Pediatric RESEARCH

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SPECIAL ARTICLE

Fifty-three years of follow-up of an infant with neonatal encephalopathy treated with therapeutic hypothermia

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INTRODUCTION

There is compelling evidence from randomized controlled trials that therapeutic hypothermia for full- or near-term neonates with moderate to severe neonatal encephalopathy (NE) significantly improves survival without a disability.[1] It is interesting to reflect that therapeutic hypothermia was being tested in a variety of ways well before the first large randomized trials, often using immersion in ice-cold water during resuscitation, followed by gradual, spontaneous rewarming.[2] The subsequent 20 years of translational studies provided a strong evidence base to enable successful phase 3 clinical trials to be performed and for the therapy to be officially adopted as the standard of care.[3] Follow-up of these trials is available to mid-childhood. Here, we report a case of NE with over 53 years of follow-up after treatment with therapeutic hypothermia by immersion. To the best of our knowledge, this is the longest follow-up recorded in the history of the treatment of NE.

Robert Carlson

In 1967, I was treated with hypothermia by immersion in ice-cold water as part of a local study, and then developed subcutaneous fat necrosis.[4] Both myself and one other case were reported by the neonatal team who looked after me to have had otherwise favorable short-term outcomes, but on the basis of this complication, these early studies of hypothermia were stopped. I was born weighing 3970 g at full term after an uncomplicated pregnancy, labor, and delivery. As reported,[4] at 1 min after birth I became apneic and did not respond to resuscitation. After 5 min, I was placed in an ice-water bath. My breathing was reported to recover after 28 min of hypothermia. At 45 min of life, my capillary pH was 6.9, but recovered steadily, and I was discharged at day 3. Subcutaneous fat necrosis developed between 2 and 4 weeks of age. The calcium deposits were largely cleared by 6 months. My serum calcium remained normal, and my weight gain and development were considered appropriate at that age, but no further follow-up was reported.

Fifty-three years after these events,[4] I have had a very normal life. Although my mother teased me about my skin in childhood, I never had any apparent skin problems as a child or later. I was a keen sportsman at school. My handwriting was never a strength, and so I taught myself to touch-type, which turned out to be an advantage in the computer age. At the same time, it is interesting to note that I can easily thread a needle. Academically, I did very well throughout school and university. I was awarded my Ph.D. in 1998, and have served at my current institution as Department Chair and Faculty Senate President.

In retrospect, I strongly believe that the benefits of treatment clearly outweighed the costs and that the abrupt cessation of these early studies of therapeutic hypothermia represented a missed opportunity. If the opinion of my parents had been sought at the time, or subsequently my opinion, we would have favored continued trialing of this promising treatment.

DISCUSSION

Meta-analysis of recent randomized controlled trials suggests that subcutaneous fat necrosis occurs in ~1% of cooled infants; interestingly, often in areas of the skin that were touching the cooling pad or blanket.[1] Speculatively, the deeper initial cooling in the early trials of whole-body immersion in ice-cold water may have increased the risk of subcutaneous fat necrosis. It is not possible to know of course whether the early resuscitative hypothermia used in this case played a role in R.C.'s highly favorable outcome, but R.C. felt that that given that the adverse effect resolved without complications and that his neurological and cognitive outcomes were highly favorable, that in retrospect this was a missed opportunity and that these studies of hypothermia were stopped too soon.

The original report highlighted that benefit of hypothermia was only proven in cardiac surgery but not in newborns and so the short-term complications were seen to outweigh potential long-term gains. This supports the importance of obtaining long-term outcome data for novel therapies. The families' views were not solicited, but may have been important, particularly in a situation such as this, as R.C. did not develop any further symptoms. A similar initial over-reaction was seen when the association of greater risk of retinopathy of prematurity with supplemental oxygen was first recognized.[5] Subsequent studies demonstrated that there is a complex balance between the risk of retinal damage and greater risk of death and disability after more restricted oxygen supplementation.[6] These historical data suggest that it may be better to try different ways to utilize new principles before abandoning an area of research altogether.

In the past 50 years, we have seen many changes in the way that research is performed and how the results can improve quality of care. One recently developed approach is the use of a Delphi process to develop a core outcome set for trials/research of specific conditions, often with a strong representation of patients or family.[7] The present case suggests two important principles. First, that long-term follow-up to establish the trajectory of recovery, and the full spectrum of effects and benefits of a new

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and possibly efficacious treatment, is vital. Second, that parental involvement must be encouraged in studies of future neuroprotective therapies. We have more work to do to reliably achieve these principles in pediatrics.

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AUTHOR CONTRIBUTIONS

R.C. conceptualized the study and reviewed and revised the manuscript. M.R.B., L.B., and A.J.G. drafted the initial manuscript, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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