Original Contribution

Factors associated with pneumonia in post–cardiac arrest patients receiving therapeutic hypothermia ☆

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ABSTRACT

Aim: The aim of this study is to investigate risk factors associated with the development of pneumonia during the first 7 days of admission in survivors of cardiac arrest receiving therapeutic hypothermia.

Methods: A total of 123 patients receiving therapeutic hypothermia after out-of-hospital cardiac arrest between January 2008 and December 2010 were enrolled. Study populations were categorized as "pneumonia present" [P (+)] and "pneumonia absent" [P (−)] contingent upon the development of pneumonia during the first 7 days of admission. Risk factors and outcomes related to development of pneumonia were determined.

Results: Fifty-nine patients (48.0 %) developed pneumonia, and P (+) patients had lower Acute Physiology and Chronic Health Evaluation II score (22 vs 26); longer durations of central venous catheter (8.9 vs 5.1 days), nasogastric tube (11.1 vs 3.8 days), mechanical ventilation (MV) (9.3 vs 3.7 days), and intensive care unit stay (10.0 vs 5.0 days); and higher rates of nasogastric feeding (66.1% vs 35.9 %), tracheostomy (52.5% vs 17.2 %), and postanoxic seizure (62.7% vs 39.1 %). In multivariate analyses, the occurrence of postanoxic seizure (odds ratio, 2.75; 95% confidence interval, 1.06-7.14; $P = .04$) and the length of MV (odds ratio, 1.33; 95% confidence interval, 1.15-1.52; $P < .001$) were independently associated with the development of pneumonia. The development of pneumonia had no significant association with survival (log-rank test, $P = .15$).

Conclusion: Postanoxic seizure and prolonged duration of MV are independently associated with development of pneumonia. It may be helpful that we give more attention to the development of pneumonia in patients with postanoxic seizure and provide prompt diagnosis and treatment of postanoxic seizure.

1. Introduction

Out-of-hospital cardiac arrest (OHCA) survivors frequently have infectious complications. Some authors propose a hypothesis that it is because resuscitation is an extreme stress with a profound decrease of cell-mediated immunity and gastrointestinal ischemia-reperfusion injury in the setting of circulatory arrest may lead to bacterial translocation from the digestive tract into the bloodstream [1-4].

Among the complications, pneumonia is the most common infection [1]. Emergency airway and vascular access, unprotected airway, pulmonary contusion during cardiopulmonary resuscitation (CPR), decreased mental status, and prolonged invasive mechanical ventilation (MV) may increase the risk for pulmonary infection in OHCA survivors [1,5,6].

Recently, comprehensive post–cardiac arrest (CA) care and the implementation of therapeutic hypothermia (TH) as a proven standard therapy have reduced brain injury and improved neurologic outcome in comatose survivors of OHCA [7]. However, prolonged hypothermia is known to decrease immune function by inhibiting the release of proinflammatory cytokines and by suppressing the chemotactic migration of leukocytes and phagocytosis [7,8]. Moreover, some studies have reported that the implementation of TH is associated with an increased incidence and risk of infection, with pneumonia being most common, especially early-onset pneumonia [5,6].

Although TH may increase the incidence of several complications including pneumonia, TH is standard care to reduce ischemic brain injury in OHCA survivors and has been used widely. Thus, this study is designed to investigate risk factors that are associated with the development of pneumonia during the first 7 days of admission in comatose survivors of OHCA patients receiving TH.

2. Methods

2.1. Study population

The setting of the study was a university hospital emergency department (ED) located in Incheon City, South Korea, with an annual

patient volume of approximately 90 000. We conducted a single-center and retrospective cohort study between January 2008 and December 2010. This study was approved by the institutional review board of our hospital.

The study population consisted of patients 18 years or older who were successfully resuscitated after nontraumatic OHCA and then treated with TH. Patients who died within the first 24 hours and with known pneumonia or other infection before CA were excluded from the analysis.

Data were obtained from a prospective registry database including all patients treated in the ED after CA and medical records at our hospital and other hospitals. The collected baseline characteristic variables of patients were sex, age, location of CA, performance of bystander CPR, interval from collapse to basic life support (BLS), interval from collapse to advanced cardiovascular life support (ACLS), interval from BLS to ACLS, interval from collapse to return of spontaneous circulation (ROSC), initial cardiac rhythm, presumed etiology of CA, total dose of epinephrine, number of vasopressors for 48 hours, number of defibrillation events, Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score, initial lactate in ED, and factors associated with TH (target body temperature [BT], cooling method, initial BT on TH start, interval from TH start to target BT, and hypotension during induction of TH).

2.2. Therapeutic hypothermia

If patients were unconscious with Glasgow Coma Scale less than 9 after ROSC, they were treated with TH, admitted to the intensive care unit (ICU), and treated with standard intensive care including invasive monitoring, hemodynamic support, MV, and analgesia sedation. The exclusion criteria of TH were shock despite the use of vasopressors (systolic blood pressure <90 mm Hg), active bleeding, trauma, or possible causes of coma other than CA (head trauma or cerebrovascular accident).

