Neuroprotective Effects of the Glucagon-Like Peptide-1 Analog Exenatide After Out-of-Hospital Cardiac Arrest

A Randomized Controlled Trial

BACKGROUND: In-hospital mortality in comatose patients resuscitated from out-of-hospital cardiac arrest (OHCA) is ≈50%. In OHCA patients, the leading cause of death is neurological injury secondary to ischemia and reperfusion. Glucagon-like peptide-1 analogs are approved for type 2 diabetes mellitus; preclinical and clinical data have suggested their organ-protective effects in patients with ischemia and reperfusion injury. The aim of this trial was to investigate the neuroprotective effects of the glucagon-like peptide-1 analog exenatide in resuscitated OHCA patients.

METHODS: We randomly assigned 120 consecutive comatose patients resuscitated from OHCA in a double-blind, 2-center trial. They were administered 17.4 μg exenatide (Byetta) or placebo over a 6-hour and 15-minute infusion, in addition to standardized intensive care including targeted temperature management. The coprimary end points were feasibility, defined as initiation of the study drug in >90% patients within 240 minutes of return of spontaneous circulation, and efficacy, defined as the geometric area under the neuron-specific enolase curve from 24 to 72 hours after admission. The main secondary end points included a composite end point of death and poor neurological function, defined as a Cerebral Performance Category score of 3 to 5 assessed at 30 and 180 days.

RESULTS: The study drug was initiated within 240 minutes of return of spontaneous circulation in 96% patients. The median blood glucose 8 hours after admission in patients receiving exenatide was lower than that in patients receiving placebo (5.8 [5.2–6.7] mmol/L versus 7.3 [6.2–8.7] mmol/L, $P<0.0001$). However, there were no significant differences in the area under the neuron-specific enolase curve, or a composite end point of death and poor neurological function between groups. Adverse events were rare with no significant difference between groups.

CONCLUSIONS: Acute administration of exenatide to comatose patients in the intensive care unit after OHCA is feasible and safe. Exenatide did not reduce neuron-specific enolase levels and did not significantly improve a composite end point of death and poor neurological function after 180 days.

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- out-of-hospital cardiac arrest
- neuroprotection

Clinical Perspective

What Is New?

- This trial demonstrated that administration of the glucagon-like peptide-1 analog exenatide to comatose patients after out-of-hospital cardiac arrest is feasible and safe.
- We found no effect of exenatide on levels of neuron-specific enolase, as a marker of neurological injury, during the first 72 hours after admission.

What Are the Clinical Implications?

- Neurological injury remains the leading cause of death in resuscitated out-of-hospital cardiac arrest patients.
- Currently, the only strategy to mitigate this is targeted temperature management, and additional strategies for neuroprotection are needed.
- Although several pharmacological interventions have been tested and found to have limited effect, preclinical and clinical data suggested beneficial effects of glucagon-like peptide-1 analogs for mitigating ischemic injury.
- The present trial suggests that exenatide for out-of-hospital cardiac arrest patients administered after reperfusion has limited neuroprotective effects; however, other pharmacological interventions can be tested in a similar setup.

The overall mortality after out-of-hospital cardiac arrest (OHCA) is ≈90%.[1] Although the in-hospital mortality after successful resuscitation and admission to an intensive care unit (ICU) has decreased in the past decade, 30% to 50% of admitted patients do not survive until hospital discharge.[2,3] The leading cause of death in OHCA patients is anoxic brain injury.[4,5] Although the mechanisms causing neurological damage are complex, they involve ischemia, reperfusion injury, and apoptosis, all of which result in tissue degeneration and corresponding loss of neurological function.[6] Preclinical data suggest that these deleterious processes can be modified for up to 6 hours.[7] Therefore, identification of new treatment options for active neuroprotection in addition to targeted temperature management (TTM) will be intuitively beneficial.

Glucagon-like peptide-1 (GLP-1) analogs are approved for the treatment of type 2 diabetes mellitus. Furthermore, they have been suggested to have anti-inflammatory properties and complex neuroprotective effects.[8] For example, in animal models, GLP-1 analogs ameliorated neurodegenerative disorders such as Alzheimer disease,[9,10] Parkinson disease,[11,12] and amyotrophic lateral sclerosis.[13,14] Moreover, GLP-1 analogs were reported to reduce the final infarct volume in stroke models,[15,16] and to reduce the infarct size in a porcine model of acute myocardial infarction (MI) and reperfusion.[17] In humans, treatment with the GLP-1 analog exenatide initiated before revascularization after MI resulted in increased myocardial salvage.[18] Furthermore, in patients with a short duration of ischemia, exenatide treatment resulted in a smaller final infarct size.[19] These findings have been confirmed by other trials.[20,21] Importantly, in these studies, exenatide was administered to acutely ill patients having ST-segment–elevation MI (STEMI), with no increased risk of adverse events, including hypoglycemia and pancreatitis.

