Association between inflammatory markers and survival in comatose, resuscitated out-of-hospital cardiac arrest patients

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ABSTRACT

Objectives: Prognostication after out-of-hospital cardiac arrest (OHCA) remains challenging. The inflammatory response after OHCA has been associated with increased mortality. This study investigates the associations and predictive value between inflammatory markers and outcome in resuscitated OHCA patients.

Design: The study is based on post hoc analyses of a double-blind controlled trial, where resuscitated OHCA patients were randomized to receive either exenatide or placebo. Blood was analyzed for levels of inflammatory markers the day following admission. Primary endpoint was time to death for up to 180 days. Secondary endpoints included 180-day mortality and poor neurological outcome after 180 days, defined as a cerebral performance category (CPC) of 3 to 5.

Results: Among 110 included patients we found significant associations between higher leucocyte quartile and increasing mortality in univariable analysis (OR 2.6 (95%CI 1.6–4.2), p < .001), as well as in multivariable analysis (OR 2.1 (95%CI 1.1–4.0), p = .02). A significant association was found between higher neutrophil quartile and increasing mortality in univariable analysis (OR 3.0 (95%CI 1.8–5.0), p < .001) as well as multivariable analysis (OR 2.4 (95%CI 1.2–4.6), p = .01). Leucocyte and neutrophil levels were predictive of poor outcome after 180 days with area under the receiver operating characteristics curves of 0.79 and 0.81, respectively. We found no associations between CRP and lymphocyte levels versus outcome.

Conclusions: Total leucocyte count and neutrophil levels measured the first day following OHCA were significantly associated with 180-day all-cause mortality and may potentially act as early predictors of outcome.

Clinical trial registration: www.clinicaltrials.gov, unique identifier: NCT02442791

Introduction

Despite improvements during the past decades, mortality after resuscitated out-of-hospital cardiac arrest (OHCA) remains high [1,2].

The high mortality after resuscitated OHCA is attributed to the post-cardiac arrest syndrome (PCAS) consisting of 4 interacting components: 1) a systemic inflammatory response similar to the systemic inflammatory response syndrome (SIRS) observed in other critical illness such as sepsis, 2) hypoxic cerebral injury, 3) myocardial dysfunction, and 4) the persistent precipitating pathology causing the cardiac arrest [3]. The inflammatory response is thought to be triggered by prolonged global ischemia during cardiac arrest followed by reperfusion after return of spontaneous circulation (ROSC). An increase in pro-inflammatory cytokines is seen as early as 3h after cardiac arrest [4,5]. Furthermore, a pronounced inflammatory response after OHCA may intensify the overall severity of combined PCAS and has been associated with increased mortality [5–7].

Prognostication of outcome after OHCA is challenging and currently, a multimodal prognostication approach after 72h from admission is recommended. Markers that would provide prognostic information at an earlier time point would be of great benefit, both to specify treatment and to provide information for relatives [8].

Most studies on inflammation after OHCA focus on circulating cytokines [6,7,9–11] and data regarding the prognostic value of readily available inflammation markers are sparse. Accordingly, the objective of the present study was to assess the value of readily and clinically accessible inflammatory markers for prediction of outcome after OHCA in patients undergoing contemporary ICU treatment. Secondarily, the objective was to assess the association between inflammatory markers and the magnitude of cerebral injury assessed by the biomarker neuron-specific enolase (NSE).
Methods

Study design

This study is a single center post hoc study of a double-blind, controlled clinical trial, where adult comatose patients resuscitated from OHCA were randomized to a 6h and 15 min infusion of the glucagon-like peptide-1 analog exenatide or placebo. All patients received targeted temperature management (TTM) at 36°C for 24h and were rewarmed at a maximum rate of 0.5°C. The study protocol and primary results have been published previously [12,13]. In this study, a total of 110 patients from one of two participating tertiary heart centers were included.

Blood was collected the day following admission and analyzed for levels of C-reactive protein (CRP), total leucocyte count, neutrophils, and lymphocytes. Blood samples were measured on standard hospital laboratory equipment using Sysmex system (Sysmex Denmark, Sysmex Deutschland GmbH, Germany). We chose a priori to include biomarker levels the day following admission, as early prognostic information would be of clinical value.

The primary endpoint was time to death for up to 180 days. Secondary endpoints included 180-day mortality and poor neurological outcome after 180 days, defined as a cerebral performance category (CPC) of 3 to 5 [14]. CPC was assessed by telephone at 180 days adjudicated by 2 intensive care consultants [12]. Further, the magnitude of cerebral injury was assessed as the geometric area under the NSE curve measured daily from 24 to 72h after admission. Levels of NSE have previously been demonstrated to be a strong marker of mortality and poor neurological outcome in resuscitated OHCA patients [15–17].

