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■ Original Article ■

Effect of Antibiotic Prophylaxis on Early-Onset Pneumonia in Cardiac Arrest Patients Treated with Therapeutic Hypothermia

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Background: Infectious complications frequently occur after cardiac arrest and may be even more frequent after therapeutic hypothermia. Pneumonia is the most common infectious complication associated with therapeutic hypothermia, and it is unclear whether prophylactic antibiotics administered during this intervention can decrease the development of early-onset pneumonia. We investigated the effect of antibiotic prophylaxis on the development of pneumonia in cardiac arrest patients treated with therapeutic hypothermia.

Methods: We retrospectively reviewed the medical records of patients who were admitted for therapeutic hypothermia after resuscitation for out-of-hospital cardiac arrest between January 2010 and July 2015. Patients who died within the first 72 hours or presented with pneumonia at the time of admission were excluded. Early-onset pneumonia was defined as pneumonia that developed within 5 days of admission. Prophylactic antibiotic therapy was defined as the administration of any parenteral antibiotics within the first 24 hours without any evidence of infection.

Results: Of the 128 patients admitted after cardiac arrest, 68 were analyzed and 48 (70.6%) were treated with prophylactic antibiotics within 24 hours. The frequency of early-onset pneumonia was not significantly different between the prophylactic antibiotic group and the control group (29.2% vs 30.0%, respectively, p = 0.945). The most commonly used antibiotic was third-generation cephalosporin, and the class of prophylactic antibiotics did not influence early-onset pneumonia.

Conclusion: Antibiotic prophylaxis in cardiac arrest patients treated with therapeutic hypothermia did not reduce the frequency of pneumonia.

Key Words: antibiotic prophylaxis; hypothermia; pneumonia.

Introduction

Infection is a common complication in patients admitted to the intensive care unit (ICU) after out-of-hospital cardiac arrest (OHCA),[1-4] and previous studies have determined that pneumonia was the most common infectious complication.[1,4,5] The lungs are prone to infection due to many factors, such as frequent mechanical complications in the upper airway and thorax after cardiac resuscitation,[6] unprotected airway, decreased mental status, emergent airway access, and prolonged mechanical ventilation.[7]

Therapeutic hypothermia can improve neurological out-

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comes and reduce mortality in resuscitated patients after OHCA[5,8,9] and is recommended for unconscious adult patients that are resuscitated after OHCA.[10] However, hypothermia can impair immune function by inhibiting the release of various inflammatory cytokines, suppressing leukocyte and phagocyte chemotaxis, and inducing insulin resistance and hyperglycemia.[10-12] A few studies have recently suggested that therapeutic hypothermia might increase infectious complications in OHCA patients. [3,13,14]

However, there is limited data on the impact of antibiotic prophylaxis during therapeutic hypothermia and the effect on infection in resuscitated patients. Although a recent study reported that prophylactic antibiotics were associated with a reduced incidence of pneumonia, there was a lack of information about the timing of pneumonia.[15] It is unclear whether prophylactic antibiotics actually reduce early-onset pneumonia in OHCA patients treated with therapeutic hypothermia.

Thus, we performed a retrospective cohort study to examine whether prophylactic antibiotics during therapeutic hypothermia can reduce episodes of early-onset pneumonia. The purpose of this study was to investigate the effect of prophylactic antibiotics on the development of early-onset pneumonia in OHCA patients treated with therapeutic hypothermia.

Materials and Methods

1) Patients and hypothermia management

This retrospective cohort study included all patients admitted to the ICU in Boramae Medical Center after being successfully resuscitated for OHCA and treated with therapeutic hypothermia from January 2010 through July 2015. Patients who died within the first 72 hours and those who presented with pneumonia before hypothermia treatment were not considered in the analysis. Patients with trauma, accidental hypothermia, in-hospital cardiac arrest, and an extra-pulmonary infection that developed within 5 days of admission were excluded. Hypothermia treatment was initiated immediately after resuscitation using a cooling pad (Arctic Sun® 5000, Medivance, Inc, Louisville, CO, USA) during the first 24 hours in order to obtain a target body temperature between 32°C and 34°C. Approval for the study was obtained from the Boramae Medical Center ethics committee (IRB No.16-2015-120/091).