Neuron-specific enolase (NSE), a widely used biomarker, is a glycoprotein present in neurons and is released from dying neurons into the blood stream, where it crosses the blood-brain barrier.[22] Consequently, the concentration of NSE in blood is correlated to the amount of dying neurons, ie, the size of a given cerebral insult.[22] Serial NSE measurements have been shown to be solid predictors of poor outcome after OHCA.[23]

The present trial investigated the neuroprotective effects, using NSE release as a predictor, of the GLP-1 analog exenatide administered within 4 hours after return of spontaneous circulation (ROSC) in comatose patients resuscitated from OHCA.

METHODS

This was a randomized double-blind clinical trial. Patients were recruited from the intensive care units of 2 tertiary heart centers. The complete trial protocol, including the rationale, design, and statistical analyses plan, has been published previously.[24]

Participants

Adult (aged ≥18 years) unconscious OHCA patients in whom the presumed cause of arrest was cardiac, and who had sustained ROSC, defined as ROSC for >20 minutes, irrespective of the initial rhythm, were screened consecutively. Main exclusion criteria included unwitnessed asystole, suspected or confirmed acute intracranial bleeding or stroke, >240 minutes from ROSC to randomization, temperature on admission <30°C, systolic blood pressure <80 mm Hg despite vasopressor or inotropic or mechanical circulatory support, and pregnancy.[24]

Intervention

Eligible patients were randomly assigned 1:1 to receive an infusion of either 17.4 μg exenatide (Byetta, Lilly) or placebo over 6 hours and 15 minutes. The study drug was infused in a solution of 248.5 mL of isotonic NaCl mixed with 1.5 mL of 20% human albumin. The placebo kit did not contain the study drug, whereas 25 μg of exenatide (Byetta, Lilly) was added to the active study drug kit. The personnel involved in care of the patients were kept blinded. The intervention period commenced as soon as possible after randomization. The study drug was administered over 6 hours and 15 minutes. The dosage and infusion rate of exenatide was based on laboratory data and a previous randomized trial of exenatide for cardioprotection in STEMI patients.[18] Details of the

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intervention, including the preparation of study drug, can be found in the trial protocol.[24] The patients received standardized intensive care treatment throughout the intervention period. All patients were sedated with propofol and fentanyl to a Richmond Agitation Sedation Scale of ≤–4, and received TTM at 36°C for 24 hours by using an automated device. Subsequently, the patients were rewarmed with a maximum rate of 0.5°C per hour, and sedation was tapered at 37°C. If patients remained unresponsive, fever control was continued for at least 72 hours post-ROSC. A standardized protocol for prognostication was applied according to international guidelines.[25] Active life support was maintained for at least 108 hours. Other clinical decisions were at the discretion of the treating physicians.

End Points

The coprimary end points were: (1) Feasibility, defined as the initiation of the trial intervention within 4 hours from ROSC in >90% patients; (2) Efficacy, defined as the geometric area under the NSE curve from 24 to 72 hours.

NSE was measured at 24 hours (NSE24), 48 hours (NSE48), and 72 hours (NSE72) after admission, and the geometric area under the NSE curve from 24 to 72 hours was used as the primary end point (12×NSE24+24×NSE48+12×NSE72, using the trapezoidal rule).[24] Determination of NSE was performed according to the Cobas 8000, e602 module, using an electrochemiluminescence immunoassay (ECLIA) kit (Roche Diagnostics). The measuring range was 0.1 to 370 μg/L, and between-run precisions at 11 μg/L and 85 μg/L were 8% and 7%, respectively.

The secondary end points included the geometric area under the S100 calcium-binding protein B (S100b) curve, absolute NSE and S100b values at 48 hours, and peak levels of creatine kinase MB and troponin T from 0 to 24 hours. Determination of S100b was performed according to the Cobas 8000, e602 module, using an ECLIA kit (Roche Diagnostics). The measuring range was 0.02 to 39 μg/L, and the between-run precision at 0.09 μg/L and 3.3 μg/L was 6%.

In addition, the secondary end points included vital status at 7 days and at least 180 days (end of study) after OHCA, assessments of the modified Rankin Scale[26] score and Cerebral Performance Category[27] at 90 days, the cumulated incidence of serious adverse events related to the study drug,[24] and a composite outcome of all-cause mortality and poor neurological function (defined as an modified Rankin Scale score of 4–6 at 30 days).

The tertiary end points included telephone-based assessment of Cerebral Performance Category and modified Rankin Scale at 180 days and vital status at 180 days stratified for cause of death (adjudicated by 2 intensive care consultants blinded to the treatment allocation).[24]

The final follow-up concluded on June 1, 2016.