Statistical analysis

Throughout, continuous variables are presented as mean ± standard deviation if normally distributed, and as median (25th percentile – 75th percentile) if otherwise. Categorical variables are presented as frequency (percentage).

To assess the associations between levels of inflammatory biomarkers and mortality, we applied the Kaplan-Meier estimator after stratification of patients based on biomarker quartiles the day following admission. Differences in mortality between quartiles were analyzed by application of the log-rank test. In case of a significant log-rank test, we applied univariable logistic regression models to obtain the odds ratio (95% confidence interval) for 180-day all-cause mortality per increase in biomarker quartile. Further, we applied multivariable logistic regression models adjusting for potential confounders, including treatment allocation, age, sex, initial shockable rhythm, time to ROSC, and percutaneous coronary intervention to assess the odds ratio (95%CI) for 180-day all-cause mortality per increase in biomarker quartile. To assess the associations between biomarker quartiles and poor neurological outcome multivariable logistic regressions models adjusting for sex, primary rhythm, time to ROSC, and admission lactate level were applied. We applied receiver operating characteristics curves to assess the predictive value of each biomarker for prediction of poor neurologic outcome after 180 days, defined as a CPC score of 3 to 5. Moreover, to assess the overall predictive value neutrophil as well as leucocyte levels were added to a multivariable model with known risk markers including age, sex, primary rhythm, time to ROSC, and admission lactate. Finally, we applied linear regression models to assess the associations between inflammatory markers and the area under the NSE curve. The area under the NSE curve was calculated as the geometric area under the curve of measurements daily from 24 to 72h after admission. The area under the NSE curve was used as a marker of the magnitude of cerebral injury, as previously applied [12,17]. As the distribution of NSE levels were substantially skewed, log-transformation (natural logarithm) was applied to approximate normal distribution prior to analysis. A significance level of 0.05 was applied throughout, and SAS version 9.4 was used for all analyses.

Ethics

The study was approved by the regional ethics committee (reference no. H-4-2013-185) and the Danish Health and Medicines Authority (EudraCT no. 2013-004311-45). The trial was conducted in accordance with national legislation and with the Helsinki Declaration. Informed consent was provided from two independent medical doctors not involved in the trial, the next of kin and from the patient’s general practitioner. Furthermore, in patients regaining consciousness, informed consent was obtained from the patient too. Further details have been previously published [12].

Results

Baseline characteristics

Of 112 randomized patients, two were excluded; one withdrew consent and one had a missing identity at time of study drug initiation. Of 110 included patients, 68 (62%) had a good neurological outcome defined as a CPC score of 1–2 while 42 (38%) had a poor neurological outcome defined by a CPC score of 3–5 180 days after OHCA (Table 1). Of 42 patients with a poor neurological outcome, 38 (90%) died. Patients with a good neurological outcome were younger and less likely to have diabetes. Further, patients with a good neurological outcome had more favorable cardiac arrest characteristics compared to patients with poor neurological outcome (Table 1).

Inflammatory markers and mortality

A total of 6 (5%) patients died prior to blood sampling the day following admission. No differences in inflammatory markers were seen between the two allocation groups. Accordingly, further analyses were based on the pooled patient population.

Patients were stratified into quartiles based on their biomarker value the day following admission (Table 2). There was an incremental increase in 180-day mortality per increasing leucocyte quartile, with a mortality of 8% in the lowest quartile increasing to a mortality of 67% in the highest quartile (p<0.001, Figure 1). There was an
Table 1. Baseline characteristics stratified by neurological outcome after 180 days.

