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ROP treatment

The further refinement of ROP treatment. Commentary on the Early Treatment of Retinopathy of Prematurity study: structural findings at 2 years of age

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Reaching the goal of early ROP treatment by recent advances in ROP management

The treatment of retinopathy of prematurity (ROP) continues to evolve, and it is good to see that earlier treatment at high-risk prethreshold ROP, compared with conventional management with treatment at threshold, improves the structural outcome, and that this is maintained at 2 years after intervention.¹ It is also encouraging to note that there was no increase in adverse ocular outcomes by this earlier treatment. Owing to reclassification of some eyes which underwent vitreoretinal surgery, there was an increase in unfavourable structural outcome between 6 and 9 months, but thereafter they were similar in indicating an encouraging degree of ocular stability.

So far so good, but the revised indications for the treatment of ROP emanating

from the Early Treatment of ROP (ETROP) randomised trial² require a major change in clinical practice that must be incorporated into clinical guidelines. Unsurprisingly, these recommendations have generated considerable published^{3–7} and unpublished debate. This broadly centres on issues relating to the breaking down of the main ETROP cohort into subgroups based on zone, stage and the presence of plus disease. Concerns have been expressed that following the ETROP recommendations will result in unnecessary treatment of eyes that fall into one or more of the categories that might resolve spontaneously, notably zone II, stage 2+. This is not a trivial issue, as the outcome of these discussions will

necessarily feed into clinical guidelines for ROP screening and treatment.

To get to the heart of the matter, we need to consider the concept of “threshold” ROP that was fundamental to the design of the CRYO-ROP study⁸ and is now firmly embedded in our clinical thinking. Threshold denotes the ROP stage at which the risk of blindness if untreated is predicted to approach 50%, and was derived from clinical information of the 1970s and 80s. Although the database that generated threshold was the best available at the time, it did not approach the robustness of the data that subsequently emerged from the CRYO-ROP study. Consequently, a risk analysis programme—RM-ROP2 model—has been developed⁹ from a subset of the CRYO-ROP study natural history data from 613 infants who developed prethreshold ROP or worse, but were not treated. This model, using both infant demographic and ROP characteristics, was used to calculate the risk of an eye with prethreshold progressing to an unfavourable outcome at 3 months post-term (defined in the CRYO-ROP study⁸). The model subdivided prethreshold eyes into two risk groups, according to a cut-off of 0.15: those with a risk of achieving an unfavourable outcome of <0.15 (ie, risk of unfavourable outcome <15%) and those with a risk between 0.15 and 1.0 (risk between 15% and 100%), which were designated low-risk and high-risk prethreshold eyes, respectively. In the CRYO-ROP study, 63% of high-risk eyes

developed threshold, with 36% of these reaching an unfavourable outcome, whereas for low-risk eyes, 14% reached threshold and 5% had an unfavourable outcome.⁹ Proof of the effectiveness of the RM-ROP2 model comes from these ETROP trial, in which only 1.3% of the low-risk prethreshold eyes (4/302) developed an unfavourable outcome.²

Having touched on the background, now to the specifics of the current debate—what do the ETROP subgroups tell us? Looking at the results for zone II, stage 2+ (table 3²) and the 2-year outcome results (table 2¹), it seems that there is no benefit from early treatment at prethreshold, as the outcome is similar for both. So, it could be suggested that this category should be removed from type 1 ROP² which requires early intervention at prethreshold. Also, the outcome for zone II, stage 2+ is worse than for stage 3+, which at first glance is not intuitive. How can these seemingly paradoxical results be explored? The RM-ROP2 model contains 10 components, and the determination of high risk and low risk is influenced by both infant demographic factors and ROP characteristics (zone, stage, presence of plus and ROP kinetics), so ROP characteristics alone do not give the whole picture. Furthermore, the model is based on the onset of prethreshold ROP—that is, “the opening of a window of time, during which earlier treatment can be offered”,⁷ and this is not necessarily the maximum severity achieved or end point. The concept that ROP may be rapidly advancing or indeed stationary at the onset of prethreshold is critical to understanding the rationale for treatment at this stage. Considering the kinetics of acute-phase ROP, it is not surprising to note therefore that zone II, stage 3+ fared better than stage 2+ in that zone, as far more of stage 2+ eyes were in transit to increasing severity and thus had a greater propensity for poor outcome. It is also obvious from the approximately 20% unfavourable outcome that stage 2+ in zone II is not benign (table 2¹).

The ETROP trial compared early treatment at prethreshold with conventional treatment at threshold, with functional acuity at 9 months corrected age as the primary outcome and structure, also at 9 months, as a secondary outcome. However, Hardy *et al*¹⁰ make the point that, although the ETROP trial presented the data by subgroup, detailed analysis of these specific within-group data has its dangers. Of course this is precisely what many of us have been doing—and ignoring the possible pitfalls! The primary aim of the ETROP trial was to study the effect of early treatment on high-risk prethreshold ROP, in which the high-risk group was considered as a single entity. Had the intention of ETROP been to study the effect of early

treatment on each of the six ROP categories listed in table 2,¹ the number needed would have had to have been greatly increased. However, Hardy *et al*¹⁰ point out that presenting the data from the subcategories does allow one to look for consistency and also for clues for future studies.

ETROP clearly shows that the major driver for treatment is now plus disease—that is, changes in the retinal vessels that indicate particularly active ROP, the major features of which are arteriolar tortuosity and venous congestion at the posterior pole. But, this creates a major dilemma in ROP screening, for the diagnosis of plus disease is based on a single image published in the International Classification of ROP over 20 years ago.¹¹ Previously, this was not perceived as a serious issue because the criterion for intervention was threshold ROP, which was based on the appearance of the retina as a whole, of which plus was but one of a number of components, rather than being the most distinct feature. The idea that, within the broad and complex spectrum of ROP, plus disease is a discrete dichotomous entity is naïve in the extreme. It is also highly likely, that plus disease, as currently defined, is located towards the severe end of the ROP severity spectrum, which presents the worrying possibility that eyes requiring treatment will not be identified early enough. There is a pressing need therefore to improve our understanding of the spectrum of vascular changes that are associated with ROP in its various stages where plus, as we currently know it, fits into this range and can then be defined. Work is afoot to quantify these vascular morphological changes both clinically and using semiautomated methods,^{12–16} but there is some way to go before these are in routine clinical use.

Important challenges in the management of ROP remain, for which there are no ready solutions, because individual ROP subcategories are relatively rare, and the numbers required to be recruited for a clinical research study to investigate each for its propensity for progression would be large; furthermore, it is simply not feasible to investigate every single component of an uncommon condition such as ROP. Thus, although there is need for further research to clarify the role of treatment in certain of the high-risk subgroups, in the meantime, a pragmatic approach based on ETROP recommendations is called for, and it is safer to consider plus disease in the context of the overall ROP picture when considering whether treatment is required. ROP is one of the few causes of childhood vision impairment in which severe visual disability could be largely preventable in the foreseeable future. Recent advances in

ROP management take us considerably closer to this goal.

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