Improving infant outcome with a 10 min Apgar of 0

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ABSTRACT

Objective Asystole at birth and extending through 10 min is rare, with current international recommendations stating it may be appropriate to consider discontinuation of resuscitation in this clinical scenario. These recommendations are based on small case series of both term and preterm infants, where death or abnormal outcome was nearly universal. Study objective was to determine recent outcome of infants with an Apgar score of 0 at 10 min despite cardiopulmonary resuscitation, treated with therapeutic hypothermia or standard treatment, in randomised cooling studies.

Design Outcome studies of infants with an Apgar of 0 at 10 min subsequently resuscitated and treated with hypothermia or standard treatment were reviewed and combined with local outcome data of infants treated with hypothermia.

Results Four recent studies (n=81) and local data (n=9) yielded a total of 90 infants with an Apgar of 0 at 10 min, with 56 treated with hypothermia and 34 controls. Primary outcome of death or abnormal neurodevelopmental outcome (18–24 months) occurred in 73% cooled and 79.5% normothermic infants (p=0.61).

Implications Although poor, the outcome for infants with an Apgar of 0 at 10 min of life has improved substantially in recent years. This may be related to treatment with hypothermia, enhanced resuscitation techniques and/or other supportive management. Current recommendations to consider discontinuation of resuscitation without a detectable heart rate at 10 min should consider these findings.

INTRODUCTION

Asystole at birth and extending through 10 min is rare, but imposes important clinical and ethical considerations. An absent heart rate (HR) at birth may reflect an intrapartum stillbirth or a state of severe and prolonged secondary apnoea which may only be reversed with effective positive pressure ventilation and in some cases more intensive resuscitation.1 Even with the recovery of spontaneous circulation, there is a high likelihood of cerebral hypoperfusion with subsequent brain injury or death.2,3

The recommended duration of resuscitation in the context of asystole has transformed over time. The 2000 Neonatal Resuscitation Guidelines suggested that discontinuation of resuscitative efforts at 15 min of life might be warranted if spontaneous circulation had not been restored.4 The rationale behind suggesting 15 min appears unclear, as the recommendation went on further to state that survival without severe disability was unlikely after 10 min of asystole. Small case series were cited which included both term and preterm apparently stillborn infants, all of whom suffered death or disability.2,5,6 The guidelines in 2005 advised that discontinuation may be warranted if there were no signs of life after 10 min of adequate resuscitation.7 Most recently, the 2010 International Liaison Committee for Resuscitation recommendation remains unchanged in considering discontinuation of resuscitation if the HR remains undetectable for 10 min. Furthermore, ‘The decision to continue resuscitation efforts beyond 10 minutes with no heart rate should take into consideration factors such as the presumed etiology of the arrest, the gestation of the baby, the presence or absence of complications, the potential role of therapeutic hypothermia, and the parents’ previously expressed feelings about acceptable risk of morbidity.’8

This most current statement raises an important question which must be considered during resuscitation of term infants, that is, whether therapeutic hypothermia may modulate outcome after prolonged asystole. A potential beneficial role of hypothermia was noted in subgroup analysis from the 10 min. Furthermore, April 2014. Revised 23 September 2014. Accepted 2 October 2014. Published Online First 23 October 2014

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severe disability at 18 months of age.10 Twenty-one per cent survived with intelligence quotients between 77 and 99 as measured on the Wechsler Preschool and Primary Scale of Intelligence III, with normal visuospatial and attention, executive function and without cerebral palsy at 6–7 years of age.10 Conversely, Sarkar et al has reported uniformly poor outcome in a group of term infants with asystole at 10 min treated with hypothermia, consistent with previous case series which took place prior to the investigational use of therapeutic hypothermia.5 11 12 13 The objective of this report was to review the recent outcome of infants ≥35 weeks gestation without an apparent HR at 10 min of life despite intensive resuscitation treated both with therapeutic hypothermia and standard care.

