75	-3.00
9	-0.50	-0.50	-0.50	-0.50	-0.50
Group 3					
10	-1.25	-1.50	-1.50	-1.50	-1.50
11	-0.75	-1.25	-2.00	-2.50	-3.00
12	-0.12	0.00	0.00	0.00	-0.25
13	-5.00	-5.00	-5.50	-6.00	-6.75
14	+3.50	+3.50	+3.00	+2.75	+2.50
15	-2.00	-2.75	-2.75	-3.00	-3.00
16	+0.75	0.50	0.00	0.00	-0.25
* Sphetizal equi	valent2.50	-2.50	-2.50	-2.75	-3.00
18	+0.50	0.00	0.00	0.00	-0.50

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50	3	4
75	2	2
90		1
97		



Ocular Adverse Events

- Volume of IB administered was 0.05cc (1.25mg). All 23 eyes which were injected with this volume required paracentesis after elevation of IOP.
- The dose of IB was modified to 0.03cc (0.75mg), which lowered the rate of IOP elevation



C	Ocular .	Adve	rse Ev	ents
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AMERICAN ACADELINY

Systemic Adverse Events

- Twenty two (7.1%) patients had some degree of psychomotor developmental retardation:
- •14 (4.5 %) apnea
- •6 (1.9 %) respiratory distress
 syndrome
- •1 patient (0.5%) -Down's syndrome
- 1 (0.5%) dysmorphic syndrome

Discussion

Capec

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Tapec

 There was no difference in the involution of the abnormal new vessels and growth of normal vasculature using 1.25mg or 0.75mg of bevacizumab; the only difference is the presence of increased IOP after the injection.

Capec Systemic Adverse Events

 No abnormal cardiovascular response was observed in any patient injected under topical anesthesia.

a.







Conclusions

Tapec

- Once the retina is detached, retinal detachment may be more likely to progress.
- Local complications of IB are mostly procedure-related but a few may be drug-related.

Conclusions

• The procedure is generally safe but there are risks involved.

Capec

 To minimize the risk, careful attention to injection technique and appropriate post injection monitoring are essential.

Conclusions

Tapec

• We believe that the systemic abnormalities in children treated with intravitreal bevacizumab for ROP in this series are sequelae of prematurity itself and not related to the medication.