| Demographics                                      | Good neurological outcome | Poor neurological outcome | p Value |
|---------------------------------------------------|---------------------------|---------------------------|---------|
| Demographics                                      | n = 68 (62%)              | n = 42 (38%)              |         |
| Male sex, n(%)                                    | 60 (88)                   | 31 (74)                   | 0.05    |
| Age, mean ± SD                                    | 58 ± 10                   | 65 ± 11                   | <0.001  |
| Medical History                                   |                           |                           |         |
| Congestive heart failure                          | 3 (4.4)                   | 4 (9.5)                   | 0.42    |
| Ischemic heart disease                            | 10 (15)                   | 9 (21)                    | 0.36    |
| Arterial hypertension                             | 25 (37)                   | 19 (45)                   | 0.38    |
| Nephropathy                                        | 2 (2.9)                   | 1 (2.4)                   | 0.86    |
| Asthma or COPD                                     | 7 (10)                    | 6 (14)                    | 0.53    |
| Diabetes                                          | 5 (7.4)                   | 9 (21)                    | 0.03    |
| Active malignancy                                 | 3 (4.4)                   | 1 (2.4)                   | 1.0     |
| Alcohol abuse                                     | 5 (7.4)                   | 8 (19)                    | 0.06    |
| Drug abuse                                        | 5 (7.4)                   | 2 (4.8)                   | 0.59    |
| Previous TIA or stroke                            | 3 (4.4)                   | 2 (4.8)                   | 1.0     |
| Previous myocardial infarction                    | 5 (7.4)                   | 5 (12)                    | 0.50    |
| Cardiac arrest characteristics, n(%)             |                           |                           |         |
| Cardiac arrest at home                            | 30 (44)                   | 32 (78)                   | 0.002   |
| Witnessed cardiac arrest                          | 63 (93)                   | 36 (86)                   | 0.33    |
| Bystander CPR, n(%)                               | 56 (82)                   | 26 (63)                   | 0.02    |
| Automated external defibrillator used, n(%)       | 13 (19)                   | 3 (7.1)                   | 0.10    |
| Shockable primary rhythm, n(%)                    | 66 (97)                   | 35 (83)                   | 0.01    |
| Times to treatment, minutes, median (IQR)         |                           |                           |         |
| Time to basic life support                        | 1 (1–2)                   | 2 (1–5)                   | 0.002   |
| Time to advanced life support                     | 6 (4–9)                   | 7 (4–10)                  | 0.43    |
| Time to return of spontaneous circulation         | 15 (10–22)                | 25 (16–37)                | <0.001  |
| Clinical characteristics on admission             |                           |                           |         |
| ST-elevation myocardial infarction, n(%)          | 44 (65)                   | 24 (57)                   | 0.43    |
| Temperature, °C, median (IQR)                     | 35.7 (35.2–36.2)          | 35.2 (34.7–36.0)          | 0.06    |
| pH, median (IQR)                                  | 7.27 (7.23–7.32)          | 7.26 (7.17–7.31)          | 0.30    |
| Lactate (mmol/L), median (IQR)                    | 2.7 (1.4–4.9)             | 4.5 (2.2–11)              | 0.007   |

Good neurological outcome: Cerebral performance category of 1 or 2.
Poor neurological outcome: Cerebral performance category of 3 to 5.

Table 2. Biomarker levels the day following admission stratified in quartiles.

| Biomarker level, n | Q1   | Q2   | Q3   | Q4   |
|--------------------|------|------|------|------|
| CRP level, n = 97  | 1–18 | 18–33| 33–61| 61–195|
| Leucocyte level, n = 97 | 6.2–9.8 | 9.8–13 | 13–17 | 17–42 |
| Neutrophil level, n = 84 | 3.2–7.1 | 7.1–10 | 10–13 | 13–27 |
| Lymphocyte level, n = 84 | 0.30–1.2 | 1.2–1.6 | 1.6–2.1 | 2.1–4.1 |

There was an incremental increase in 180-day mortality per increasing neutrophil quartile, with a mortality of 5% in the lowest quartile increasing to a mortality of 67% in the highest quartile (plog-rank < 0.001, Figure 1). There was an association between higher neutrophil quartile and increasing mortality in univariable analysis (OR 3.0 (95%CI 1.8–5.0), p < .001), as well as in multivariable analysis (OR 2.4 (95%CI 1.2–4.6), p = .01).

There were no associations among inflammatory markers and cerebral injury.

Predictive value of inflammatory markers

The area under the receiver operating characteristics curves (AUCROC) was 0.52 for CRP, 0.79 for leucocytes, 0.81 for neutrophils, and 0.54 for lymphocytes for prediction of poor neurological outcome after 180 days.

A multivariable model with known risk markers increased AUCROC to 0.91, which was not significantly higher (p = .61). Adding neutrophil levels to the model increased AUCROC to 0.92, which was not significantly higher (p = .41).

Inflammatory markers and neurological outcome

In univariable analysis, increasing leucocyte and neutrophil quartiles were both associated with an increased risk of poor neurological outcome after 180 days (OR 2.5 (95%CI 1.6–4.0), p < .001 and OR 3.0 (95%CI 1.5–5.1), p < .001, Table 3). These associations remained significant in multivariable analyses (OR 2.2 (95%CI 1.2–4.1), p = .02 and OR 2.7 (95%CI 1.4–5.2), p = .005, Table 3). No associations between CRP or lymphocyte quartiles and poor neurological outcome were found (Table 3).