Monitoring and Approvals

The trial was conducted in accordance with the standards for good clinical practice, and monitored by the independent good clinical practice units at Bispebjerg Hospital, Denmark and Region Southern Denmark. A Data Safety Monitoring Committee surveyed the study with full access to the study database on request. The study protocol and any amendments, including written information and consent forms, were formally approved by the regional ethics committee (ie, the institutional review board) before the initiation of the trial (reference no. H-4-2013-185). The Danish Health and Medicines Authority approved the study (EudraCT no. 2013-004311-45). The full protocol is available at www.clinicaltrials.gov (unique identifier: NCT02442791), and a design article and statistical analysis plan has been published.[24]

Statistical Analyses

Because no difference in feasibility between groups was expected, we chose to power the study according to differences in the area under the NSE curve. Previous studies have found NSE values of ≈20 μg/L at 72 hours, and we expected a median area under the NSE curve from 24 to 72 hours of 1200 μg×48 hours/L, assuming a standard deviation of 30%.[24] Previously, a cutoff value of 33 μg/L has been suggested to distinguish patients with a poor versus a good outcome with a false-positive rate approaching zero, and, based on this, we chose a minimal clinically relevant difference of 20% in NSE levels.[24] The α-level was set at 0.025 for the coprimary end point. The study was powered to detect a 20% difference in the area under the NSE curves with a power of 90%, if 50 patients were randomly assigned to each treatment group. We anticipated that 10% of NSE values would be missing and therefore planned to include 120 patients in total. The trial analyses were performed on a modified intention-to-treat population, defined as all patients randomly assigned with valid informed consent.

Differences in demographics and clinical values at admission between the 2 treatment groups were analyzed by the χ^2 test (for categorical data), the independent sample *t* test (for continuous data), or the independent sample *t* test following logarithmic transformation or the nonparametric Mann-Whitney test (for skewed data), as appropriate. Crude survival data stratified to the treatment groups were plotted on a Kaplan-Meier curve, and differences were tested with the log-rank test. Crude hazard ratios were reported, and an additional analysis adjusted for site, sex, age, shockable primary rhythm, and time to ROSC was performed using proportional hazard models.

Subgroup analyses were performed according to the following predefined design variables: age above/below median, sex, shockable primary rhythm, shock at admission, diagnosed with acute MI, and time to ROSC above/below median.

All tests were 2-sided; a significance level of 0.025 was applied to the primary end points, whereas 0.05 was applied to all other tests. We expected >5% missing NSE and S100b values, and, as per the statistical analysis plan,[24] >5% missing data in NSE and S100b values resulted in multiple imputations by chained equations, with generation of 10 imputations by 50 iterations (the variables used for imputations were site, shockable primary rhythm, bystander cardiopulmonary resuscitation, time to ROSC, STEMI, lactate on admission, treatment allocation, S100b values, NSE values, outcome at 180 days, and time to death). Nonnormally distributed variables were $\log_{10}$ transformed before imputing. The *t* tests were then performed on imputed data sets, and mean and median values were obtained from these analyses. The median value and interquartile range for each variable in each data set were determined, and the mean median value and mean interquartile range for

all 10 data sets were reported. SAS software, version 9.4, was used for the statistical analyses. Multiple imputations were performed with R software, version 3.2.2, using the mice package.[28,29]

RESULTS

We screened 288 patients admitted after OHCA between June 2014 and November 2015, of whom 134 met the inclusion criteria (Figure 1). A total of 120 (90%) patients were enrolled. One patient withdrew consent, and 1 patient was dropped because of missing identity. Hence, our modified intention-to-treat population consisted of 118 patients; 60 patients were allocated to exenatide and 58 patients were allocated to placebo (Figure 1). Randomization was well balanced with no difference in baseline characteristics between the 2 intervention groups (Table 1). The median temperature between 2 and 24 hours after admission ranged from 36.0°C to 36.1°C in both groups (online-only Data Supplement Figure I).

Intervention and Feasibility

Infusion of the study drug was initiated in 114 patients (97%, Figure 1). One patient receiving exenatide died of circulatory collapse, and 1 patient receiving placebo died of cerebral herniation because of a rapidly expanding subdural hematoma during the intervention. Thus, the infusion was completed in 112 patients. The median time from ROSC to study drug initiation was 162 (120–201) minutes, and the study drug was initiated within 240 minutes from ROSC in 110 (96%) patients. The median time from ROSC to initiation of the study drug was similar in patients receiving exenatide and placebo (155 [118–195] minutes versus 182 [128–203] minutes, P=0.16).

Biochemical Outcomes

The median blood glucose 8 hours after admission was 5.8 (5.2–6.7) mmol/L in patients receiving exenatide in comparison with 7.3 (6.2–8.7) mmol/L in patients receiving placebo (P<0.0001). A total of 105 (94%) eligible patients had at least 1 valid NSE measurement and thus constituted the population in which the highest NSE value and the area under the NSE curve from 24 to 72 hours could be estimated. NSE was measured and analyzed in 94 (84%), 83 (75%), and 62 (57%) eligible patients at 24, 48, and 72 hours after target temperature, respectively.

