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Clinical Paper

Prophylactic antibiotics are associated with a lower incidence of pneumonia in cardiac arrest survivors treated with targeted temperature management☆

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ABSTRACT

Introduction: Prophylactic antibiotics (PRO) reduce the incidence of early-onset pneumonia in comatose patients with structural brain injury, but have not been examined in cardiac arrest survivors undergoing targeted temperature management (TTM). We investigated the effect of PRO on the development of pneumonia in that population.
Methods: We conducted a retrospective cohort study comparing patients treated with PRO to those not receiving PRO (no-PRO) using Northern Hypothermia Network registry data. Cardiac arrest survivors ≥18 years of age with a GCS < 8 at hospital admission and treated with TTM at 32–34 °C were enrolled in the registry. Differences were analyzed in univariate analyses and with logistic regression models to evaluate independent associations of clinical factors with incidence of pneumonia and good functional outcome.
Results: 416 of 1240 patients (33.5%) received PRO. Groups were similar in age, gender, arrest location, initial rhythm, and time from collapse to return of spontaneous circulation. PRO patients had less pneumonia (12.6% vs. 54.9%, $p < 0.001$) and less sepsis (1.2 vs. 5.7%, $p < 0.001$) compared to no-PRO patients. ICU length of stay (98 vs. 100 h, $p = 0.2$) and incidence of a good functional outcome (41.1 vs. 36.6%, $p = 0.19$) were similar between groups. Backwards stepwise logistic regression demonstrated PRO were independently associated with a lower incidence of pneumonia (OR 0.09, 95% 0.06–0.14, $p < 0.001$) and a similar incidence of good functional outcome.
Conclusions: Prophylactic antibiotics were associated with a reduced incidence of pneumonia but a similar rate of good functional outcome.

1. Introduction

Targeted temperature management (TTM) as an element of post-resuscitation cardiac arrest care has been associated with improvements in post-discharge neurological function, favorable discharge disposition, and reduced mortality.[1–4] Despite widespread adoption of TTM in this patient population, our

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understanding of its complications and their impact on clinical outcomes has been slow to evolve.[5–10]

Infections, especially early-onset pneumonia, are common complications after cardiac arrest, with or without TTM, though temperature management is believed to exacerbate this problem.[11–16] A two-center study focusing on early-onset pneumonia reported an incidence of 65% among cardiac arrest survivors, many of whom were treated with TTM.[17] A more recent multicenter randomized study of TTM after cardiac arrest reported pneumonia occurred in 52% of patients treated at 33 °C and 46% of patients at 36 °C ($p = 0.09$).[18] The incidence of pneumonia during TTM after cardiac arrest exceeds the 9–27% incidence in the general medical–surgical critical care population.[19]

Prophylactic antibiotics (PRO) have been shown to reduce the incidence of early-onset pneumonia among comatose patients requiring intubation by up to 64% but there are no prospective studies evaluating the effect of PRO on pneumonia incidence or functional outcome in cardiac arrest survivors treated with TTM.[20,21] The objective of this study was to determine if PRO were associated with a lower incidence of pneumonia and improved functional outcome compared to no prophylactic antibiotics (no-PRO) by retrospectively examining the Northern Hypothermia Network registry and to establish effect size to design a prospective randomized trial.

2. Methods

This retrospective cohort study examined data from the Northern Hypothermia Network, a multinational, web-based registry of post-resuscitation cardiac arrest care with contributions from 38 hospitals in the United States and Europe (Denmark, Germany, Iceland, Luxembourg, Norway, and Sweden). Forty-five percent of the centers were University hospitals, which contributed 73% of the patients. Local institutional review boards approved patient participation, and when required, the national data security systems approved registry participation within each country. The Institutional Review Board at Maine Medical Center approved participation in the registry, as well as this analysis, waiving the need for informed consent.

2.1. Patients

Patients were entered in the registry from October 2004 to October 2008 if they suffered a cardiac arrest, were ≥18 years of age , and had a Glasgow Coma Score (GCS) < 8 at hospital admission, and were treated with TTM at 32–34 °C. Participating institutions treated patients in accordance with their own protocols and were responsible for data integrity; on-site data audits were not performed.