PATIENTS AND METHODS

This review comprises outcome data obtained from previous studies which took place between 2000 and 2009, in respect of infants ≥35 weeks gestation with no detectable HR at 10 min who underwent resuscitation, and were subsequently treated with therapeutic hypothermia or normothermia. The Steering Committee of the NICHD whole-body cooling follow-up study, Total Body Hypothermia for Neonatal Encephalopathy (TOBY) (DA) and Infant Cooling Evaluation (ICE) (S) trials were contacted and agreed to provide outcome data for enrolled infants without an apparent HR at 10 min treated with hypothermia versus normothermia.9 13 14 Data published by Sarkar et al including infants treated with selective head cooling (SHC) or whole-body cooling were also included for analysis.12 Abnormal outcome for all studies was defined as death or moderate/severe disability at follow-up.12 13 14 More specifically, the TOBY trial defined the primary outcome as death or severe neurodevelopmental disability in survivors at 18 months of age, defined as a Bayley Scale of Infant Development (BSID-III) Mental Developmental Index (MDI) score <70, a score of 3–5 on the Gross Motor Function Classification System (GMFCS), or bilateral cortical visual impairment with no useful vision.13 In the NICHD trial, the primary outcome was death or moderate/severe disability at 18–22 months of age. Severe disability was defined as Bayley II MDI score <70, GMFCS score 3–5, blindness or hearing deficit with amplification. Moderate disability was defined as an MDI of 70–84 with one of the following: GMFCS score of 2, persistent seizure disorder or hearing deficit with amplification.9 The primary outcome assessed by Sarkar et al12 was death, and the primary composite outcome in the ICE trial was mortality or major sensorineural disability at 2 years of age.14 Major sensorineural disability was defined as neuromotor delay (cerebral palsy with the child not able or unlikely to walk at 2 years, a BSID-II Psychomotor Developmental Index <–2 SDs, a Motor Composite Scale score on the BSID-III of <–2 SDs or a disability level on the GMFCS of 2–3), developmental delay (a BSID-II MDI of <–2 SDs or a Cognitive Scale score or a Language Composite Scale score on the BSID-III of <–2 SDs), blindness and/or deafness requiring amplification.14

We reviewed our local 6 years experience (2007–2012) of infants treated with SHC in the neonatal intensive care unit at New York-Presbyterian Hospital (NYPH)/Weill Cornell Medical Center (WCMC). The NYPH study population included inborn and referred infants eligible for SHC if gestational age (GA) ≥36 weeks with presence of additional clinical criteria outlined in the Cool Cap Study protocol, amplitude-integrated electroencephalogram (aEEG) evidence of moderate/severe suppression or seizures and/or clinical evidence of Sarnat Stage 2 or 3 encephalopathy.15 16 Infants underwent a neurological examination by a single examiner (JMP) at neurodevelopmental follow-up and a BSID-III at 18 months of age. Severe disability in the local cohort was defined as cognitive score <70 or global developmental delay at most recent developmental clinic follow-up, and moderate disability as a cognitive score <85.

The WCMC institutional review board approved review of the data at this site. Data were analysed by SPSS V20 (IBM Statistics 20). Clinical characteristics between groups were compared with Wilcoxon rank-sum for unmatched, non-parametric data. Two-sided p values ≤0.05 were considered significant.

RESULTS

Four randomised trials from the time of the investigational use of hypothermia (2000–2009) were identified with outcome data available between 18 months and 24 months of age (table 1).9 12–14 17 The duration of follow-up differs among studies and has been listed for each study accordingly.