There was no significant difference in the median area under the NSE curve between the group allocated to exenatide versus placebo (1307 [884–2093] μg×48 hours/L versus 1192 [888–1930] μg×48 hours/L, P=0.46; Figure 2A). The mean median level of area under the NSE curve in imputed data sets was 1357 (815–2173) μg×48 hours/L in patients receiving exenatide in comparison with 1209 (797–2006) μg×48 hours/L in patients receiving placebo. Statistical significance was not reached in any of the 10 imputed data sets of the comparisons between groups. There were no significant differences in the maximum NSE level measured between 24 and 72 hours or any single time point (Figure 2A). The use of multiple imputations did not affect these results, and no significant differences in NSE were found between groups. The median area under the NSE curve in patients who died within 180 days was 2003 (1824–6384) μg×48 hours/L in comparison with 990

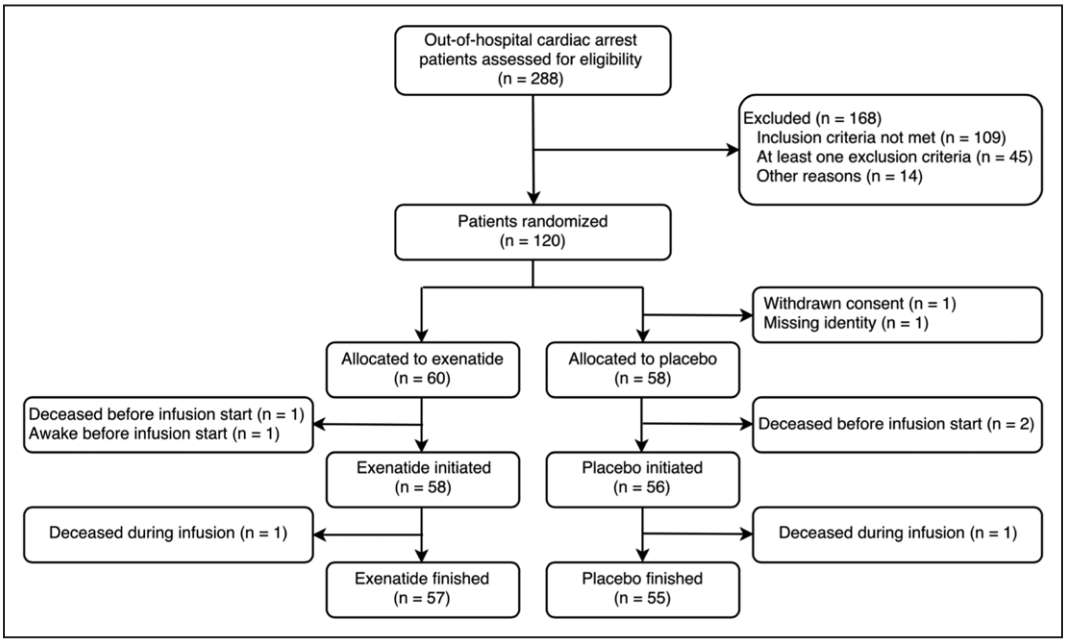

Figure 1. CONSORT flowchart displaying trial profile.

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Table 1. Baseline Characteristics

	Exenatide n=60	Placebo n=58	*P* Value
Demographics			
Male sex, n (%)	51 (85)	47 (81)	0.57
Age, mean (SD)	59 (12)	62 (11)	0.10
Medical history, n (%)			
CPC 1–2	59 (98)	58 (100)	0.58
Congestive heart failure	5 (8)	2 (4)	0.44
Ischemic heart disease	9 (15)	13 (22)	0.30
Arterial hypertension	23 (38)	26 (45)	0.47
Nephropathy	2 (3)	1 (2)	1.0
Asthma or COPD	5 (8)	8 (14)	0.34
Diabetes mellitus	5 (8)	10 (17)	0.15
GLP-1 treatment	0 (0)	1 (2)	0.49
Active malignancy	2 (3)	2 (3)	1.0
Alcohol abuse	9 (15)	5 (9)	0.28
Drug abuse	5 (8)	2 (4)	0.44
Previous TIA or stroke	3 (5)	2 (4)	1.0
Previous myocardial infarction	6 (10)	5 (9)	0.80
Previous percutaneous coronary intervention	6 (10)	4 (7)	0.74
Previous coronary artery bypass grafting	3 (5)	5 (9)	0.49
Previous valve surgery	1 (2)	2 (3)	0.62
Implantable cardioverter-defibrillator	1 (2)	1 (2)	1.0
Cardiac arrest characteristics, n (%)			
Cardiac arrest at home	35 (59)	33 (57)	0.69
Witnessed cardiac arrest	55 (92)	52 (90)	0.71
Bystander CPR	46 (78)	42 (78)	0.33
Shockable primary rhythm	52 (87)	55 (95)	0.13
Time to treatment, min, median (IQR)			
Time to basic life support	1 (1–3)	1 (1–2)	0.35
Time to advanced life support	7.5 (4.5–11)	5.0 (3.0–8.5)	0.05
Time to return of spontaneous circulation	18 (11–29)	18 (13–27)	0.88
Clinical characteristics on ICU admission			
ST-segment–elevation myocardial infarction, n (%)	34 (57)	37 (64)	0.43
Glasgow Coma Score, median (IQR)	3 (3–3)	3 (3–3)	0.13
Temperature, °C, mean±SD	35.5±1.0	35.6±0.79	0.44
Serum pH, mean±SD	7.23±0.13	7.25±0.11	0.47
Serum lactate, mmol/L, mean±SD	4.6±4.0	4.7±4.4	0.77
Serum creatinine, μmol/L, median (IQR)	106 (87–124)	110 (91–131)	0.25
Serum blood glucose, mmol/L, median (IQR)	11 (8.4–13)	11 (8.8–15)	0.64

COPD indicates chronic obstructive pulmonary disease; CPC, Cerebral Performance Category; CPR, cardiopulmonary resuscitation; GLP-1, glucagon-like peptide-1; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation; and TIA, transient ischemic attack.