2.2. Data Set

Thirty-eight centers from seven countries contributed patients. Demographics, arrest-related factors, and data definitions followed Utstein guidelines, including the site of cardiac arrest, presence of witnesses, bystander cardiopulmonary resuscitation (CPR), initial rhythm, use of defibrillation, cause of the arrest, and total ischemic time (arrest to return of spontaneous circulation [ROSC]).[22] Treatment data included the use of percutaneous coronary intervention (PCI), method of maintaining hypothermia, desired target temperature, and whether PRO were administered (antibiotics were recorded in the registry as prophylactic if administered by protocol before an infection was diagnosed). The specific antibiotic, dose, frequency, route, or duration was not recorded.

Serious infections were recorded in the registry as pneumonia, sepsis, or other. It was possible for patients to have more than one serious infection. Pneumonia was diagnosed by the treating team and was defined as new or progressive consolidation on a chest radiograph, and at least two of the following findings: fever, leukocytosis, or the presence of purulent tracheobronchial secretions. Registry data did not allow for a distinction between pulmonary aspiration and pneumonia. Oxygenation information and microbiological isolates were unavailable. Outcome data included intensive care unit (ICU) length of stay (LOS), time from arrest to hospital discharge, and cerebral performance category (CPC) scores during a follow-up call or visit 6 months after hospitalization.[23] Follow-up was performed in an outpatient clinic or via telephone by a neurologist, behavioral therapist, cardiologist, intensivist, or research assistant.

2.3. Outcomes

The primary objective of this study was to determine if PRO were associated with a decreased incidence of pneumonia compared to no-PRO. The secondary objective was to determine if PRO were associated with a good functional outcome, defined as a CPC score of 1–2 during the 6-month follow-up.

2.4. Statistical Analysis

Proportions are expressed as absolute numbers and percentages. Continuous data are expressed as mean ± SD, or as median with interquartile range when data were not normally distributed. Differences of proportions were assessed using the Chi-square test. Continuous variables were compared using Student's *t*-test. Backward stepwise logistic regressions were conducted using SAS version 9.3 and were guided by the significance of the calculated Chi-square statistic for effects in the model and the Nagelkerke generalized coefficient of determination. The Hosmer–Lemeshow statistic was used to assess goodness-of-fit of the models and their ability to effectively estimate the outcomes of interest.[24]

Continuous variables entered into the pneumonia model included age (by year), weight (kg), height (cm), body mass index (BMI), time to ROSC (by minute), total ischemic time (by minute), and ICU LOS (by day). Dichotomous variables included PRO, hyperglycemia (serum glucose > 8 mmoL/L for more than 4 h during TTM), treatment with PCI, surface cooling, endovascular cooling, gender (female as control), smoker, witnessed arrest, bystander CPR, initial rhythm (ventricular tachycardia or fibrillation as control), and a history of congestive heart failure, insulin-dependent diabetes mellitus (IDDM), non-insulin-dependent diabetes mellitus (NIDDM), pulmonary disease, kidney disease, or substance abuse. The same variables were entered into the functional outcome model in addition to presence of pneumonia and use of antibiotics as treatment. Variables were selected due to physiological plausibility and their influence on the outcomes of interest in previous studies.[5,6,16,17] Two-tailed tests of significance were used, and $p \leq 0.05$ was considered significant.

3. Results

Data from 1240 patients were evaluated (Table 1). Patients were 61.0 (±15.8) years of age and predominantly male (71.9%). Patients were treated to target temperatures of 32 °C ($n = 73$, 5.9%), 33 °C ($n = 1061$, 85.8%), or 34 °C ($n = 103$, 8.3%). Maintenance of the target temperature was accomplished with surface cooling in 80% of patients. Serious infection information was available for 1206 (97.3%) patients. Pneumonia was the most common infection which occurred in 40.4% of patients.

Antibiotics were prescribed as prophylaxis in 416 (33.5%) patients and for treatment in 604 (50.1%). The distribution of PRO and no-PRO at the 38 contributing centers is presented in Fig. 1.