

Recommendations in the face of uncertainty: should extremely preterm infants receive chest compressions and/or adrenaline in the delivery room?

Dominic Wilkinson^{1,2,3}, Neil Marlow⁴, Dean Hayden⁵, Helen Mactier^{6,7}

Affiliations:1. Oxford Uehiro Centre for Practical Ethics, Faculty of Philosophy, University of Oxford, UK. 2. John Radcliffe Hospital, Oxford, UK. 3. Murdoch Children's Research Institute, Melbourne. 4. UCL Elizabeth Garrett Anderson Institute for Women's Health, University College, London. 5. Austin Health, Melbourne. 6. Princess Royal Maternity Hospital, Glasgow. 7. University of Glasgow

Correspondence: Prof Dominic Wilkinson, Oxford Uehiro Centre for Practical Ethics, Suite 8, Littlegate House, St Ebbes St, Oxford, OX1 1PT, UK. Tel: +44 1865 286888, Fax: +44 1865 286886 Email: dominic.wilkinson@philosophy.ox.ac.uk

Acknowledgements: The authors would like to acknowledge the wider BAPM perinatal framework working group who contributed to discussions around recommendations in the framework including the issues discussed in this paper.

The 2009 British Association of Perinatal Medicine (BAPM) framework recommended against advanced resuscitation measures (Delivery Room Cardio-pulmonary Resuscitation, DR-CPR) in extremely preterm infants, noting that: “There is no evidence to support the use of epinephrine by any route, or chest compressions, during resuscitation at gestational age < 26 weeks.”[1] However, in the updated 2019 framework, published in this issue, the working group reached the opposite conclusion: “In the absence of sufficient evidence to justify a different approach in extremely preterm babies, if advanced resuscitation is considered appropriate, the Working Group recommends applying newborn resuscitation algorithms as used in more mature babies.” (see page...).

This was one of the more controversial elements of the new framework, generating a number of comments during the consultation phase. In this commentary, we will outline the arguments behind the changed recommendation.

Concern

There are three essential reasons why neonatologists might be concerned about providing DR-CPR to extremely preterm infants. Firstly, these measures seem to be antagonistic to the philosophy of providing gentle support and maintaining physiological stability in the critical early phase of their care. Sudden changes in intrathoracic pressure or blood pressure might increase the risk of intraventricular haemorrhage. Secondly, DR-CPR might be associated with such low survival that it is regarded as futile.[2] Thirdly, there may be a worry that even if infants survive after DR-CPR, they would be so severely impaired that it would have been better if they had died. The 2009 BAPM framework cites a single-centre study from the early 1990s, in which nine of 13 surviving infants following CPR were severely impaired.[1]

Evidence

There remains no randomised controlled trial (RCT) evidence to guide the provision of DR-CPR in extremely preterm infants. (Though, of note, there is no RCT evidence for such measures in other preterm or term infants either). However, there have been multiple studies comparing the outcome of extremely preterm infants who received DR-CPR with those extremely preterm infants who did not. A 2009 meta-analysis of such studies found that DR-CPR was associated with a higher mortality rate (OR 2.83, CI 1.92-4.16), though the limited evidence available suggested no difference in neurodevelopmental disability in childhood.[3] A recent study from the Canadian Neonatal Network reported on the outcome of 2068 extremely preterm infants, of whom 190 received DR-CPR. That study found that those infants who received DR-CPR had a higher risk of mortality and, if they survived, of neurodevelopmental impairment.[4]

Argument

While it is certainly true that provision of advanced resuscitation measures has been statistically associated with adverse outcomes in extremely preterm infants, there are several reasons why it is not necessarily justified on that basis to withhold CPR.

The first is that it would be a mistake to infer causation from association. Infants who have more extensive resuscitation are likely to have been born in poorer condition than those who had less extensive resuscitation. It is hardly surprising that as a group they have worse outcomes. In the Canadian cohort, infants who received DR-CPR were smaller, more likely to be outborn, and less likely to have received antenatal steroids.[4] The authors performed a multi-variate analysis to account for such risk factors, but residual confounding is likely.

