Low blood pressure in extremely preterm infants: does treatment affect outcome?

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Do extremely immature preterm infants with blood pressure which is believed to be low have reduced systemic perfusion, reduced cerebral oxygen delivery, increased cerebral injury, an increase in acute complications of prematurity and an increase in long-term disability? If so, below what value of blood pressure do these adverse outcomes increase?

These unanswered questions are of vital importance; extremely preterm infants have high rates of developmental delay and disability, blood pressures are often numerically very low and many preterm infants receive treatments which are potentially toxic with the goal of increasing their blood pressure. Unfortunately, it is not at all clear whether the common treatments for low blood pressure improve systemic flow or cerebral perfusion, or among the available options, which treatments are effective? The reason for this poverty of information is the lack of adequate trials. There are no controlled studies of

Editorial on the paper by Wells Logan et al (see page F321)

hypotension therapy in the preterm newborn which include an untreated group, so changes in systemic perfusion or indirect measures of cerebral blood flow cannot necessarily be ascribed to the intervention. In addition, the small number of comparative trials that have been performed have all been vastly underpowered, and have concentrated on short-term physiological end points, usually blood pressure. One study which compared the effects of dopamine and epinephrine on indices of cerebral perfusion showed an increase of about 20% in cerebral blood volume after 2 h of treatment, in association with about a 50% increase in mean blood pressure, with no difference between the groups; there was no untreated hypotensive control group. Whether the increase in cerebral blood volume (probably due to an increase in cerebral blood flow) was due to the medications cannot be determined from a trial such as this, in a group of babies who in any case have a spontaneous increase in cerebral blood flow and blood pressures during the first few days of life.

Despite the lack of evidence, there is no lack of recommendations to treat at specific blood pressures, often with fluid boluses followed by potent vasoactive amines, usually dopamine. In reality, it is even unclear whether fluid boluses actually increase blood pressure; small physiological studies without control groups suggest that the effects, if any, are transient. In addition, the extra sodium load of a fluid bolus is significant, and the total administered with two boluses of 10 ml/kg of normal saline is within the range of sodium administration that has been shown to worsen survival and outcomes. Dopamine infusion, on the other hand, appears to be effective for increasing blood pressure (often largely by vasoconstriction), but there is a lack of controlled data about effects on systemic oxygen delivery or cerebral perfusion.
and very limited data on long-term outcomes.

Despite this lack of good information, treatment of low blood pressure among very immature babies is widespread. The extremely low gestational age newborn (ELGAN) study is a large multicentre prospective cohort study of ELGANs. This important collaborative effort showed that 82% of infants less than 28 weeks' gestation received some therapy to increase their blood pressure, and 54% received inotrope/vasopressors. This study also showed that the most important determinant of treatment, with either fluid boluses or inotrope/vasopressors, was the identity of the unit in which the infant was treated, and not the degree of illness or the degree of hypotension. Not for the first time in neonatology, variations in practice, which might have dramatic effects on survival or outcomes, are shown to vary according to fashion and taste, rather than according to reliable scientific data.

The new ELGAN publication by Logan et al explores the associations between hypotension treatment and developmental outcomes at 2 years of corrected age. The authors found no clear association between hypotension, defined as the lowest recorded blood pressure in the lowest quartile for gestational age, and evaluations of development.

This article adds substantially to our understanding of the importance of hypotension and its treatment in the extremely preterm infant. Previous studies that investigated the association between lower blood pressures and poor long-term outcomes were often subject to systematic biases and had insufficient sample sizes to allow multivariate modelling. Logan et al used a statistically appropriate definition of hypotension, that is, a blood pressure which is in the lowest quartile of recorded blood pressures for infants of a similar gestational and postnatal age. When the authors analysed their data by comparing infants who received inotropes with those who did not, there was a non-significant increase in adverse outcomes associated with the use of vasopressors (OR 1.4, 95% CI 0.98 to 2.0, for a Bayley Mental Development Index <70). This study adjusted the analysis for the hospital centre where the infant was treated. The advantage of this approach is that infants treated in different hospitals may be more alike in terms of long-term outcomes, than infants from other centres, who may come from families with different social and economic backgrounds. The disadvantage of such an approach is that it may dilute the effects of the overall treatment philosophy which also clearly differs from one centre to another. Recall that in the previous ELGAN publication the proportion of infants receiving vasopressors in different neonatal intensive care units ranged from 6% to 64%. Thus, a centre which treats 64% of their ELGANs with vasopressors may have overall different outcomes than a centre which treats 6%; if this is the case, the difference may be because of the treatment philosophy, or because of other factors which differ between the centres.

The finding of no correlation between lowest recorded blood pressure and outcome does have limitations. Many of the infants had intermittent measurement of blood pressure, so periods of hypotension may have been missed. It is also possible that the duration of low blood pressure is important; this was not analysed in this study. As a result, these observational data should not lead to major changes in clinical practice; they do, however, point out the limitations in our current knowledge and give even more support to the performance of prospective controlled clinical trials for the management of hypotension in the preterm. Such trials may be very difficult to perform, as neonatologists are often convinced that a higher blood pressure must be better for the baby and are so used to treating low blood pressure numbers that equipoise may be difficult to find. However, at least three such trials have been designed and will shortly commence enrolment. The trials differ in detail but all of them compare an aggressive approach to the treatment of hypotension with a more restricted approach (‘permissive hypotension’). The precise interventions used in each trial are different, but together with a planned prospective meta-analysis, the trials will yield important clinical information.

While awaiting the results of these trials, it is important for clinical practice to take into account the results of this new publication and of other studies and reviews. The following points are key:

1. Many infants with low blood pressure have normal systemic flow.
2. There is no clear evidence that infants with numerically low blood pressures but without evidence of shock have worsened outcomes.
3. There is no evidence that treating numerically low blood pressures improves outcomes.
4. There is no evidence base to determine the choice of one intervention over another.

The next few years should enable us to develop rational approaches to this common problem, or perhaps to find that it is often not even a problem.

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