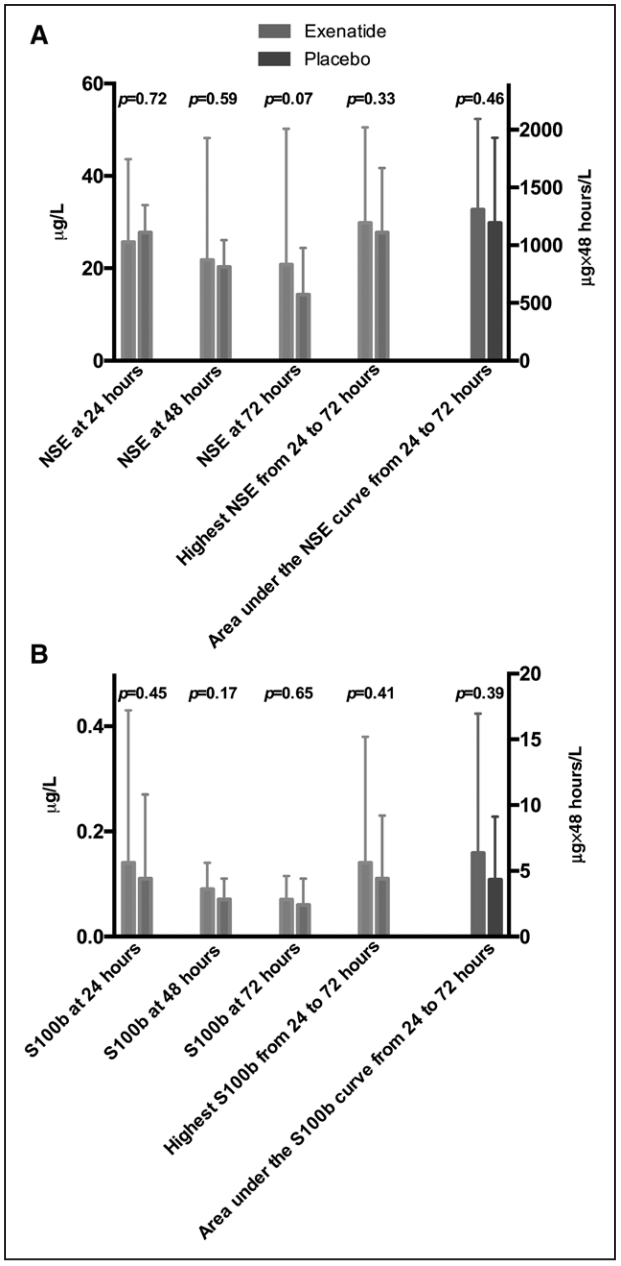

Figure 2. The median NSE (A) and S100b (B) values with error bars displaying interquartile ranges.
Differences between the allocation groups were tested with the nonparametric Mann-Whitney test. NSE indicates neuron-specific enolase; and S100b, S100 calcium-binding protein B.

(770–1464) µg×48 hours/L in patients surviving to 180 days ($P<0.0001$).

S100b was measured simultaneously with NSE. A total of 98 (88%), 82 (75%), and 61 (56%) patients had a valid S100b measurement at 24, 48, and 72 hours, respectively. There were no significant differences in any single S100b value, maximum S100b value from 24 to 72 hours, or the area under the S100b curve from 24 to 72 hours between the 2 groups (Figure 2B). There were no significant differences in any other prespecified outcomes.[24]

Clinical Outcomes

Three patients died in the period from randomization to intervention. Two more patients died during the intervention period of 6 hours and 15 minutes, one in each allocation group (Figure 1). The median time to follow-up was 268 days, with no patients lost.

Within 7 days, 8 (13%) patients allocated to exenatide and 10 (17%) patients allocated to placebo died ($P=0.56$, Table 2). After 180 days, 17 (28%) patients allocated to exenatide and 22 (38%) patients allocated to placebo had died ($p_{log\text{-}rank} = 0.31$, Figure 3). The crude hazard ratio for exenatide versus placebo was 0.73 (95% confidence interval, 0.40–1.3; $P=0.31$). The hazard ratio for exenatide after adjustment for potential prespecified confounders was 0.62 (95% confidence interval, 0.32–1.2; $P=0.15$).

The allocation groups did not differ significantly with regard to the composite outcome of death and poor neurological function assessed after 30, 90, and 180 days (Table 2).

In a logistic regression model, the crude and adjusted odds ratios for poor neurological outcome (Cerebral Performance Category 3–5) were 0.76 (95% confidence interval, 0.36–1.6; $P=0.48$) and 0.54 (95% confidence interval, 0.18–1.6; $P=0.27$) for exenatide versus placebo, respectively.

