Neurodevelopmental Outcomes of Preterm Infants With Retinopathy of Prematurity by Treatment

Because most studies regarding neurodevelopment in retinopathy of prematurity (ROP) are small and single-center studies, we commend the authors for this retrospective multicenter analysis of prospectively collected data comparing anti–vascular endothelial growth factor (VEGF) with laser treatment. Although they found no difference in their primary outcome of severe neurodevelopmental impairment (NDI) or death, when examined separately, they found a higher rate of death but not of NDI. Unfortunately, as a nonrandomized study, it suffers from imbalance in baseline characteristics, which limits robustness.

First, as the authors acknowledge, infants who received bevacizumab were smaller and sicker. At baseline, infants treated with bevacizumab had lower median birth weight ($P = .02$), gestational age ($P = .05$), and ventricular enlargement ($P = .06$). Other differences that reveal that infants in the anti-VEGF group were sicker include longer median time on ventilation ($P = .04$), on supplemental oxygen ($P = .01$), and in the hospital ($P = .06$). None of these factors were considered for statistical adjustment. Instead, the multivariate model included severe intraventricular hemorrhage and white-matter injury (WMI), but the groups were not different with respect to these characteristics at baseline ($P = .83$ and 0.40, respectively).

There was also a significant difference within the subanalysis of patients who died: 50% of those treated with anti-VEGF had a 5-minute Apgar score <5, whereas only 15% of those treated with laser surgery had such scores. Although not reported, this is indeed significant ($P = .038$; $\chi^2$ test).

Second, zone of ROP at treatment was not evaluated as a potential confounder. Because smaller infants are more likely to have zone I ROP, and many physicians prefer anti-VEGF for posterior ROP, there may have been treatment bias. Zone of ROP is a known predictor of neurodevelopment, and an analysis stratified by zone at treatment should be performed.

Third, although the sensitivity analysis to compare infants at centers that treated exclusively with laser surgery or bevacizumab revealed a significant difference in death (but not in NDI), baseline characteristics at these centers were not presented. Again, selection bias related to characteristics of specific NICU populations may have influenced outcomes.

Finally, these findings contrast with those of other published studies with less inherent bias. A prospective case-control study revealed no difference in Bayley Scales of Infant Development scores, which were used to compare 38 patients with severe ROP receiving bevacizumab with 31 untreated controls with similar baseline characteristics. We also recently published a before-and-after study in which we compared infants treated with laser surgery (before 2011) with those treated with bevacizumab (after 2011), with no differences in baseline characteristics between the 2 groups ($n = 46$ and 40, respectively). We found no difference in the rates of death, cerebral palsy, sensorineural hearing loss, bilateral visual impairment, or Bayley Scales of Infant Development scores. Finally, the Bevacizumab Eliminates the Angiogenic Threat for Retinopathy of Prematurity (BEAT-ROP) group also reported no differences when comparing a small number of patients from a single-center study ($n = 16$).

We agree on the need for rigorous appraisal of ROP therapy. In the interim, treatments proven to prevent blindness should not be withheld without strong evidence. As 1 of the defining criteria for severe NDI, blindness clearly influences neurodevelopment. Ultimately, because this study does not contain groups with similar baseline systemic and ROP characteristics or properly account for baseline imbalances, it should not guide treatment.

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