American Journal of Emergency Medicine 33 (2015) 1166–1170

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Original Contribution

Hypoxic hepatitis in survivors of out-of-hospital cardiac arrest☆

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ARTICLE INFO

Article history:
Received 4 April 2015
Accepted 13 May 2015

ABSTRACT

Introduction: Hypoxic hepatitis (HH) is commonly observed in out-of-hospital cardiac arrest (OHCA) survivors. The objective of this study was to investigate the incidence, clinical courses, and outcomes of as well as predisposing factors for HH in OHCA survivors.

Methods: The study was based on a registry of cardiac arrest cases from 2009 to 2012 at a tertiary university hospital. We assessed patients' serum aminotransferase levels on return of spontaneous circulation (ROSC) and at 6, 12, 24, 48, and 72 hours postarrest. Hypoxic hepatitis was defined as a rapid increase in serum aminotransferase that reached at least 20 times the upper limit of normal. The patients were classified into 2 groups: the HH group and the non-HH group; we then analyzed the outcomes of the HH group. Independent predisposing factors to HH in this cohort were identified.

Results: Of a total of 535 OHCA cases, 148 patients were enrolled in this study. Hypoxic hepatitis was identified in 13.5% (n = 20) of them. Serum aminotransferase rapidly increased in the first day after return of spontaneous circulation. Of the patients who developed HH, 5 (25%) survived to hospital discharge, and none of these individuals had good neurologic outcomes (Glasgow-Pittsburgh cerebral performance categories 1 and 2). Using multivariate logistic regression, we found that the no flow time was independent predictors of HH (odds ratio, 1.085 [95% confidence interval, 1.027-1.146]; $P = .003$).

Conclusions: Hypoxic hepatitis occurred frequently in survivors of OHCA. The no flow time was an independent risk factor for HH, which was significantly related to death and poor neurologic outcomes.

1. Introduction

Hypoxic hepatitis (HH) is frequently observed in critically ill patients and is associated with poor outcomes [1]. In HH, hypoperfusion with subsequent ischemia and passive congestion of the liver, severe systemic arterial hypoxemia, and/or impaired hepatic oxygen extraction induces centrilobular liver cell necrosis [2-5]. According to Henrion et al [2,6], a diagnosis of HH could be clinically assumed if the following 3 conditions are met: (1) an appropriate clinical setting of cardiac, respiratory or circulatory failure; (2) a sharp increase in serum aminotransferase levels that reach at least 20 times the upper limit of normal; (3) the exclusion of other causes of acute liver cell necrosis, particularly viral or drug-induced hepatitis.

Hypoxic hepatitis is commonly observed in out-of-hospital cardiac arrest (OHCA) survivors. During cardiac arrest, ischemic tissue damage occurs because of a loss of blood supply. In addition, reperfusion injuries often develop in the first several hours after the return of spontaneous circulation (ROSC). Ischemia and reperfusion injuries may affect not only the brain but also all of the organs. Finally, cardiac arrest is an important cause of HH. The 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation (CPR) and Emergency Cardiovascular Care recommend the following for patients resuscitated from cardiac arrest: "optimize cardiopulmonary function and vital organ perfusion" and "reduce the risk of multiple organ injury and support organ function" [7]. However, there are little clinical data on extracerebral organ injuries in patients who achieved ROSC. In particular, there is little information on the postresuscitation states associated with HH. We examined patients' serial aminotransferase levels during the 72 hours after arrest and evaluated the clinical courses of these patients.

The aim of this study was to identify the incidence, clinical courses, and outcomes of as well as predisposing factors for HH in OHCA patients who achieved ROSC.

2. Methods

This was a single-center retrospective, observational, registry-based study that took place from January 1, 2009, to December 31, 2012. Cardiopulmonary resuscitation and post–cardiac arrest care were performed in accordance with the American Heart Association's guidelines [7], and the treatment team provided sufficiently prolonged life support to patients who did not regain consciousness. Out-of-hospital cardiac arrest registry data were collected prospectively

☆ Conflicts of interest: The authors do not have any financial or other relationships that might pose any conflicts of interest.

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http://dx.doi.org/10.1016/j.ajem.2015.05.008
0735-6757/

according to the Utstein Style guidelines at a teaching hospital in South Korea. The institutional review board of the Catholic University of Korea, Seoul Saint Mary's Hospital, approved the study protocol before data analysis.

All adult (age >19 years) patients who achieved ROSC after resuscitation from OHCA and survived for at least 24 hours after ROSC were considered eligible for this study. To eliminate nonhypoxic causes of acute liver injury, exclusion criteria included traumatic cardiac arrest patients, diagnoses of other known causes of acute hepatitis or hepatocellular injury (viral hepatitis infection, ingestion of hepatotoxic toxins or drugs, and other causes), and malignant infiltration.

Out-of-hospital records included demographic information, such as sex, age, and underlying diseases. Resuscitation variables included first monitored heart rhythms, the presence of witnesses, bystander CPR performance, total number of defibrillations, cumulative amount of epinephrine given, no flow time (time from collapse to chest compression), and low flow time (time from chest compression to ROSC). The use of therapeutic hypothermia, hospital mortality, and neurologic outcomes at discharge were evaluated. Neurologic outcomes were assessed using the Glasgow-Pittsburgh cerebral performance categories (CPC) assessment and were dichotomized as either good neurologic outcomes (CPC 1 and 2) or poor neurologic outcomes (CPC 3-5) [8].