Table 2. Composite Outcome of Death and Poor Neurological Function Assessed as a CPC >2 and a mRS Score >3 at 30, 90, and 180 Days After OHCA

Time of Assessment	Modality, n (%)	Exenatide n=60	Placebo n=58	*P* Value
7 days				
	Mortality	8 (13)	10 (17)	0.56
30 days				
	Mortality	15 (25)	21 (36)	0.19
	CPC score ≥3	23 (38)	25 (43)	0.60
	mRS score ≥4	21 (35)	23 (41)	0.48
90 days				
	Mortality	16 (27)	22 (38)	0.19
	CPC score ≥3	19 (32)	25 (43)	0.20
	mRS score ≥4	19 (32)	24 (41)	0.27
180 days				
	Mortality	17 (28)	22 (38)	0.27
	CPC score ≥ 3	20 (33)	23 (40)	0.48
	mRS score ≥ 4	20 (33)	23 (40)	0.48
Follow-up				
June 1, 2016	Mortality	19 (32)	23 (40)	0.36

CPC indicates Cerebral Performance Category; mRS, modified Rankin Scale; OHCA, out-of-hospital cardiac arrest.

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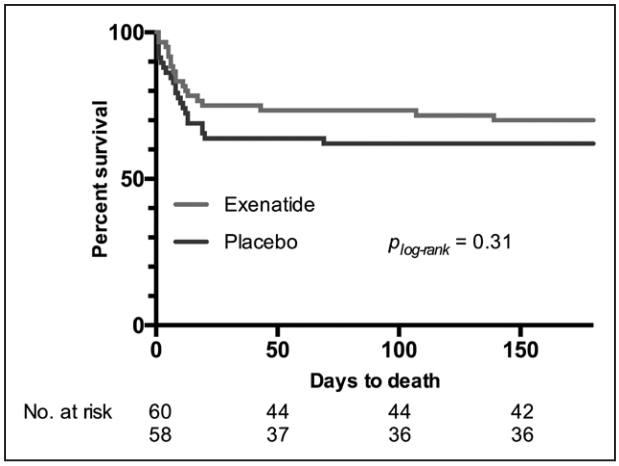

Figure 3. Survival rate from out-of-hospital cardiac arrest to 180 days stratified by treatment allocation.

Of 17 deceased patients in the exenatide group, 13 (76%) died of a neurological cause in comparison with 14 (64%) of 22 deceased patients in the placebo group (*P*=0.57).

Treatment group allocation had no effect on mortality and predefined design variables (age, sex, shockable rhythm, shock at admission, diagnosed acute MI, and time to ROSC).

Adverse Events

One or more of the predefined serious adverse events[24] occurred in 32 (53%) patients allocated to exenatide and in 35 (60%) patients allocated to the placebo group (*P*=0.44). There were no differences in the median highest measured serum amylases at admission between the patients allocated to exenatide versus placebo (95 upper normal limit [UNL] [65–191] versus 98 UNL [64–152]; *P*=0.34) (Table 3). No cases of pancreatitis were observed. Of the patients receiving exenatide, 3 (5%) had at least 1 blood glucose measurement <3 mmol/L in comparison with 1 (2%) patient receiving placebo (*P*=0.62) (Table 3). All events of hypoglycemia were reversed with an infusion of glucose with no long-term sequelae.

DISCUSSION

In this 2-center randomized trial, exenatide infusion was initiated in >90% of the randomly assigned eligible patients within 240 minutes after ROSC. The area under the NSE curve between 24 and 72 hours after admission did not differ between the exenatide and placebo groups. Moreover, exenatide was not associated with an increased risk of adverse events.

Exenatide, a GLP-1 analog, has been approved for the treatment of type 2 diabetes mellitus, and regulates the plasma glucose through glucose-dependent insulin secretion and by decreasing glucagon release.[30] GLP-1 analogs protect the myocardial and brain cells against ischemia and reperfusion injury–related cell death through complex intracellular signaling pathways.[31–33] The ongoing neuronal death after OHCA involves a combination of necrosis and apoptosis, which occurs during the first few hours to several days after cardiac arrest and restoration of perfusion. Although the mechanisms remain largely unknown, intracellular glutamate-mediated calcium intake leading to increased oxidative stress and mitochondrial dysfunction has been recognized as a major part of these processes.[34] The blood-brain barrier is permeable to exenatide. In vitro studies on human neuronal cells have shown that exenatide provided protection from glutamate-dependent cell death and oxidative stress.[35] The timeframe in which neuronal apoptosis can be modified in vivo remains unknown; however, animal studies have suggested a window of up to 6 hours.[7] The HACA trial (Hypothermia After Cardiac Arrest) demonstrated a neuroprotective effect of therapeutic hypothermia with the target temperature being reached 8 hours after ROSC.[36] Clinically, previous studies have shown the benefits of exenatide on myocardial salvage[18] and left ventricular function[20] in STEMI patients. In these previous studies, exenatide was administered before the primary percutaneous coronary intervention and, thus, before the coronary reperfusion. In the present study, exenatide was administered early in the ICU following ROSC, therefore, after cerebral reperfusion and possibly after coronary reperfusion. We believe that a neuroprotective agent should be administered as soon as possible after ROSC or even, if logistically feasible, during resuscita-

