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Original Article

An investigation of the use of SCUBE1 protein as an early prognostic marker in predicting prognosis after cardiopulmonary resuscitation in cardiac arrest patients

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Abstract

Aim: To evaluate the usefulness of Signal Peptide-CUB-EGF Domain-Containing Protein-1 (SCUBE1) protein as an early prognostic marker in predicting survival, resuscitation success, and good neurological outcome following cardiopulmonary resuscitation (CPR) in cardiac arrest patients.

Material and Methods: Non-traumatic cardiac arrest patients presenting to the emergency department over a six-month period were included in the study. Blood specimens were collected for SCUBE1 measurement at the start of CPR. SCUBE1 levels investigated at the start of CPR were compared, and their usefulness in predicting patients with long-term survival and exhibiting good neurological prognosis was evaluated.

Results: The study group consisted of 65 non-traumatic cardiac arrest patients. Sustained return of spontaneous circulation (ROSC) was achieved in 26 (40%) of these 65 patients, and five (7.7%) cases concluded with good neurological prognosis after three months. Comparison of the patient groups with and without sustained ROSC in terms of SCUBE1 levels investigated at the start of CPR revealed no statistically significant difference between them (p=0.462). However, comparison of the patient groups with good and poor neurological prognosis in terms of SCUBE1 levels at the start of CPR revealed that SCUBE1 levels were twice as high in the poor neurological prognosis group as in the good neurological prognosis group, although the difference was not statistically significant.

Conclusion: SCUBE1 levels measured at the start of CPR are not sufficient for predicting post-CPR survival and good neurological outcome.

Keywords: Advanced cardiac life support; cardiopulmonary resuscitation; signal peptide

INTRODUCTION

Cardiopulmonary arrest (CPA) represents the abrupt loss of spontaneous respiration and blood flow. Cardiopulmonary resuscitation (CPR) refers to the entirety of basic and advanced life support procedures performed to restore spontaneous heart beat and respiration and heart functions in patients undergoing cardiac arrest (CA). CA cases seen in the emergency department are generally of cardiac origin, the most common cause being ischemic heart disease (1,2). Sudden cardiac arrest (SCA) is one of the most current and important subjects in emergency medicine, and one that has not been entirely resolved. The approach to the CA patient is set out in the International Liaison Committee on Resuscitation (ILCOR) (consisting of relevant associations, organizations, and unions) guideline, which is updated every five years (3).

Despite various advances in CPR, post-CA mortality and morbidity are still high. Patient courses following CPR may range from complete healing to mild or moderate symptoms, a persistent vegetative state, or even death (4). The decision to initiate CPR in the management of these critical patients, how long it should be maintained, and when to conclude CPR are of great importance. There is also a need for reliable parameters capable of use in

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predicting prognosis following CPR and of acting as guides to clinicians. Various clinical scales, electrophysiological techniques and imaging methods can be used as early determinants of post-CA recovery. Various studies have focused on biochemical markers as early predictors of post-CA prognosis (4-9). However, these studies are few in number and involve various limitations. The first reference to the potential use of biochemical markers for prognostic purposes appeared in the 2015 CPR current guideline, but none was described as being sufficient by itself (10). No specific threshold value and narrow confidence interval values capable of predicting poor neurological outcomes have been identified in studies to date. Novel and practical biochemical markers are therefore needed.

Signal Peptide-CUB-EGF Domain-Containing Protein-1 (SCUBE1) is a novel molecule principally derived from platelets, with matrix-dependent or soluble forms, shown to be capable of an adhesive role in platelet-platelet or platelet-matrix interaction, and of biological importance in the cardiovascular system (11-13). No previous studies have investigated SCUBE1 levels in CA patients and predicting post-CPR survival and neurological outcomes.

Early and accurate prediction of patients survival after successful resuscitation after CA remains a major challenge. Various studies have been conducted on some biomarkers to be used in predicting prognosis after CA (14). Based on this purpose, in our study, the usability of SCUBE1 as a prognostic marker was investigated in CA patient groups who applied to the emergency department and undergoing CPR.

MATERIAL and METHODS

Study Design

This prospective, single-center clinical study was intended to evaluate the usefulness of SCUBE1 as an early prognostic marker in predicting prognosis in CA patients following CPR. Following receipt of approval from the Regional Education and Research Hospital local ethical committee (Decision No. 2014/25), non-traumatic CA patients presenting to the emergency department of the same hospital over a six-month period were collected for the study. We planned to evaluate patients' three-month survival and neurological outcomes after CPR.

Establishment of the Study Groups

Inclusion Criteria

In- or out-of-hospital non-traumatic CA cases aged over 18 presenting due to CA with CA rhythms determined as non-pulse electrical activity (NEA), asystole, ventricular fibrillation (VF) and non-pulse ventricular tachycardia (nVT) were enrolled in the study.