2) Data collections and outcomes

We retrospectively reviewed all medical records and data from our electronic medical records database. The following information was recorded and analyzed: age, sex, clinical parameters, cause of cardiac arrest, duration of cardiopulmonary resuscitation and hypothermia treatment, application of prophylactic antibiotics, development of early-onset pneumonia, length of mechanical ventilation and ICU stay, in-hospital mortality, and neurological outcome. Poor neurological outcome was defined as a cerebral performance category score[16] of 3-5 at hospital discharge.

Prophylactic antibiotic therapy was defined as parenteral administration of any antibiotics within the first 24 hours without any evidence of infection. Antibiotic selection was based on data from microbiological examination of previous studies [1,3,4,13,17], patient medical history, or physician preference. Early-onset pneumonia was considered present when a new pulmonary infiltrate developed on chest radiography and persisted for at least 48 hours in conjunction with presence of purulent tracheobronchial secretion and detection of infiltrate within the first 5 days. Patients were assessed by two independent investigators (two pulmonologists) in order to verify the diagnosis of early-onset pneumonia.

3) Statistical analysis

Proportions are expressed as percentages, and continuous data are expressed as medians with interquartile ranges. The Mann–Whitney U test was used for quantitative variables, and the Chi-square test or Fisher's exact test was used to compare proportions. Binary logistic regression models were used to identify risk factors of early-onset pneumonia. Two-tailed tests of significance were used, and $p < 0.05$ was considered significant. Statistics were calculated using SPSS 18.0 (SPSS Inc., Chicago, IL, USA).

Results

During the study period, 128 patients were admitted to the ICU for therapeutic hypothermia after cardiac arrest. In this

Table 1. Characteristics of patients treated with therapeutic hypothermia: with or without prophylactic antibiotics

	Total (n = 68)	Prophylactic antibiotics (+) (n = 48)	Prophylactic antibiotics (-) (n = 20)	p-value
Age (years)	57.0 [43.8-68.8]	58.5 [39.0-68.0]	54.0 [48.0-70.8]	0.819
Gender (male)	54 (79.4)	37 (77.1)	17 (85.0)	0.532
Smoking				0.360
Current smoker	24 (36.4)	15 (32.6)	9 (45.0)	
Ex-smoker	11 (16.7)	8 (17.4)	3 (15.0)	
Never smoker	31 (47.0)	23 (50.0)	8 (40.0)	
Pack-year	5.0 [0-20.0]	0 [0-22.5]	10.5 [0-20.0]	0.572
Etiology of cardiac arrest				0.228
Cardiac	48 (70.6)	33 (68.8)	15 (75.0)	
Hanging	12 (17.6)	8 (16.7)	4 (20.0)	
Asphyxia	4 (5.9)	3 (6.3)	1 (5.0)	
Respiratory	4 (5.9)	4 (8.3)	0 (0)	
Underlying disease				
Hypertension	36 (52.9)	24 (50.0)	12 (60.0)	0.452
Diabetes	18 (26.5)	13 (27.1)	5 (25.0)	0.859
Chronic renal failure	8 (11.8)	4 (8.3)	4 (20.0)	0.221
Heart failure	6 (8.8)	3 (6.3)	3 (15.0)	0.349
Coronary artery disease	14 (20.6)	7 (14.6)	7 (35.0)	0.097
Cerebrovascular disease	11 (16.2)	9 (18.8)	2 (10.0)	0.487
Malignancy	6 (8.8)	5 (10.4)	1 (5.0)	0.662
Asthma	2 (2.9)	2 (4.2)	0 (0)	1.000
Initial WBC (/μL)	12185 [9555-14902]	12910 [10818-15243]	10380 [8758-12555]	0.011
Initial CRP (mg/dL)	0.14 [0.03-0.50]	0.19 [0.04-0.50]	0.06 [0.02-0.73]	0.327
Witnessed arrest	46 (67.6)	33 (68.8)	13 (65.0)	0.763
Bystander CPR	26 (39.4)	16 (34.8)	10 (50.0)	0.245
No flow time				
Median, minutes	5.0 [0-11.0]	6.0 [0-17.0]	3.0 [0-9.8]	0.144
≥ 5 minutes	38 (55.9)	30 (62.5)	8 (40.0)	0.089
Low flow (minutes)				
Median (minutes)	23.5 [13.5-23.5]	23.0 [15.5-33.5]	24.0 [9.3-30.8]	0.467
≥ 15 minutes	51 (75.0)	37 (77.1)	14 (70.0)	0.539
Time from ROSC to < 34°C (minutes)	124.0 [77.0-270.8]	124.0 [72.0-234.3]	127.0 [78.5-299.5]	0.360
Duration of hypothermia (minutes)	1440 [1418-1483]	1440 [1414-1526]	1446 [1423-1483]	0.755
Seizure	19 (27.9)	13 (27.1)	6 (30.0)	0.807

Data is expressed as number (percentage) or median [IQR].
WBC: white blood cell; CRP: cardiopulmonary resuscitation, ROSC: return of spontaneous circulation.

cohort, 38 patients died within the first 72 hours, 17 patients exhibited pneumonia before hypothermia, and another 5 patients had missing data. Therefore, 68 patients were included in the analysis.