Table 3. Incidence of Adverse Events Stratified for Treatment Allocation

Adverse Event, n (%)	Exenatide n=60	Placebo n=58	*P* Value
Within 24 h from admission			
Death	1 (2)	5 (9)	0.11
Lowest blood glucose <3 mmol/L	3 (5)	1 (2)	0.62
Within 7 days from admission			
Death between 24 and 48 h from admission	1 (2)	1 (2)	1.0
Death between 48 and 72 h from admission	0 (0)	1 (2)	0.49
Serum amylases >3 UNL*	5 (8)	2 (3)	0.44
Renal replacement therapy	3 (5)	6 (10)	0.32
Ventricular arrhythmia†	4 (7)	7 (12)	0.36
Pneumonia and sepsis	7 (12)	5 (9)	0.58

*Upper reference limit (120 U/L).
†Ventricular tachycardia, ventricular fibrillation, or torsade de pointes.
UNL indicates upper normal limit.

tion. However, a window of opportunity of several hours may still exist,[7] consistent with the treatment plan applied in the present study.

NSE is a glycolytic enzyme present in cells of neuroectodermic origin including neurons, and is released into the bloodstream at a rate proportional to the degree of neuronal damage.[22] Recently, NSE was proved to be a reliable risk marker of poor neurological outcome in the comatose patients resuscitated from OHCA, with an area under the operating receiver curve of 0.85,[23] which is in agreement with the present study. In addition, NSE may be a useful surrogate marker in smaller clinical trials,[24,37] with the advantage that NSE measurements can be blinded to the treating physicians and staff. Furthermore, the geometric area under the NSE curve has the advantage of combining serial measurements as a marker of the total NSE release from the neuronal degradation over time.[22] However, we did not observe a reduction of NSE levels in the patients treated with exenatide in comparison with placebo.

The present trial found no significant differences in the secondary end points including mortality, poor neurological function, or S100b levels. Despite these neutral findings, the study did indicate a nonsignificant absolute difference of 10% in 180-day mortality in favor of exenatide. This nonsignificant difference was predominant in the first 30 days. The absolute difference in mortality was 4% at 7 days and 11% at 30 days. There was only a minor difference in mortality from neurological injury between the 2 allocation groups (76% versus 64%, n=1). It suggests that the effect of exenatide on mortality, if present, is not caused by neuroprotection, but may be associated with other factors including anti-inflammation, glucose-dependent glucose regulation, and cardioprotection.

OHCA is a severe condition with a high mortality and morbidity, in particular, in patients not regaining consciousness quickly following resuscitation. Recently, the TTM trial (Target Temperature Management After Cardiac Arrest) randomly assigning 939 OHCA patients to TTM at either 33°C or 36°C showed a 180-day mortality of 47%[38] in comparison with 33% in the present trial. The 2 studies had similar inclusion and exclusion criteria.[39] However, a comparison of the medical history showed that the TTM participants had slightly more prearrest comorbidity[38] than in this study. Furthermore, with regard to the cardiac arrest and admission characteristics, the TTM trial participants had less bystander cardiopulmonary resuscitation (73% versus 78%), less shockable primary rhythm (80% versus 91%), and less frequent STEMI (40%–42% versus 60%) than the present study participants had.[38] Irrespective of the differences in baseline characteristics, patients were enrolled consecutively with an exceptionally high inclusion rate for an acute study. Therefore, the reported baseline characteristics should be considered representative of the OHCA population in our region, and the presented mortality is similar to the mortality in historic cohorts from our hospital.[40] Some features of the enrolled population may result in more favorable outcomes than in the general European and North American populations, which should be considered if the results are applied to other populations. The majority of patients died of neurological injury (64%), cardiogenic shock (17%), and multiorgan failure (7%), which corresponded well with the causes of death found in previous case series and trials.[5,38]

Our analyses did not reveal any significant differences in adverse events between the 2 treatment groups, suggesting that exenatide can be safely administered to comatose OHCA patients. Acknowledging the limited statistical power in the present study, the combination of decreased mortality and low adverse event rate was intriguing. There is a potential for investigating this trend in a larger cohort, potentially with exenatide being initiated intra-arrest, or soon after ROSC, to validate the mortality reduction observed in the present underpowered study, limiting the risk of a type 2 error.