Exclusion Criteria

Patients brought to the emergency department due to CA but aged under 18 years, with trauma-related CA, pregnant women, subjects with suspected intoxication, terminal stage cancer patients, or from whom blood specimens could not be collected (or with insufficient blood specimens) for SCUBE1 measurement, patients not followed-up for any reason during the study, and patients not undergoing CPR in the emergency department were excluded. Patients refusing to give consent to inclusion in the study, despite relatives being informed about the study, were also excluded.

Study Protocol

All patients arriving at the emergency department in the form of non-traumatic CA, irrespective of whether CPR was initiated before hospital, were recorded for the purpose of establishing a potential study group. A standard advanced cardiac life support (ACLS) protocol was applied to all patients. As required under the protocol, CPR was routinely performed in accordance with the American Heart Association (AHA) guideline. Venous blood specimens were collected for SCUBE1 measurement at the start of CPR. Patients' demographic characteristics, arrest-related information, and details of the CPR applied were recorded.

Palpable pulses for 30 sec following discontinuation of CPR or measurable blood pressure was defined as ROSC, and continuation of spontaneous circulation for at least 20 min without external chest compression was defined as sustained ROSC. These patients' CPR procedures were observed and recorded onto study forms. Post-resuscitation care of all patients with post-CPR ROSC or sustained ROSC was performed in line with the AHA guideline (without application of therapeutic hypothermia) in the relevant wards or intensive care units. Patients' post-CPR treatment and follow-up on the ward or in intensive care outside the emergency department were observed and recorded throughout the study. Patients were observed until discharge or exitus in this follow-up.

Patients capable of being discharged and/or their relatives were contacted by telephone exactly three months after application of CPR for the investigation of three-month prognosis and mortality. Living patients' neurological outcomes were evaluated through invitations to hospital for checks based on their Glasgow Outcome Score (GOS: 5, good recovery, 4: moderate disability, 3: severe disability, 2: persistent vegetative state, 1: dead).

Blood Specimen Collection, Storage, and Study

Five milliliters of blood was collected from the patient group and placed into citrate tubes for study. The specimens were then centrifuged at 4000 cycles for 15 min at +4 degrees. Next, 1 cc was collected from the serum, placed into Eppendorf tubes, and stored at -80 degrees until the day of study. The Eppendorf tubes were removed from the -80 degree environment 24 h before the start of SCUBE 1 investigation and placed in +4 degrees. The thawed sera were brought to room temperature, and SCUBE1 levels were measured.

Determination of SCUBE1 Levels

SCUBE1 levels in the serum samples were determined using a double antibody sandwich ELISA kit (YH Biosearch,

Cat No. YHB2700Hu, Shanghai, China) in line with the manufacturer's instructions. Specimen absorbances were measured at a 450 nm wavelength on a microplate reader spectrophotometer (Versamax, Molecular Devices, California, USA). The results were expressed as ng/mL. The CV% for the analysis was calculated as 9.4.

Study Endpoints

All patients in our study were grouped on the basis of whether or not sustained ROSC was achieved in terms of evaluating the success of early CPR.

Further grouping was performed, involving good or poor prognosis, in terms of evaluating three-month survival and neurological outcomes. Patients in whom ROSC or sustained ROSC could not be established during CPR, patients who died in hospital even though sustained ROSC was achieved. Patients who died within three months after CPR, and discharged patients with GOS ≤2 three months after CPR were classified as the poor prognosis group. Discharged patients with GOS ≥3 three months after CPR constituted the good prognosis group.

Determination of the diagnostic value of SCUBE1 levels of patients with and without sustained ROSC following CPR was adopted as the primary endpoint of the study. Determination of whether the SCUBE1 levels of patients with good or poor prognosis based on GOS three months after CPR was adopted as the secondary endpoint.

Statistical Analysis

SPSS (Statistical Package for Social Sciences forWindowsv.23.0) and MedCalc software were used for statistical analyses. The Shapiro Wilk test was applied to determine whether data were normally distributed at two-group comparisons. Since data were not normally distributed, descriptive statistics were expressed as median and 25-75th percentiles. The Mann Whitney U test was used for two-group comparisons. Receiver operating characteristic (ROC) curves were produced to determine cut-off values for biochemical marker investigated at the start of CPR for predicting sustained ROSC and three-month good prognosis after CPR, and sensitivity, specificity, negative predictive values (–PV), negative likelihood ratio (-LR) and positive predictive values (+PV), positive likelihood ratio (+LR) were calculated. $p<0.05$ was regarded as statistically significant.