Of relevance, term infants who receive cardiac compressions at birth also have been reported to have higher rates of adverse outcome in multivariate analysis.[5] Neonatologists don't usually think

that it was the DR-CPR in these infants that causes their worse outcome. It is of course possible that chest compressions or adrenaline does lead to worse outcome in extremely preterm, or even term infants, but we are unable to reach that conclusion from existing evidence.

Secondly, publications since the 1990s have challenged the notion that it is futile to provide DR-CPR to extremely preterm infants. Sixty percent of ELBW infants who received DR-CPR in the Canadian cohort survived, and 78% of survivors were not severely impaired.[4]

Thirdly, even if it were the case that DR-CPR were causally linked with worse outcome, it doesn't follow that we should withhold such measures in infants who fail to respond to lesser forms of stabilisation and resuscitation. That would only follow if we thought that the outcome in these infants would be better if they had no DR-CPR. But that depends on one of two assumptions: that DR-CPR has no impact on survival, implying that resuscitation would lead to the same number of survivors, but with more disability – or that DR-CPR increases survival only at the cost of such severe disability that it would be better if the infants had not survived. Once those assumptions are unpacked it becomes clear that they are problematic. The first assumption seems on the face of it unjustified. We simply do not know whether DR-CPR alters survival. It may do, or it may not, but we don't know. The second assumption seems to be false. As the Canadian study makes clear, many extremely preterm infants who receive CPR/adrenaline in the delivery room survive without severe disability.

Recommendations in the face of uncertainty.

What should we conclude from available evidence? Existing evidence does not establish that DR-CPR is harmful overall for extremely preterm infants, but nor does it establish that it is of benefit.

One potential conclusion (which is not included in the new framework) is that there is a need for trials of different approaches to managing infants who remain bradycardic after initial measures to establish ventilation. Given the lack of evidence and potential risks, it would be ethical to perform a randomized trial (though we freely accept that such a trial would be extremely challenging to perform).

A second conclusion is that it is not possible to recommend a different approach to DR-CPR in extremely preterm compared with other infants. Of note, none of the international resuscitation guidelines (eg AAP, ILCOR, ERC) endorse withholding DR-CPR from a subgroup of neonates (such as those who are <26 weeks gestational age).

It does not follow from the above that neonatologists should feel compelled to perform prolonged cardiac compressions in 22 or 23 week infants. Rather, as with the other elements of the revised framework, it is appropriate to consider interventions on a case by case basis in consultation with parents. Clinicians should discuss the possibility of more extensive forms of resuscitation with parents prior to extremely preterm delivery and involve them in decisions. In some extremely preterm infants who are already designated to fall into a "high risk" category (see page...), clinicians may consider that the failure to respond to initial measures (including intubation and ventilation) would indicate that the baby now has an "extremely high risk" of adverse outcome, and that it would be in their best interests to move to palliative (comfort-focused) care. In other situations, it will not be clear that DR-CPR is contraindicated. Parents might decide that notwithstanding the higher risk of mortality and longer-term impairment that they would wish DR-CPR to be applied if their baby remains bradycardic. It would be ethically appropriate to support that choice.

1. Wilkinson AR, Ahluwalia J, Cole A, et al. Management of babies born extremely preterm at less than 26 weeks of gestation: a framework for clinical practice at the time of birth. *Arch Dis Child Fetal Neonatal Ed* 2009;**94**:F2-5.
2. Lantos JD, Miles SH, Silverstein MD, et al. Survival after cardiopulmonary resuscitation in babies of very low birth weight. Is CPR futile therapy? *N Engl J Med* 1988;**318**:91-5 doi:10.1056/NEJM198801143180206.
3. Shah PS. Extensive cardiopulmonary resuscitation for VLBW and ELBW infants: a systematic review and meta-analyses. *J Perinatol* 2009;**29**:655-61 doi:10.1038/jp.2009.71.
4. Fischer N, Soraisham A, Shah PS, et al. Extensive cardiopulmonary resuscitation of preterm neonates at birth and mortality and developmental outcomes. *Resuscitation* 2019;**135**:57-65 doi:10.1016/j.resuscitation.2019.01.003.
5. Shah PS, Beyene J, To T, et al. Postasphyxial hypoxic-ischemic encephalopathy in neonates: outcome prediction rule within 4 hours of birth. *Arch Pediatr Adolesc Med* 2006;**160**:729-36 doi:10.1001/archpedi.160.7.729.