Some potential limitations should be considered when interpreting the results of this trial. The trial was underpowered to detect the differences in mortality and poor neurological function. Instead, a surrogate marker of brain injury (ie, NSE) was used. The difference in mortality between the treatment groups occurred very early, even before the serial blood sampling could be finished. This may have introduced a bias that could weaken the application of NSE as a surrogate end point. Furthermore, considering the similar rates of neurological death between the treatment groups, NSE may have been a suboptimal surrogate marker of outcome in this trial. The physiological effects of exenatide outside those related to diabetes mellitus remain poorly understood, and we have been unable to find an explanation in the literature for the higher variance of NSE in the exenatide group versus the placebo group (Figure 2A). Furthermore, only 105 (94%) eligible patients had at least 1 valid NSE measurement. The missing data were a result of challenges with having blood samples taken outside the regular time slots for blood draws in our ICU. We had anticipated this might be a challenge and thus predefined the use of multiple imputations to handle the missing values. This did not modify the finding of no difference in NSE values between the 2 groups. In addition, the study drug was administered after reperfusion (ie, after ROSC and, in most cases, after percutaneous coronary intervention), which could have reduced the potential organ-protective effects of the treatment. Several factors may have contributed to the delay in administration of the study drug. First, one of the predefined exclusion criteria was persistent shock, and thus some patients needed to be stabilized in the ICU before randomization. Second, Danish legislation

on clinical trials enrolling incapacitated patients in a pharmaceutical trial requires consent from 2 legal guardians (defined as medical doctors not involved in the care of the patient or in the study group), thus delaying randomization. We chose to administer the study drug after hospital admission because our region's emergency services are run by different providers, which could have made it difficult to include all eligible patients. Furthermore, administration of the study drug would have been difficult to accomplish in a blinded fashion in the prehospital setting. Future studies could aim to administer exenatide earlier, if logistically feasible. Despite these potential limitations, this was a double-blind, randomized controlled trial enrolling consecutive comatose OHCA patients; therefore, the risk of bias and confounding should be limited.

In conclusion, acute administration of exenatide to comatose patients in the ICU after OHCA is feasible and appears safe. Exenatide did not reduce the NSE levels and did not improve a composite end point of death and poor neurological function after treatment for 180 days.

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DISCLOSURES

None.

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FOOTNOTES

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Neuroprotective Effects of the Glucagon-Like Peptide-1 Analog Exenatide After Out-of-Hospital Cardiac Arrest: A Randomized Controlled Trial

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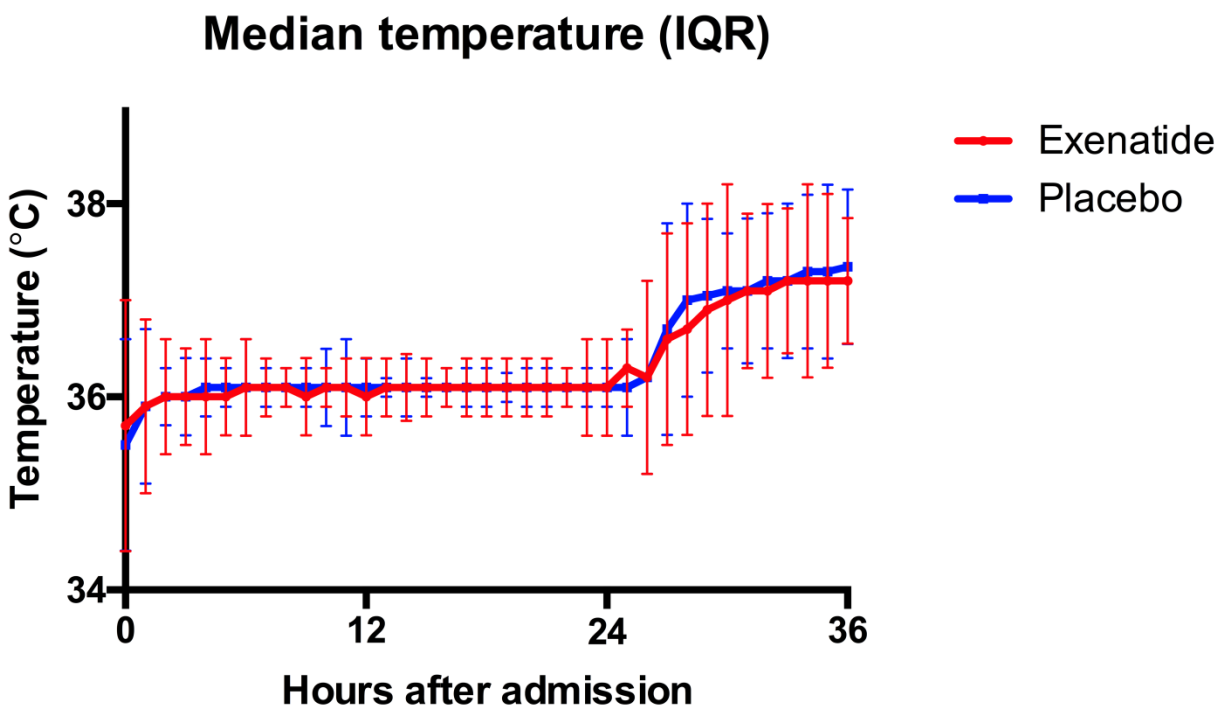
SUPPLEMENTAL MATERIAL

Supplemental Figure 1.



Supplemental Figure Legends

Supplemental Figure 1.: Median temperature (°C) with error bars displaying inter quartile range (IQR) the first 36 hours after admission, stratified by treatment allocation.