RESULTS

General Clinical and Demographic Characteristics

Since 17 of the total 82 CA patients met at least one of the exclusion criteria during the study, these were excluded, and the study group finally consisted of 65 non-traumatic CA patients. A flow chart for the patient group observed during the study is shown in Figure 1. Clinical and demographic characteristics of the patients included in the study are shown in Table 1.

Table 1. Demographic and clinical characteristics of the patients in the study

Age	**Median (25-75%)**	**71.0 (56.5-78)**
Sex	Male n, %	37, 56.9%
	Female n, %	28, 43.1%
Arrest type	In-hospital n, %	23, 35.4%
	Out-of-hospital n, %	42, 64.6%
CA witness status	Witnessed CA n, %	41, 63.1%
	Unwitnessed CA n, %	24, 36.9%
Pre-hospital CPA application	CPR applied n, %	42, 64.6%
	CPR not applied n, %	23, 35.4%
Cause of arrest	Cardiac n, %	47, 72.3%
	Non-cardiac n, %	18, 27.7%
Arrest rhythm	VF n, %	5, 7.7%
	NEA or asystole n, %	60, 92.3%

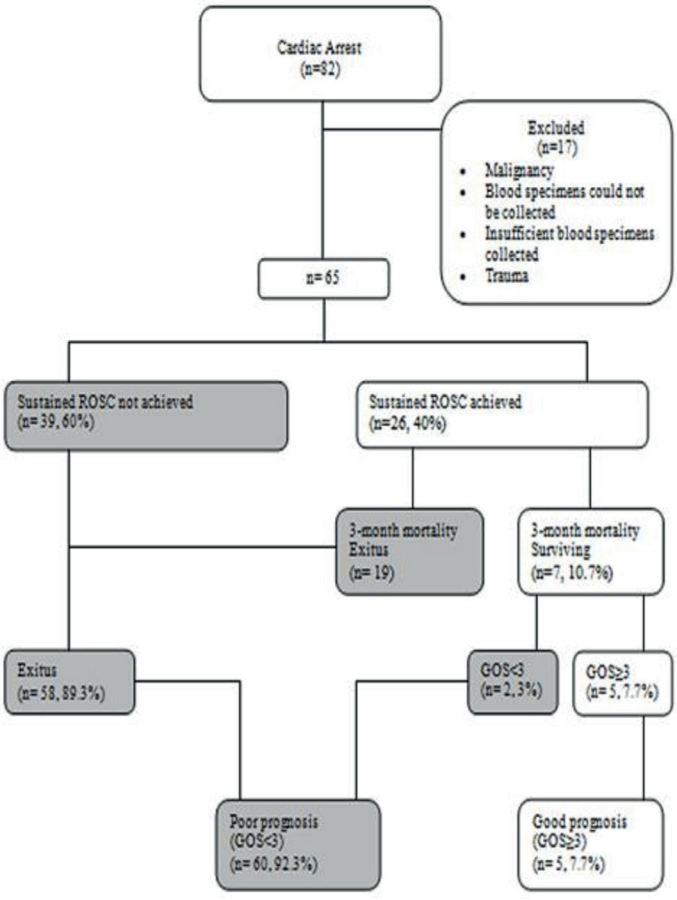

Figure 1. Study group flow chart

Determination of the usefulness of SCUBE1 levels investigated at the start of CPR in predicting patients with sustained ROSC

Sustained ROSC was achieved in 26 (40%) patients in this study, but not in the other 39 (60%). SCUBE1 levels at the start of CPR patients in the groups with and without sustained ROSC are shown in Table 2. Based on these findings, SCUBE1 appears not to be a marker of establishment of sustained ROSC. Results for ROC analysis performed in order to determine the optimal SCUBE1 cut-off level predicting whether or not sustained ROSC would be achieved are shown in Table 3 and Figure 2. The ROC area under the curve (AUC) for SCUBE1 was 0.54±0.07 (95% CI: 0.412-0.664). The optimal SCUBE1 cut-off value at optimal sensitivity (34.62%) and specificity (84.62%) was 31 ng/ml.

