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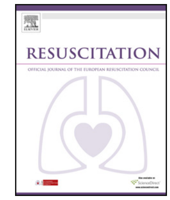

Clinical Paper

High cumulative oxygen levels are associated with improved survival of children treated with mild therapeutic hypothermia after cardiac arrest☆,☆☆

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A B S T R A C T

Aim: The aim of this study was to analyze the relationship between the partial pressure of arterial oxygen (PaO_2) and in-hospital (IH) mortality in children after cardiac arrest (CA) using the conventional cutoff analysis, which was compared with the cumulative analysis, a new method in PaO_2 analysis. Additionally, we analyzed this relationship for children with and without mild therapeutic hypothermia (MTH; 32–34 °C).

Methods: This observational cohort study included all children (aged >28 days) with CA and return of spontaneous circulation (ROSC) between 2002 and 2011.

The first research question was the association between PaO_2 and IH mortality after ROSC. This was analyzed for three hyperoxia cutoff values, and for three time intervals using the cumulative PaO_2 determined with the area under the curve (AUC). For the second research question, these analyses were repeated for children with and without MTH.

Results: Of the 200 patients included (median age 2.6 years), 84 (42%) survived to hospital discharge. Fifty-eight children (29%) were treated with MTH.

With the cutoff analysis and the AUC analysis we found no relationship between PaO_2 and IH mortality. However, analysis of the MTH-group showed a lower IH mortality in children with high cumulative PaO_2 levels on two of the three time intervals. Multivariable analysis showed significantly higher odds of survival (0.643 (95% confidence interval (CI) 0.424–0.976), 0.554 (95%CI 0.335–0.916)).

Conclusions: Cumulative PaO_2 analysis showed that the IH mortality is significantly lower in MTH-treated children with high PaO_2 levels. The effects of cumulative PaO_2 on the outcome need to be studied further, and this will help us to achieve individualized goal-directed therapy.

1. Introduction

Cardiac arrest (CA) in children is uncommon and associated with high mortality (50–90%).[1–6] Oxygen therapy has always been important in the treatment of CA. However, there is increasing evidence for the adverse effects of oxygen. Oxidative stress and reperfusion promote free radical-generated injury contributing to neurologic injury and cardiac dysfunction, and they seem to be associated with increased mortality after CA.[7,8] Furthermore, a meta-analysis of animal studies by Pilcher et al. showed that treatment with 100% oxygen after resuscitation resulted in significantly worse neurological deficit scores than oxygen administered at lower concentrations.[9]

Observational studies in humans examined the influence of arterial oxygen (PaO_2) on in-hospital (IH) mortality. They used

Abbreviations: APLS, advanced pediatric life support; AUC, area under the curve; BLS, basic life support; CA, cardiac arrest; CI, confidence interval; OH, out-of-hospital; IH, in-hospital; MTH, mild therapeutic hypothermia; NICU, neonatal intensive care unit; OR, odds ratio; PaO_2, partial pressure of arterial oxygen; ICU, intensive care unit; ROSC, return of spontaneous circulation; SIRS, systemic inflammatory response syndrome.

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different time intervals after return of spontaneous circulation (ROSC) and different definitions of hyperoxia, or included only patients treated with mild therapeutic hypothermia (MTH), which resulted in contradictory conclusions.[10–16] Most studies used an arbitrary cutoff value to describe the influence of PaO_2 on the IH mortality. Only two studies used an alternative method. Janz et al. used PaO_2 as a continuous value and Ferguson et al. modeled the first PaO_2 within the first hour after ROSC in a non-linear matter.[11,13]

In contrast with previous studies, we hypothesized that not a single value above a previously set cutoff, but rather the cumulative PaO_2 during the first 24 h after ROSC (especially the first 6 h) is associated with worse survival of children with CA. Our first research question was the association between PaO_2 and the IH mortality, analyzed with the commonly used cutoff method and compared with a cumulative method. In addition, although the evidence for the protective effects of MTH is debatable, we hypothesized that MTH is protective against the effects of hyperoxia, as it is the only post-resuscitation intervention, introduced in our hospital in 2007, in accordance with international guidelines.

2. Methods

This observational cross-sectional cohort study was performed at the intensive care unit (ICU) of the Erasmus MC – Sophia Children's Hospital, a tertiary-care university hospital. Our hospital provides health care to children in the southwest of The Netherlands (total population of approximately 4.2 million people), and this population is a representative sample of the Dutch population.