Locally, 100 infants have been treated with SHC between 2007 and 2012, of whom nine presented without an apparent HR at 10 min of life. The results of the hypothermia studies conducted in recent years yielded 81 infants. These infants combined with the nine local infants provided a total of 90 infants with an Apgar score of 0 at 10 min; 56 treated with hypothermia and 34 with normothermia (table 1).9 12–14 17 Mortality or abnormal neurodevelopmental outcome occurred in 41/56 (73%) of infants treated with hypothermia versus 27/34 (79%) of the normothermic control infants. Overall, 15/56 (27%) treated with hypothermia and 7/34 (21%) of the normothermic infants are developmentally normal at follow-up (p=0.61). Overall mortality was 45/90 (50%) of infants with an Apgar score of 0 at 10 min.

The 9 infants (6 females and 3 males) assigned an Apgar score of 0 at 10 min treated with SHC at NYPH had mean GA 39±0.9 weeks and birth weight of 3582±650 grams. Labour complications included placental abruption (n=3), non-reassuring fetal heart tracing with bradycardia (n=3), with 6 delivered via emergent C-section. All 9 infants received cardio-pulmonary resuscitation (CPR), with median of 3 rounds of epinephrine (range 0–7). One infant received 5 doses of intratracheal epinephrine, with epinephrine administered via the intravenous route in the remaining infants. Postnatal pH was 6.89±0.15 and base deficit −22.1±3.6 mEq/L. Eight infants exhibited severe and 1 infant moderate encephalopathy on physical exam, with moderate aEEG suppression in 4 and severe aEEG suppression in 5 infants. Five children (55%) are developing normally at 18 months of age, with cognitive scores ranging from 85 to 100 in four patients, and one infant developing normally at 18 months by report. Abnormal outcome included one infant with a cognitive score of 75 at 18 months, another with severe motor delay at 15 months and a third with global developmental delay and seizures at 2 years of age. One infant died at 8 months of age.

DISCUSSION

This small selected cohort demonstrates that infants with a 10 min Apgar of 0 who receive intensive resuscitation with subsequent recovery of spontaneous circulation and treated with therapeutic hypothermia or those who were not cooled in the randomised hypothermia studies, were more likely to survive with normal neurodevelopmental outcome as compared with studies performed prior to the investigational use of therapeutic hypothermia. This improved outcome in the treatment group may partly reflect a neuroprotective effect of hypothermia. However, the improvement in outcome in non-cooled controls

in the modern era may, alternatively, reflect more optimised CPR or advancement in supportive measures following an asphyxial event. Although there was no significant difference in outcome between treated and control groups, the study was not powered to detect such a difference.

Previous studies indicate that an ‘apparently stillborn’ infant without an HR at 1 min of life can be successfully resuscitated in most cases with up to 84% survival to hospital discharge. Outcome data of infants without a perceptible HR at 10 min of life has been less promising. There is a paucity of data regarding term and near-term infants with an Apgar of 0 at 10 min of life. The few case series cited in the 2000 and 2005 Neonatal Resuscitation Guidelines justifying discontinuation of resuscitation at 10 min are small, include both term and preterm infants and took place between 1982 and 1999.2 3 11 Thus, Jain et al8 reported on the largest series of 58 term and preterm infants with an Apgar of 0 at ≥10 min, with death occurring in all infants except one survivor who was subsequently diagnosed with cerebral palsy. Haddad and colleagues demonstrated a similar dismal prognosis, with 14/16 (87.5%) of term and preterm infants with an Apgar of 0 at ≥10 min, with death occurring in all infants except one survivor who was subsequently diagnosed with quadriplegia.2 The distant time frame in which these studies took place, heterogeneous patient population and small overall sample size led to this review of more recent reports of term and near-term infants eligible for therapeutic hypothermia who presented with asystole at 10 min, to potentially guide future recommendations for duration of resuscitation.