Table 1 shows the baseline characteristics of the 68 patients. The median age was 57 years, and 79.4% (n = 54) were male. Most of the OHCAs were related to cardiac etiology (n = 48, 70.6%), followed by asphyxiation (n = 12,

Table 2. Effect of prophylactic antibiotics

	Total (n = 68)	Prophylactic antibiotics (+) (n = 48)	Prophylactic antibiotics (-) (n = 20)	p-value
Early-onset pneumonia	20 (29.4)	14 (29.2)	6 (30.0)	0.945
Detection of causative micro-organism within 5 days	3/14 (21.4)	2/10 (20)	1/4 (25)	1.000
Duration of mechanical ventilation, days	9.5 [4.0-16.0]	10.0 [4.0-16.0]	8.0 [3-16.8]	0.483
Length of ICU stay, days	12.0 [5.3-18.0]	12.0 [5.3-18.8]	10.0 [4.0-18.0]	0.627
In-hospital mortality	11 (16.2)	7 (14.6)	4 (20.0)	0.719
CPC 3-5	46 (67.6)	34 (70.8)	12 (60.0)	0.384

Data is expressed as number (percentage) or median [IQR].
ICU: intensive care unit; CPC: cerebral performance category.

Table 3. The class of prophylactic antibiotics

	Total (n = 68)	Pneumonia (+) (n = 20)	Pneumonia (-) (n = 48)	p-value
Prophylactic antibiotics	48 (70.6)	14 (70.0)	34 (70.8)	0.945
Ceftriaxone	24 (35.3)	6 (30.0)	18 (37.5)	0.555
Ceftriaxone + azithromycin	1 (1.5)	0 (0)	1 (2.1)	1.000
Ceftriaxone + clindamycin	12 (17.6)	3 (15.0)	9 (18.8)	1.000
Ceftriaxone + levofloxacin	1 (1.5)	0 (0)	1 (2.1)	1.000
Levofloxacin	1 (1.5)	0 (0)	1 (2.1)	1.000
Piperacillin/tazobactam	6 (8.8)	2 (10.0)	4 (8.3)	1.000
Piperacillin/tazobactam + levofloxacin	2 (2.9)	2 (10.0)	0 (0.0)	0.083
Meropenem	1 (1.5)	1 (5.0)	0 (0)	0.294

Data is expressed as number (percentage).

17.6%). Prophylactic antibiotics were initiated in 48 (70.6%) of 68 patients, and these patients were regarded as the prophylactic antibiotic group. Initial white blood cell count was higher in the prophylactic antibiotic group. There were no other significantly different baseline characteristics between the prophylactic antibiotic group and the control group.

Among the 68 patients analyzed in this study, early-onset pneumonia occurred in 29.4% (n = 20), and the in-hospital mortality rate was 16.2% (n = 11) (Table 2). Prophylactic antibiotics did not decrease the rate of early-onset pneumonia (prophylactic antibiotic group, 29.2%; control group, 30.0%; p = 0.945). The most commonly used antibiotic for prophylaxis was third-generation cephalosporin (n = 24, 35.3%), and the class of prophylactic antibiotics did not influence the occurrence of early-onset pneumonia (Table 3). Microbiological samples were collected within 5 days of admission in 35 patients. In general, clinicians ordered a microbiological examination when patients had new infiltrates on chest radiograph or fever after therapeutic hypothermia. Among the 20 of those patients with early-onset pneumonia, causative micro-organisms were detected in 3 patients. Methicillin-resistant *Staphylococcus aureus* was found in 2 patients in the prophylactic antibiotic group, and *Klebsiella pneumoniae* was found in 1 patient in the control group. Additionally, antibiotic prophylaxis did not influence the duration of mechanical ventilation (prophylactic antibiotic group, 10 days; control group, 8 days; p = 0.483) or the length of ICU stay (prophylactic antibiotic group, 12 days; control group, 10 days; p = 0.627). In-hospital mortality and poor neurological outcome were not significantly different between the 2 groups.