Inflammatory markers and cerebral injury

Higher levels of leucocytes and neutrophils were associated with higher levels of the area under the NSE curve, which was used as a marker of the magnitude of cerebral injury.
There was no association between levels of CRP or lymphocytes and NSE (Figure 2).

**Discussion**

We demonstrated that high levels of leucocytes and neutrophils the day following admission for OHCA are significantly associated with 180-day mortality even after adjustment for known potential confounders. Furthermore, increasing levels of leucocytes and neutrophils were associated with increasing levels of NSE, which was applied as a marker of the magnitude of cerebral injury.

The systemic inflammatory response seen shortly after ROSC is characterized by an intense increase in various cytokines and inflammatory markers [5]. However, data supporting the prognostic value of leucocyte levels is inconsistent. A recent observational study including 321 cardiac arrest patients showed a significantly higher level of total leucocytes at admission in non-survivors [18]. A retrospective cohort study from 2010 demonstrated no difference in leucocyte levels the day following initiation of TTM in survivors versus non-survivors in 34 patients after cardiac arrest [19].

However, Böttiger et al. found a significantly increased concentration of elastase, a specific marker of *in vivo* polymorph nuclear leucocyte (PMN) activation, during CPR in patients who did not achieve ROSC as compared to patients who achieved ROSC [20]. While increased leucocyte levels may simply be a non-causal risk marker of poor outcome, leucocytes have been suggested to be involved in reperfusion injury by obstructing capillaries due to their size and to cause tissue damage because of the release of oxygen-free radicals and release of the proteolytic enzyme elastase [20,21].

We found that leucocyte and neutrophil levels were predictors of poor outcome. This is in contrast to one previous study, which did not find any difference in neutrophil levels or leucocyte levels between survivors and non-survivors in 95 patients after OHCA or IHCA, either during TTM or after rewarming [22]. However, leucocyte and neutrophil levels did not significantly improve the predictive value of a multivariable model with known risk markers for outcome which is in agreement with the COMMUNICATE study [18]. While leucocyte and neutrophil levels did not improve the overall predictive value of a multivariable model, being in the lowest quartile was associated with a very low risk for poor outcome.
of 8% and 5%, respectively. As such, leucocyte and neutrophil levels may act as early identifiers of low risk patients.

A high level of CRP has previously not been predictive of outcome with sufficient precision for clinical use, which is in accordance with our findings [9,11,19,23]. This may be due to the fact that CRP is a secondary organ derived inflammatory marker, which typically reaches peak values 3–4 days following cardiac arrest [19] whereas our data were collected the day following admission. We chose to include inflammatory markers drawn the day following admission, but the optimal timing of potential predictive biomarkers could be tested in future trials.

The biomarker NSE is a small protein present in cells of neuroectodermic origin including neurons. A previous study suggests that NSE is released into the blood stream at a rate proportional to the degree of neurological damage [24]. Previously, NSE has been shown as strong predictor of mortality and poor neurological outcome after OHCA [16,25]. Our results suggest an association between elevated levels of leucocytes and neutrophils with NSE levels, suggesting an association between the inflammatory response and cerebral injury as part of the PCAS. Whether this association is causal remains unknown.

Our results support the association between the magnitude of the inflammatory response and increased mortality after OHCA. Further, our findings suggest that easily obtainable total leucocyte and neutrophil levels may be potential early predictors of outcome. The challenge with prognostication after OHCA is to reach a false-positive rate very close to zero in order to prevent withdrawal of care. Contemporary guidelines suggest a multimodal prognostication strategy to avoid false-positive results [26], and it is unlikely that leucocyte and neutrophil levels can challenge this strategy. However, our results suggest that leucocyte and neutrophil levels may potentially help to identify low risk patients, with the important caveat that the results should be validated in prospective cohorts with identification of potential cut-off values. To determine the potential causality of the inflammatory response severity with outcome, further prospective studies targeting inflammation with fast-acting anti-inflammatory interventions would be required.

The current study has some general limitations that need to be addressed. Primarily, this includes post hoc analyses of a clinical trial, and accordingly, results should be viewed as hypothesis generating only. Secondly, the sample size is too small for a reasonable estimation of relevant cutoff concentrations for the biomarkers included. Furthermore, differential count with assessment of neutrophil and lymphocyte levels were only completed in 81% of eligible patients, which introduces a risk of bias for those biomarkers. Finally, we were not able to account for all baseline differences due to the risk of overfitting with limited data available.

Conclusion

Total leucocyte count and neutrophil levels measured the first day following OHCA were significantly associated with
180-day all-cause mortality, even after adjustment for confounding factors, and may potentially act as early predictors of outcome. Leucocyte count did however not improve the predictive power of a model based on clinical variables and resuscitation measures.

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