Therapeutic hypothermia was performed by surface (exovascular) or internal (endovascular) cooling techniques as soon as possible after ROSC. The surface cooling technique was performed by the application of a water-circulating hydrogel pad (Arctic Sun; Medivance, Inc, Louisville, CO), and the internal cooling technique was performed by insertion of an intravascular cooling catheter (CoolLine; Alsius Corporation, Irvine, CA) connected to a cooling device (CoolGard 3000; Alsius Corporation) into the right internal jugular vein. The core temperature was measured by rectal probe. The target temperature was 32°C to 34°C, and the duration of maintenance was 24 hours. The rewarming rate was 0.3°C per hour with the same device. Exovascular and endovascular techniques were alternately selected. Continuous midazolam and fentanyl were given for sedation analgesia, and vecuronium was administered to control shivering.

Daily neurologic assessments including motor and brain stem reflex were performed. Portable electroencephalography (EEG) was checked within 7 days after admission at least once, and EEG were interpreted by certified electroencephalographers, at bedside and post hoc, with bipolar and monopolar montages. Postanoxic seizure was diagnosed in the presence of clinical, electrographic, or electroclinical abnormalities suggestive of postanoxic seizure [9,10].

2.3. Pneumonia analysis

According to commonly used criteria, a diagnosis of pneumonia was retained in the presence of clinically compatible findings at auscultation and a new or progressive pulmonary infiltrate on chest x-ray (persistent for at least 48 hours) associated with a positive quantitative culture of distal pulmonary secretion samples. The specimens were obtained from endotracheal aspirates or with a blind protective specimen catheter (significant thresholds: 10^6

colony-forming unit/mL and 10^3 colony-forming unit /mL, respectively). Body temperature and white blood cell count were not considered, as they are affected by hypothermia. Despite a negative quantitative culture, the diagnosis was retained when the previous signs were present with associated purulent endotracheal aspirates and hypoxemia (PaO_2/fraction of inspired oxygen <240) not explained by pulmonary edema, pulmonary embolism, or atelectasis [6].

All data were retrospectively reviewed by 2 investigators to diagnose pneumonia that developed during the first 7 days of admission. Each case of disagreement between prospective diagnosis and retrospective assessment was resolved by consensus between the investigators, with the help of a third expert if necessary.

We divided the study population into 2 groups, "pneumonia present" [P (+)] and "pneumonia absent" [P (−)], contingent upon the development of pneumonia during the first 7 days of admission. We then compared risk factors associated with the development of pneumonia during the first 7 days of admission and outcome between the 2 groups.

We collected the risk factors associated with pneumonia as reported in previous studies and other alleged factors [1,5-7,11-13]. The collected variables were number and duration of central venous catheter (CVC) placements, factors related to nasogastric tube (NG tube), nasogastric feeding, reintubation, tracheostomy, length of MV, length of ICU stay, duration of sedation, blood glucose levels, immunosuppression, age, APACHE II score on ICU admission, and postanoxic seizure. Factors related to CA, CPR, and TH were compared between the 2 groups.

2.4. Assessment of neurologic outcome

At 1 month after the CA, we assessed the clinical neurologic outcome of patients using Cerebral Performance Category (CPC). The *performance categories* were defined as follows: CPC1, "conscious and alert with normal neurologic function or only slight cerebral disability"; CPC2, "conscious with moderate cerebral disability for part-time work in sheltered environment or independent existence"; CPC3, "conscious with severe cerebral disability precluding independent existence"; CPC4, "comatose or in a persistent vegetative state"; and CPC5, "brain dead or death." The patients were then classified into 2 groups based on neurologic outcomes: the "good neurologic outcome" group (CPC1 and CPC2) and the "poor neurologic outcome" group (CPC3-CPC5).

2.5. Statistical analysis

Data were analyzed using SPSS (SPSS version 17.0; SPSS, Inc, Chicago, IL). Continuous data are presented as the median and interquartile range or mean and SD as appropriate. Univariate analysis was performed by using the Mann-Whitney U test or the Student t test for continuous variables or the χ^2 test for categorical variables. All variables found to be significant by univariate analysis (with selected $P < .10$ in the factor analysis), then underwent multivariate logistic regression analysis by the backward stepwise method. Survival curves were determined by the Kaplan-Meier method, and the log-rank test was used to compare curves. All statistical tests were 2 sided, and $P < .05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics of study populations

During the study period, 175 patients were admitted to ICU. Of these 175 patients, 133 patients received TH. Two patients who died within the first 24 hours and 8 patients who already had pneumonia before CA were excluded. Consequently, the remaining 123 patients were enrolled in this study (Fig. 1). Of these patients, 59 patients