Based on these data, there appears to be a significant improvement in survival in infants assigned an Apgar score of 0 at 10 min in recent years, with absence of primary outcome of death or moderate/severe disability observed in both infants treated with hypothermia and normothermic controls. One may attribute this, in part, to the neuroprotective effect conferred by hypothermia. However, the significant improvement in the normothermic group suggests advancement in other aspects of management, including advanced resuscitation techniques and postresuscitative measures. Delivery room resuscitation has substantially improved between the time period prior to the availability of therapeutic hypothermia and today, including exclusive administration of chest compressions with the two-thumb encircling hands technique, emphasis on intravenous epinephrine as the favoured route of administration, as well as close attention to oxygen administration, temperature control and postresuscitation supportive measures.8

There are several limitations to this review. First, this is a selected cohort, and in two reports, outcomes were assessed only in hypothermia-treated infants without presence of controls. Additionally, the more severe cases of hypoxic-ischemic encephalopathy may not have been treated with hypothermia, further increasing the chance of selection bias. The patients represent those who survived delivery room resuscitation, some of whom were referred to a tertiary cooling centre. This makes it impossible to delineate the number of infants with an Apgar of 0 at 10 min who died in the delivery room, thus potentially overrepresenting infants with a normal outcome. Additionally, the patient sample size is small, and the supportive care provided for patients treated with hypothermia was likely variable between centres. As many infants are transferred from referring institutions, there is incomplete information on efficacy of resuscitative measures for infants delivered at outside hospitals, specifically whether measures were truly effective from the initiation of resuscitation (i.e. due to delays in intubation, difficulty obtaining intravenous access, etc.). Presumably, most infants were assigned an Apgar score >0 by 15 min of life, however, this information was not available. Finally, the age at follow-up is a limitation as the availability of therapeutic hypothermia. To optimise informed decision making in the future and improve knowledge of patient outcome, a registry of all infants with an Apgar of 0 at 10 min should be established. This, ultimately, could lead to modifications in the suggested duration of resuscitative efforts.

CONCLUSION

Although the outcome of infants without an HR at 10 min of life remains poor, there has been significant improvement in recent years. Improved outcome may be related, in part, to enhanced resuscitation techniques, postresuscitation care or the availability of therapeutic hypothermia. To optimise informed decision making in the future and improve knowledge of patient outcome, a registry of all infants with an Apgar of 0 at 10 min should be established. This, ultimately, could lead to modifications in the suggested duration of resuscitative efforts.

Table 1 Summary of outcome studies of infants with an Apgar score of 0 at 10 min from the time of the investigational use of therapeutic hypothermia

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Gestational age for inclusion (weeks)</th>
<th>Apgar 0 at 10 min n</th>
<th>Age at follow-up (months)</th>
<th>Cooled</th>
<th>Control</th>
<th>Cooled</th>
<th>Control</th>
<th>Cooled</th>
<th>Control</th>
<th>Abnormal=Death or moderate/severe neurodevelopmental outcome.</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOBY</td>
<td>2002–2006</td>
<td>≥36</td>
<td>33</td>
<td>18</td>
<td>16</td>
<td>17</td>
<td>5</td>
<td>11</td>
<td>4</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>ICE</td>
<td>2001–2007</td>
<td>≥35</td>
<td>11</td>
<td>24</td>
<td>5</td>
<td>6</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Sarkar</td>
<td>2003–2009</td>
<td>≥36</td>
<td>12</td>
<td>9–24</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>NYPH</td>
<td>2007–2012</td>
<td>≥36</td>
<td>9</td>
<td>18–24</td>
<td>9</td>
<td>0</td>
<td>5</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>90</td>
<td>56–34</td>
<td>15</td>
<td>27%</td>
<td>41</td>
<td>73%</td>
<td>7</td>
<td>21%</td>
<td>27 (79%)</td>
</tr>
</tbody>
</table>

Abnormal=Death or moderate/severe neurodevelopmental outcome.

ICE, infant cooling evaluation; NYPH, New York–Presbyterian Hospital; TOBY, total body hypothermia for neonatal encephalopathy.
study, performed data analysis, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Competing interests None.

Ethics approval WCMC IRB.

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REFERENCES