2.1. Patient selection

This study concerned all patients aged >28 days and <18 years with documented CA between January 2002 and December 2011, and admitted to the ICU of the Erasmus MC – Sophia Children's Hospital. CA was defined as absent pulse rate or the need for cardiac compressions. Treatment of children with CA in our hospital has been in line with the European Resuscitation Council guidelines for pediatric life support.[17]

The inclusion criteria were as follows: (1) all children resuscitated in-hospital (e.g. emergency department, ward, or ICU) and out-of-hospital, and consecutively admitted to our ICU, and (2) children resuscitated in a regional hospital or other university hospital, and after ROSC consecutively admitted to our ICU. Neonatal resuscitations, children with cyanotic congenital heart disease, and children without an arterial line were excluded. In addition, only data of the first CA episode were included when a child had multiple arrests.

Hypothermia was introduced as treatment after CA in children with post-resuscitation coma in 2007. Hypothermia was started as soon as possible following ROSC. Hypothermia was achieved by administering a bolus of cold fluids and applying external cooling using a mattress with Blanketrol® III (Cincinnati Sub-Zero Products, Inc., Sharonville, OH, USA). The target temperature is 32–34 °C for 24 h following ROSC, after which they were rewarmed passively at a rate of 0.5 °C per 2 h. The target temperature must have been reached for MTH to be effective. Children in whom the target temperature range was not reached were classified as "without MTH".

2.2. Data collection

All CA data were retrospectively collected. CA data were derived from ambulance registration forms, clinical medical records, electronic medical records, Patient Data Management System (PDMS), and CA registration forms. The starting point of the time interval of collected data ($T = 0$) was defined as the actual time of ROSC or, if unknown, the time of ICU admission.

The following data were collected: (1) basic patient characteristics (e.g., gender, age, and medical history), (2) CA characteristics (e.g., type of resuscitation (basic life support (BLS)/advanced pediatric life support (APLS)), etiology of arrest, first monitored rhythm, bystander cardiopulmonary resuscitation (CPR), and location), and (3) outcome (IH mortality).

For all children, laboratory values (arterial pH, lactate, and PaO_2) and data regarding MTH (time period before MTH reached, lowest temperature if >34 °C) were retrospectively collected. The laboratory values of all children were automatically recalculated to the value at 37 °C, as this is a standard procedure in our hospital.[18]

2.3. Statistical analysis

The primary outcome measure was IH mortality. The first research question was the association between PaO_2 and IH mortality. The second question was the influence of MTH on this association.

In the first analysis of the first research question, we explored the association between PaO_2 and IH mortality for different cutoff values of hyperoxia (>200, >250 and >300 mmHg) as proposed in the literature.[13–16] Logistic regression analysis was applied to explore the influence of hyperoxia on IH mortality with the highest PaO_2 over the first 24 h. In the multivariable analysis, we calculated an adjusted odds ratio (OR) for pre-selected variables: age, gender, type of resuscitation (BLS/APLS), location, rhythm, lowest pH and highest lactate.

In the second analysis of the first research question, the "area under the curve" (AUC) of PaO_2 was calculated for each patient to determine the influence of the cumulative PaO_2 on IH mortality. The trapezoidal method was used. A minimum of four PaO_2 measurements and an overall time interval of at least 12 h were required to include the arterial measurements and their corresponding time points in the analysis. This resulted in a cumulative PaO_2 over the 0–6 h, 6–24 h, and 0–24 h interval after ROSC. The AUC was corrected for the time in which the PaO_2 was measured, as not all patients had a 24 h time period in which PaO_2 was measured. This resulted in a cumulative PaO_2 per hour, which was converted into the cumulative PaO_2 by multiplying with 6, 18, or 24, respectively.

In univariable logistic regression analyses, the assumption that the AUC of PaO_2 had a linear effect on the logit of IH mortality was tested using the Box–Tidwell test (i.e., an interaction term between the covariate and its natural logarithm was added to the model). If any significant interaction between the covariate and its natural logarithm was present, the linearity assumption was violated. Univariable and multivariable logistic regression analysis (with the same preselected variables as in the cutoff analysis) was applied to evaluate the relationship between cumulative PaO_2 and IH mortality over the three time intervals after ROSC. In advance of the regression analysis, the original AUC variables were rescaled by dividing by 100 to obtain more distinctive results out of the logistic regression analysis.

The same analyses were performed regarding the influence of MTH on the association between PaO_2 and IH mortality.

Univariable comparison of the distribution of patient characteristics and clinical data between survivors and non-survivors was performed by independent sample *t*-tests for normally distributed data, and Mann–Whitney *U* tests for non-normally distributed data. Normality was examined with the Kolmogorov–Smirnov test. Fisher's exact test was used for comparison of dichotomous data. Statistical significance was considered with two-tailed p-value of ≤ 0.05.