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Hypothermia or normothermia to improve survival after in-hospital cardiac arrest?

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English key words: heart arrest, survival, induced hypothermia, infant, child.
Palabras clave en español: paro cardiaco, supervivencia, hipotermia inducida, lactante, niño.

Reception date: July 4, 2017 • **Acceptance date:** July 6, 2017
Publication date: July 12, 2017

Evid Pediatr. 2017;13:39.

HOW TO CITE THIS ARTICLE

Martín-Crespo Blanco MC, Aizpurua Galdeano P. ¿Hipotermia o normotermia para mejorar la supervivencia tras parada cardiaca intrahospitalaria? Evid Pediatr. 2017;13:39.

This article is available at http://www.evidenciasenpediatria.es/EnlaceArticulo?ref=2017;13:39
 • ISSN: 1885-7388

Hypothermia or normothermia to improve survival after in-hospital cardiac arrest?

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Original article: Moler FW, Silverstein FS, Holubkov R, Slomine BS, Christensen JR, Nadkarni VM, *et al.* Therapeutic hypothermia after in-hospital cardiac arrest in children. N Engl J Med. 2017;376:318-29.

Abstract

Authors' conclusions: among comatose children who survived in-hospital cardiac arrest, therapeutic hypothermia, as compared with therapeutic normothermia, did not confer a significant benefit in survival with a favorable functional outcome at 1 year.

Reviewers' commentary: in the controversy over the alleged benefits of therapeutic hypothermia, the results of this study found no differences to support its use against normothermia to improve survival with a favorable functional outcome after in-hospital cardiac arrest in children.

Key words: heart arrest, survival, induced hypothermia, infant, child.

¿Hipotermia o normotermia para mejorar la supervivencia tras parada cardiaca intrahospitalaria?

Resumen

Conclusiones de los autores del estudio: la hipotermia terapéutica en los niños comatosos que sobreviven a un paro cardiaco intrahospitalario, en comparación con la normotermia terapéutica, no produce un beneficio significativo en la supervivencia con un desarrollo funcional favorable al año.

Comentarios de los revisores: en la controversia acerca de las supuestas ventajas de la hipotermia terapéutica, los resultados de este estudio no han encontrado diferencias que apoyen su uso frente a la normotermia para mejorar la supervivencia con buena función tras parada cardiaca intrahospitalaria en niños.

Palabras clave: paro cardiaco, supervivencia, hipotermia inducida, lactante, niño.

STRUCTURED ABSTRACT

Objective: to compare the efficacy of therapeutic hypothermia versus therapeutic normothermia in children and adolescents who were resuscitated after in-hospital cardiac arrest.

Design: multicentre randomised clinical trial with blind evaluation.

Setting: Paediatric intensive care units at 37 children's hospitals in the United States, Canada, and the United Kingdom.

Study sample: 329 children aged 48 hours to 18 years who experienced in-hospital cardiac arrest, received chest compressions for at least 2 minutes and remained dependent on mechanical ventilation after return of spontaneous circulation. The exclusion criteria were a score of 5 or 6 in the Glasgow Coma Scale motor response subscale, severe bleeding, pre-existing illness with a life expectancy of less than 1 year or decision by the clinical team to withhold aggressive treatment. The 329 children were randomly assigned to therapeutic hypothermia or therapeutic normothermia with the use of permuted blocks stratified according to clinical centre and age category. In the final sample, 161 received hypothermia and 160 normothermia.

Intervention: treatment was initiated within 6 hours of the return of spontaneous circulation, and consisted in maintaining the target temperature for 120 hours in both groups. The target central temperature in the hypothermia group was

33°C (range, 32°C to 34°C) for 48 hours, followed by rewarming for a minimum of 16 hours until reaching 36.8°C (range, 36°C to 37.5°C), which was maintained for the remainder of the 120 hours. The normothermia group was maintained at a target central temperature of 36.8°C (range, 36°C to 37.5°C) for the entire 120 hours.

