Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Mintz-Hittner HA, Kennedy KA, Chuang AZ. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. N Engl J Med 2011;364:603-15.

Supplemental Appendix

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List of Contents

Table 1: Summary of Changes to Protocol

Protocol Number	Version Date	Suggested By	Changes
1	8/28/07		
2	2/10/09	DSMB	(1) Changed Electro-Retinograms to Visual Evoked Responses.
			(2) Maximum number of IVB injections to be 2 doses/infant.
			(3) Changed IVB needle to 31 gauge, 5/16 inch.
			(4) Added ocular examinations at ages 8 and 10 months for IVB infants (both IVB and CLT infants had ocular examinations at ages 6 months and 1 year).
			(5) Conscious sedation not required for IVB injections.
			(6) Intubations not required for CLT.
			(7) Primary outcome defined as successful treatment, i.e., no recurrence of ROP requiring re-treatment (IVB or CLT) in either eye before 54 weeks postmenstrual age (no eye would be allowed to become blind without all possible interventions including vitrectomy).
			(8) RetCam Reading Center to see photographs (IVB and CLT eyes) taken at 54 weeks: (a) to study masked: posterior retinas of all eyes masked (cropped to include optic nerve and macula but to conceal laser marks) and (b) to review unmasked: all eyes designated as recurrences.
3	6/1/09	DSMB	(1) Primary outcome defined as failed treatment, i.e., recurrence of ROP requiring re-treatment (IVB or CLT) in either eye before 54 weeks postmenstrual age.
			(2) Data analysis specified as whole group (150 infants), then subgroups.
			(3) Ocular outcomes of each infant to be a 3-valued variable: 0 = no recurrence; 1 = one eye recurred; 2 = both eyes recurred.
4	10/20/09	FDA	(1) Removed Visual Evoked Responses--insufficient number of infants tested.

			(2) RetCam photographs were to have been documented at "ages 6 months (54 weeks postmenstrual age) and 12 months (80 weeks)"--however, some variability was to be allowed: 54 weeks (window of 50 to 70 weeks) and 80 weeks (window of 75 to 100 weeks).
5	12/28/10	Update	(1) Last infant (#150) enrolled on 8/3/2010.
			(2) Last infant (#150) reached primary outcome on 11/14/2010.
			(3) Enrollment ceased; follow-up to continue.
			(4) Recent IVB references added to protocol.
			(5) Discrepancies noted in protocol corrected: corrected in all sections: Primary outcome: recurrence of ROP requiring re-treatment (IVB or CLT) in either eye before 54 weeks postmenstrual age.

Supplementary Methods

Intravitreal Injection of Bevacizumab

The infant was attached to a continuous cardio-respiratory monitor and a continuous pulse oximeter with specialized NRP-certified personnel in attendance at all times. At the discretion of the attending neonatologist, but not usually, the infant was premedicated with an oral, intramuscular, or intravenous sedative drug. A drop of tetracaine hydrochloride 0.5% or proparacaine hydrochloride 0.5% ophthalmic solution was placed into the conjunctival sac for local analgesia. A sterile speculum for use in preterm infants was placed between the lids of the right eye. Antisepsis was achieved with a drop of povidone iodine 5% ophthalmic solution placed between the lids into the conjunctival sac. Excessive povidone iodine was removed with a sterile cotton tip

applicator from the temporal lid margin. The infant's eye was stabilized with a sterile toothed forceps, cotton tip applicator, or scleral depressor. Bevacizumab (0.625 mg in 0.025 mL) in a single-use syringe with a 5/16th inch, 31 gauge needle attached was injected into the vitreous in a sterile manner behind the lens (about 2.5 mm posterior to the limbus aiming toward the posterior vitreous). Povidone iodine antisepsis was applied to the eye again. The sterile speculum was removed from between the lids. The same procedure was followed for the left eye. An ophthalmic antibiotic drop was prescribed for both eyes to be used every six hours for seven days.

Conventional Laser Therapy (CLT):

Except for seven CLT infants (at two sites) who received conscious sedation, the infant was placed under general anesthesia (endotrachial intubation) attached to a continuous cardio-respiratory monitor and a continuous pulse oximeter with anesthesia-certified personnel in attendance at all times. A sterile speculum for use in preterm infants was placed between the lids of the right eye. The infant's eye was stabilized with a sterile toothed forceps, cotton tip applicator, or scleral depressor. The diode laser indirect ophthalmoscope with a 28D lens (resulting in a 560 micrometer lesion) was utilized to apply multiple applications at approximately 810 nanometers (red part of the optical spectrum) to the retina. The pulse duration, pulse interval, and the power varied at different sites, but all treatment was confluent. If any areas were skipped, the surgeon was allowed to fill in these skipped areas within one week of the initial treatment. Under direct visualization with the indirect ophthalmoscope, a variable number of laser pulses were applied to destroy the retinal layers of the avascular retina (source of angiogenic factors). Following these applications, the lid speculum was removed, and an antibiotic

and dilating drop of choice were instilled between the lids of the right eye. The same procedure was followed for the left eye. Ophthalmic antibiotic, dilating, and anti-inflammatory drops were prescribed for both eyes to be used every six hours for a variable number of weeks.

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