Serum levels of aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), total bilirubin, lactate dehydrogenase (LDH), creatine phosphokinase (CPK), and lactate and renal function tests were investigated. Serum samples from patients were collected serially immediately after ROSC and 6, 12, 24, 48, and 72 hours after ROSC. In patients with HH, we investigated the time required to return to normal levels of serum aminotransferase. Hypoxic hepatitis was defined as a rapid increase in serum aminotransferase as levels reaching at least 20 times the upper limit of normal with no other obvious explanation for the increase other than HH [2,8-12]. Based on the definition of HH, the patients were classified into 2 groups: the HH group and the non-HH group.

The categorical variables were expressed as the numbers and the percentages, and the continuous data were expressed as the means ± SD or the medians and interquartile range (IQR) according to a normal distribution. Comparisons of categorical variables between groups were made using either the χ^2 test or Fisher exact test as appropriate. In addition, continuous variables were compared between groups using *t* tests or Mann-Whitney *U* test. Predictive factors were evaluated using multivariate logistic regression analyses and odds ratios; 95% confidence intervals (CIs) were estimated in the logistic regression models. Bivariate associations between aminotransferase and other laboratory values were evaluated using Pearson correlation coefficient. The above statistical analyses were performed using SPSS 16 (SPSS Chicago, IL). A $P < .05$ was considered statistically significant.

Table 2
Multivariate logistic regression analysis of independent risk factors for hypoxic hepatitis

Variables	Odds ratio for hypoxic hepatitis	95% CI	*P*
Nonshockable rhythm	3.969	0.856-18.405	.078
No flow time	1.085*	1.027-1.146	.003

* Per minute.

3. Results

During the enrollment period, a total of 535 OHCA cases were identified, 259 (35.1%) of which were achieved ROSC. Of these patients, 92 who died within 24 hours after ROSC, 9 who experienced traumatic cardiac arrest, 4 who ingested toxins or drugs, and 6 who had malignant infiltration were excluded. In total, 148 patients were enrolled in the present study.

The baseline characteristics, resuscitation variables, survival discharges, and neurologic outcomes of the patients are summarized in Table 1. The mean patient age was 54.8 ± 16.4 years; 107 patients (72.3%) were male, and 41 patients (27.7%) were female. A total of 108 patients (73.0%) had a witness present during cardiac arrest, and 70 patients (47.3%) received basic life support from bystanders. In the first monitored rhythm, shockable rhythm was identified in 45 patients (30.4%). Patients had a median interval from collapse to chest compression of 3.5 minutes (IQR, 0.0-9.0 minutes), and the median low flow time was 23.0 minutes (IQR, 14.0-31.0 minutes). Therapeutic hypothermia was performed in 118 patients (79.7%). Fifty-six patients (37.8%) died before discharge, and 95 patients (64.2%) had a CPC of 3 to 5.

Hypoxic hepatitis was identified in approximately 13.5% (n = 20) of the patients. To evaluate the risk factors for HH, we categorized patients into an HH group and a non-HH group (n = 128) and examined the characteristics of each group (Table 1). The percentage of patients with a shockable rhythm was significantly lower in the HH group than in the non-HH group (10.0% and 33.6%, respectively, $P = .037$). The no flow time was significantly longer in the HH group compared with the

Table 1
Baseline demographic and clinical characteristics of the overall cohort and comparison between the HH and non-HH groups

	Total cohort (n = 148)	HH group (n = 20)	Non-HH group (n = 128)	*P*
Male, n (%)	107 (72.03)	11 (55.0)	96 (75.0)	.104
Age, mean ± SD, y	54.8 ± 16.4	51.3 ± 19.0	55.3 ± 16.0	.311
Underlying disease				
AMI, n (%)	13 (8.8)	3 (15.0)	10 (7.8)	.386
Angina pectoris, n (%)	8 (5.4)	0 (0.0)	8 (6.2)	.599
CHF, n (%)	10 (6.8)	3 (15.0)	7 (5.5)	.136
Arrhythmia, n (%)	7 (4.7)	0 (0.0)	7 (5.5)	.594
Hypertension, n (%)	44 (29.7)	3 (15.0)	42 (32.8)	.124
DM, n (%)	28 (18.9)	2 (10.0)	26 (20.3)	.368
Lung disease, n (%)	14 (9.5)	2 (10.0)	12 (9.4)	1.000
Renal disease, n (%)	12 (8.1)	1 (5.0)	11 (8.6)	1.000
Shockable rhythm, n (%)	45 (30.4)	2 (10.0)	43 (33.6)	.037
Witnessed, n (%)	108 (73.0)	12 (60.0)	96 (75.0)	.180
Bystander CPR, n (%)	70 (47.3)	6 (30.0)	64 (50.0)	.147
Defibrillation, median (IQR)	1.0 (0.0-2.0)	0.0 (0.0-1.0)	1.0 (0.0-2.0)	.085
Epinephrine, median (IQR), mg	2.0 (1.0-4.0)	3.0 (1.0-6.5)	2.0 (1.0-4.0)	.123
No flow time, median (IQR), min	3.5 (0.0-9.0)	9.0 (0.3-20.8)	3.0 (0.0-7.0)	.023
Low flow time, median (IQR), min	23.0 (14.0-31.0)	25.0 (18.3-36.0)	22.0 (12.3-30.8)	.137
Therapeutic hypothermia, n (%)	118 (79.7)	13 (65.0)	105 (82.0)	.130
Hospital mortality, n (%)	56 (37.8)	15 (75.0)	41 (32.0)	<.001
Poor neurological outcome, n (%)	95 (64.2)	20 (100.0)	75 (58.6)	<.001

Abbreviations: AMI, acute myocardial infarction; CHF, congestive heart failure; DM, diabetes mellitus.