Outcome measurement: The primary outcome was survival with a favourable outcome at 12 months of followup, defined as score of 70 or higher on the Vineland Adaptive Behavior Scales, second edition (which has a mean of 100 and a standard deviation of 15). The authors excluded 31 patients in the hypothermia group and 29 in the normothermia group from the analysis because they had a baseline score in the Vineland-II scale of less than 70 before cardiac arrest, or a score of 3 to 6 in the Pediatric Overall Performance Category or Pediatric Cerebral Performance Category scales (moderate disability [3], severe disability [4], coma [5] or brain death [6]). Secondary outcomes were survival at 12 months and change in neurobehavioral function, compared to baseline (before cardiac arrest).

Main results: the median age of the patients was 1 year, and the cause of arrest was cardiac in 65%. Fifty-one percent of patients in the hypothermia group and fifty-eight percent in the normothermia group were receiving extracorporeal membrane oxygenation at the time of randomization.

The trial was stopped prematurely due to futility (lack of efficacy) after randomization of 329 patients (out of the 558 initially expected). Among the 257 children with a baseline Vineland-II score of 70 or higher before arrest, there was no difference in the proportion alive at 1 year with a score of 70 or higher between the hypothermia and normothermia groups: 36% versus 39%, with a relative risk (RR) of 0.92 and a 95% confidence interval (95 CI) of 0.67 to 1.27. There were also no differences between these groups in mortality at 1 year (RR, 1.07; 95 CI, 0.85 to 1.34) or changes in neurobehavioural functioning at 1 year.

Conclusion: in comatose children that survived in-hospital cardiac arrest, therapeutic hypothermia did not confer a significant benefit with respect to survival with a good functional outcome at 1 year compared with therapeutic normothermia.

Conflicts of interest: several authors disclosed having receiving funds during the study.

Funding sources: grants from the National Heart, Lung and Blood Institute and other institutions

COMMENTARY

Justification: based on the volume of publications devoted to the indications of hypothermia after cardiac arrest in the past 10 years, we can infer that there is a growing interest in this approach, with the number of articles indexed in PubMed tripling over this period.

Adults have been the target population in most published studies, so this study broadens their scope by studying the paediatric population and in-hospital cardiac arrest, independent of its cause.

The main outcomes assessed in the literature are 1-year survival, neurologic functioning and protection against oxidative stress, which are the supposed beneficial effects of hypothermia compared to normothermia that have spurred the interest in the former approach.[1,2]

Scientific rigour/validity: the population under study was clearly defined, as were the exclusion criteria. Patients were randomly assigned by permuted blocks stratified by centre and age category. Only evaluators were blinded to the treatments, as the characteristics of the intervention prevented blinding the research team and health care staff.

Targeted temperature management was maintained for 120 hours in both groups (in the hypothermia group, hypothermia was maintained for 48 hours, followed by 16 hours of rewarming and maintenance of normothermia for the remainder of the 120 hours). Patients in both groups were otherwise managed the same way. Central temperature was controlled with dual monitoring (oesophageal, rectal or vesical, with a temperature management unit) except in patients undergoing extracorporeal membrane oxygenation (ECMO), in whom a single monitor was used.

The study was discontinued prematurely before attainment of the target trial enrolment due to futility, which was established by an interim efficacy analysis performed by an independent team designated by the National Heart, Lung and Blood Institute. This is a significant limitation, as it diminishes the power of the study to find differences between groups. The analysis was made by intention to treat.

Clinical relevance: the study assessed an important clinical outcome, survival with favourable functional outcome at 1 year, and did not find differences between therapeutic hypothermia and therapeutic normothermia (RR, 0.92; 95 CI, 0.67 to 1.27). The evidence found by a systematic review published in 2015[3] was also insufficient to recommend hypothermia as being superior to therapeutic normothermia. Therefore, studies on the cost-effectiveness of both treatments are needed.

Applicability to clinical practice: amid the controversy regarding the presumed advantages of therapeutic hypothermia, this study did not find any differences supporting its use as opposed to normothermia in survival with good functioning following in-hospital cardiac arrest in the paediatric population. Thus, this article does not warrant adjusting current recommendations for everyday clinical practice.

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