Factors associated with early-onset pneumonia were evaluated. We observed a trend towards a longer duration of hypothermia in patients with early-onset pneumonia (early-onset pneumonia, 1,456 [1,440-1,643] min; control, 1,440 [1,385-1,460] min, p = 0.054). A binary regression model showed that a hypothermia duration ≥ 24 hours might be associated with early-onset pneumonia, although this result

Table 4. Factors associated with early-onset pneumonia

	OR	95% CI	p-value
Age, years ≥ 60	0.725	0.251-2.089	0.551
Gender (male)	1.685	0.416-6.831	0.465
Ever-smoker	0.629	0.219-1.810	0.390
Etiology of cardiac arrest			
Cardiac	1		
Non-cardiac	2.000	0.661-6.055	0.220
Initial WBC ≥10,000/ (/μL)	2.833	0.723-11.108	0.135
Initial CRP ≥ 1 mg/dL	2.333	0.620-8.780	0.210
Witnessed arrest	1.645	0.509-5.313	0.405
Bystander CPR	0.422	0.137-1.427	0.172
No flow time ≥ 5min	0.714	0.251-2.036	0.529
Low flow time ≥ 15min	0.489	0.154-1.548	0.224
Duration of hypothermia ≥ 24 hours	3.400	0.873-13.239	0.078
Prophylactic antibiotics	0.961	0.307-3.007	0.945
Seizure	1.615	0.523-4.988	0.404

OR: odds ratio; CI: confidence interval; WBC: white blood cell; CRP: C-reactive protein; CPR: cardiopulmonary resuscitation.

Table 5. Outcome according to development or absence of early-onset pneumonia

	Total (n = 68)	Pneumonia (+) (n = 20)	Pneumonia (-) (n = 48)	p-value
Duration of mechanical ventilation (days)	9.5 [4.0-16.0]	11.0 [5.0-19.8]	8.5 [3.0-16.0]	0.238
Length of ICU stay (days)	12.0 [5.3-18.0]	12.0 [7.3-19.8]	11.5 [4.0-18.0]	0.235
In-hospital mortality	11 (16.2)	2 (10.0)	9 (18.8)	0.487
CPC 3-5	46 (67.6)	15 (75.0)	31 (64.6)	0.403

Data is expressed as number (percentage) or median [IQR].
ICU: intensive care unit; CPC: cerebral performance category.

was not statistically significant (odds ratio [OR], 3.400; 95% confidence interval [CI], 0.873-13.239 p = 0.078) (Table 4). Outcomes including duration of ICU stay and mechanical ventilator support, in-hospital mortality, and neurological outcome were not associated with development of early-onset pneumonia (Table 5).

Discussion

In this study, prophylactic antibiotic therapy during hypothermia treatment in patients that survived after OHCA was not associated with reduced incidence of early–onset pneumonia. Additionally, it did not affect the duration of mechanical ventilation, the length of ICU stay, in-hospital mortality, or poor neurological outcome.[18]

Infectious complications are frequent after cardiac arrest and may be even more frequent after therapeutic hypothermia.[3] Pneumonia is the most common type of infection associated with therapeutic hypothermia.[19,20] Perbet et al.[13] reported that therapeutic hypothermia was the single independent risk factor that increased the risk of early-onset pneumonia (OR, 1.9; 95% CI, 1.28-2.80; p = 0.001). The incidence of early-onset pneumonia has been reported to range from 33% to 65%[3,13,21,22] given the extreme variability of the diagnostic criteria used for this complication. The incidence of early-onset pneumonia in this study was slightly lower than that reported previously. We excluded patients who presented with pneumonia after return of spontaneous circulation but before induction of therapeutic hypothermia, which might have contributed to the lower incidence of early-onset pneumonia.

Currently, there is insufficient data to support the use of prophylactic antibiotic therapy after OHCA, although it is frequently used in practice. In the study performed by Perbet et al.,[13] prophylactic antibiotics, defined as antimicrobial therapy prescribed in the first 12 hours in the absence of pneumonia, were administered to 176 (27%) of patients, and 78% were treated with therapeutic hypothermia. In that study, the incidence of early-onset pneumonia in patients with and without antibiotic prophylaxis was 68.2% (120/176) and 64.3% (299/465), respectively. However, antibiotic prophylaxis did not influence the incidence of early-onset pneumonia in that study (OR, 1.30; 95% CI, 0.88-1.92, p = 0.18). In contrast, another retrospective cohort study reported that prophylactic antibiotics were associated with a reduced incidence of pneumonia in cardiac arrest survivors treated with therapeutic hypothermia.[15] Prophylactic antibiotics were prescribed in 33% of patients, and pneumonia developed in 12.6% of patients with prophylactic antibiotics and 54.9% of patients without (p < 0.001). However, early- and late-onset pneumonia were not distinguished in that study. Thus, the efficacy of prophylactic antibiotics for early-onset pneumonia remains unclear.

