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Resuscitation

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Editorial

Neurocognitive outcomes in survivors of pediatric E-CPR: Has the Golden age arrived?

The use of extracorporeal cardiopulmonary resuscitation (E-CPR) is increasing.[1] Nevertheless, because of the low quality of evidence with high risk of bias, E-CPR is of uncertain efficacy.[2] In children, recent data from the Get With The Guidelines-Resuscitation registry found that E-CPR for in-hospital cardiac arrest (IH-CA) of duration ≥10 min was associated with improved adjusted and propensity score matched outcomes of survival to hospital discharge, and survival to hospital discharge with favorable neurological outcome.[3] After >35 min of chest compressions, E-CPR survival to discharge was 33%, with good neurological outcome in 63% of these survivors.[4] This survival and neurological outcome advantage was not confirmed in the Therapeutic Hypothermia after Pediatric Cardiac Arrest In-Hospital (THAPCA-IH) trial, where extracorporeal membrane oxygenation (ECMO) prior to temperature intervention was not associated with 12-month survival, and associated with worse adjusted 12-month survival with parent-reported Vineland Adaptive Behavior Scales (VABS) ≥70.[5] This may be due to the differing inclusion criteria, in THAPCA-IH being duration of IH-CA ≥2 min. The most recent American Heart Association guidelines stated that E-CPR "may be considered for pediatric patients with cardiac diagnoses who have IH-CA in settings with existing ECMO protocols, expertise, and equipment".[6]

There is limited information regarding the long-term neurocognitive outcomes in children having CA, including after E-CPR.[7] In one single center study, young children with cardiac disease having E-CPR had 43% survival to age 5 years, with intelligence quotients shifted to the left of population norms, and 24% having score <70.[8] In this issue of Resuscitation the THAPCA-IH Trial Investigators describe 12-month outcomes in survivors who had E-CPR: of 329 patients in THAPCA-IH, 269 had broadly normal pre-arrest function (defined as VABS ≥ 70), and of these 135 survived for 12 months with 127 (94%) having some follow-up.[9] In E-CPR survivors (n = 57) the mean change in VABS composite score was -13 (SD 22) with a score <70 in 16/55 (29%), impaired cognitive performance (score <70 on Mullen Scales of Early Learning or Wechsler Abbreviated Scale of Intelligence) in 20/44 (45%), and moderate or more neurologic impairment on Paediatric Resuscitation after Cardiac Arrest score in 19/47 (40%).[9] These scores, particularly the more objective cognitive performance scores, are concerning because in the normative population the mean (SD) scores are 100 (15), and a score <70 is expected in only 2.27% of the population; all the scores were significantly shifted to the left of population norms. Of some reassurance, these outcomes in E-CPR survivors were comparable to the IH-CA outcomes in survivors who had later ECMO (n = 14), or no ECMO (n = 56).[9]

The authors are to be congratulated for this impressive multicenter endeavor. Limitations of the trial are discussed by the authors and must be considered. The sample size of pediatric E-CPR survivors is the largest reported for long-term follow-up, but was nevertheless modest for most outcomes, with significant loss to follow-up; for example, after E-CPR 44/57 (77%) had neurocognitive outcome assessed and 47/57 (82%) had neurological examination. Comparisons of these outcomes between E-CPR, later ECMO, and no-ECMO groups is severely limited by the small numbers in each group. The outcomes were obtained from the THAPCA-IH trial, and thus subject to the eligibility criteria of that trial [e.g., comatose and ventilated after IHCA of at least 2 min and randomized within 6 h, without limitations of care]. Most of the patients (75% of survivors after E-CPR) were <3 year old at 12-month follow-up, and the usefulness of VABS and neurocognitive scores at that age to predict school-age outcomes is limited.[10] Although we do not know to which group (hypothermia or normothermia) the survivors were randomized to, this should not affect the findings as the THAPCA trials found lack of efficacy of hypothermia.[11] Despite these limitations, the outcomes reported clearly help us in counselling parents regarding expectations, and confirm the importance of long-term neurocognitive follow-up and intervention in children after CA.

In going forward, we want to emphasize two points that will ultimately help clinicians in neuro-prognosis after IH-CA. First, we consider the self-fulfilling prophecy from early withdrawal of life-sustaining therapy (WD) for anticipated poor neurological outcome. In systematic reviews of neuro-prognosis in adults after CA the included studies are of low/very-low quality because prognostic tests are not blinded and are used in making the decision to WD.[12,13] One multicenter study in adults found that WD at <72 h after out-of-hospital CA for anticipated poor neurological outcome occurred in 33% who died in hospital, while it was predicted that these patients otherwise would have had 26% survival and 16% (64% of survivors) functionally favorable survival.[14] In adults admitted to rehabilitation with disorders of consciousness almost half achieved daytime independence at home and 22% had return to school/work by one-year.[15] In the THAPCA-IH trial the numbers with WD and the reasons for this WD were not reported, potentially biasing the reported outcomes.

This leads to our second point. The current study found concerning outcomes for many survivors of IH-CA. We urgently need more study to help predict poor neurologic prognosis after pediatric CA.[7] We believe there are three time-periods where

robust information is missing. First, especially in the setting of E-CPR, demographic and CA variables need to be examined to determine predictors of poor neurologic outcome before the decision is made to implement E-CPR. Recent studies suggest that compression rate[16] and diastolic blood pressure[17] may be particularly important. Since not all patients are offered E-CPR, introducing selection bias, large sample sizes with many co-variates will be required to adjust for confounding. Second, post-resuscitation variables that should be therapeutically optimized need to be determined. Recent data suggest that post-CA PaCO2 and mean arterial pressure may be particularly important.[18] Third, clinical, electrophysiologic, and radiology variables in patients who remain comatose need evaluation for early neuro-prognostication. In adults, the most robust predictors assessed at 72 h are bilaterally absent pupillary and corneal reflexes, and bilaterally absent N20 wave on somatosensory evoked potentials. Less robust predictors that may be considered in combination include status myoclonus at $\leq$48 h, neuron specific enolase at 48–72 hours, unreactive burst-suppression or status epilepticus on electroencephalogram, and diffuse anoxic injury on CT and/or MRI scan.[12,13] This is often based on few studies of low/very-low quality, subject to the self-fulfilling prophecy.[12,13] For CT and MRI more data is needed, as studies are further limited by lack of pre-defined cutoffs for interpretation, variability in scanners, and selection bias.[19,20] The THAPCA-IH trial found that risk factors for not attaining 12-month survival with VABS $\geq$ 70 included ECMO, asystole, non-VF/VT rhythm, blood lactate, and non-open-chest compressions.[5] But most of the variables mentioned above were not available.

Again, we congratulate the THAPCA-IH Investigators for their important work. They have provided us with important information on 12-month outcomes after E-CPR in children.[9] Much work remains to be done to help predict these long-term outcomes of children having CA, while avoiding self-fulfilling prophecies. We need help in deciding who needs E-CPR, how to improve outcomes, and when to consider WD for predicted severe or worse disability.

Financial disclosure

This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors declare that there is no conflict of interest.

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http://dx.doi.org/10.1016/j.resuscitation.2019.04.001