Perbet et al.[13] reported that therapeutic hypothermia was the single factor associated with early-onset pneumonia, but that the duration of hypothermia did not affect the development of early-onset pneumonia. Conversely, another study reported higher risk of pneumonia when therapeutic hypothermia was used over a longer period of time (≥ 48-72 hours).[23] Polderman[24] reported that nosocomial infection appeared to be closely linked to a longer duration of hypothermia, especially hypothermia that persisted for > 24 hours. In the current study, patients with early-onset pneumonia were likely to have a longer duration of hypothermia, although this result was not statistically significant. Because the duration of hypothermia could be a confounder of early-onset pneumonia, we performed subgroup analysis with patients whose duration of hypothermia was ≤ 24 hours. Among 38 patients with a duration of hypothermia ≤ 24 hours, the prophylactic antibiotics group showed fewer cases of early-onset pneumonia, although this result was not statistically significant (prophylactic antibiotics group, 21.4%; control group, 30.0%; p = 0.673). Therefore, additional study will be needed to analyze the effect of prophylactic antibiotics on the development of early-onset pneumonia with controlled duration of hypothermia in a large study population.

A previous study performed by Woo et al.[22] showed that postanoxic seizure developed in 48.8% (60/123) of patients treated with therapeutic hypothermia. They reported that postanoxic seizure was an independent risk factor of pneumonia after therapeutic hypothermia, and that aspiration during seizure triggered the occurrence of this complication. The mechanism of early-onset pneumonia after OHCA may be primarily a consequence of the combination of aspiration pneumonitis and aspiration pneumonia.[18] In our study, the incidence of seizure in patients with early-onset pneumonia was higher than in those without, but the difference was not statistically significant. The incidence of seizure in our study was lower than that in the previous study by Woo et al., which might have affected the results.

The present study is the first to specifically evaluate the association of prophylactic antibiotic use during hypothermia and the development of early-onset pneumonia within 5 days of admission. Our data suggest that prophylactic antibiotic therapy during hypothermia treatment in patients that survive OHCA does not reduce development of pneumonia. Additionally, because the etiology of arrest might affect the outcome, we performed subgroup analysis after excluding patients with cardiac arrest of noncardiac etiology. Among 48 patients with cardiac etiologies, the proportion of patients that developed early-onset pneumonia was not statistically different between the prophylactic antibiotics group and the control group (prophylactic antibiotics group, 24.2%; control group, 26.7%; p = 0.857).

However, there were several limitations to our study. First, it was a single-center retrospective study with only 68 patients, which could account for the lack of statistical power. Next, the definition of early-onset pneumonia is currently debated, and diagnosis of early-onset pneumonia after OHCA can be difficult due to confounding factors, such as sepsis-like syndrome after cardiopulmonary resuscitation and influences of therapeutic hypothermia.[25] In this study, early-onset pneumonia was defined based on the timing of onset in relation to cardiac arrest, with a previous study classifying early-onset pneumonia as pneumonia that develops within 3 to 5 days after cardiac arrest.[18] Because there is not currently a diagnostic consensus, we modified our study to adhere to the previously used definition.[18,26]

However, our findings are still limited because our analysis was not restricted to bacteriologically-proven infection. Further studies to evaluate the effect of prophylactic antibiotics on early-onset pneumonia based on a microbiologically-confirmed diagnosis are needed. Third, selection bias may have occurred. Prophylactic antibiotics were more likely to be administered in patients who had leukocytosis, which is affected by hypothermia as well as infection or inflammatory processes. Finally, we could not evaluate aspiration of oro-pharyngeal or gastric contents, which has been considered a mechanism of early-onset pneumonia after OHCA. [18]

In conclusion, prophylactic antibiotic therapy during hypothermia treatment in patients admitted to the ICU after OHCA did not reduce the incidence of early-onset pneumonia. Because of the limitations to this study, additional well-designed prospective studies are needed to further evaluate the influence of prophylactic antibiotics on early-onset pneumonia.

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