Table 2. SCUBE1 levels according to whether or not sustained ROSC was achieved and good-poor prognosis at the end of 3 months

	SCUBE1 (Median, 25-75%, ng/ml)	p value
Sustained ROSC,		
Achieved	42.05 (27.07-156.02)	0.462
Not achieved	48.2 (32.8-147.2)	
3-month prognosis		
Good	23.70 (18.35-82.55)	0.058
Poor	46.35 (31.62-152.95)	

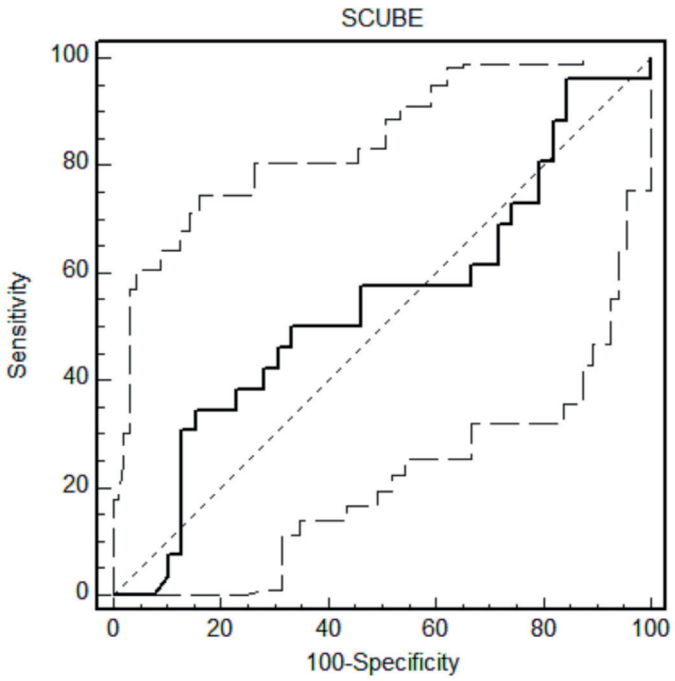

Figure 2. SCUBE1 levels predicting sustained ROSC according to ROC curves

Determination of the usefulness of SCUBE1 at the start of CPR in predicting patients with good prognosis based on three-month GOS

Post-CA three-month prognoses were also evaluated in this study. Good prognosis was determined in five (7.7%) patients and poor prognosis in 60 (92.3%). SCUBE1 levels at start of CPR in the good and poor prognosis patient groups are shown in Table 3. Based on those results, SCUBE1 did not emerge as a predictive marker of good prognosis. However, SCUBE1 levels were twice as high in the poor prognosis group than in the good prognosis group. Results of ROC analysis performed to determine the optimal SCUBE1 cut-off point for predicting good prognosis following CA are shown in Table 3 and Figure 3. The ROC AUC determined for SCUBE1 was 0.757±0.09 (95% CI: 0.634-0.854). The optimal SCUBE1 cut-off value at optimal sensitivity (60%) and specificity (90%) was 23.7 ng/ml.

Table 3. SCUBE1 optimal cut-off values

SCUBE1 value	Sensitivity	Specificity	+LR	-LR	+PV	-PV
31*	34.62	84.62	2.25	0.77	60	66
23.7**	60	90	6	0.44	33.3	96.4

* SCUBE1 levels predicting sustained ROSC selected according to ROC curves
** SCUBE1 levels predicting good prognosis 3 months post-CA selected according to ROC curves

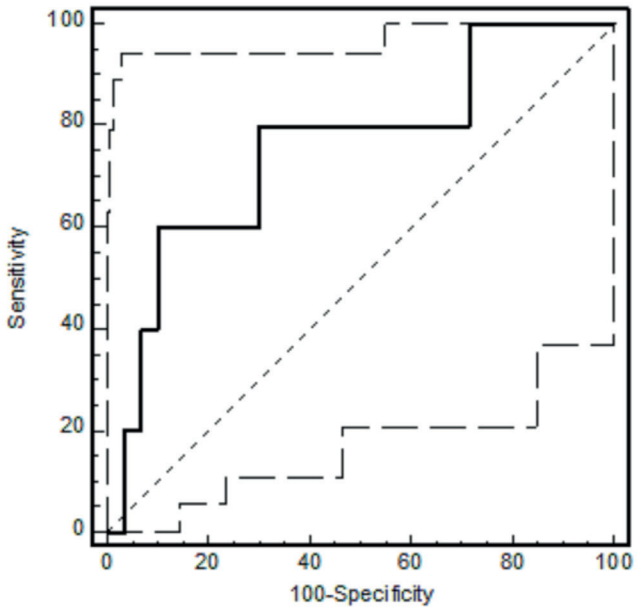

Figure 3. SCUBE1 levels predicting good prognosis 3 months post-CA according to ROC curves

DISCUSSION

The primary objective of resuscitation is the restoration and sustaining of spontaneous circulation. Establishment of ROSC following resuscitation is the first finding showing 'unbiased' success of resuscitation (15). The establishment of sustained ROSC, defined as maintenance of ROSC for at least 20 min, indicates successful survival (16). The number of studies investigating whether ROSC will be achieved or sustained following CPR is very limited. Wang et al. compared the lactate levels of in-hospital CA

patients and reported that lactate levels investigated during CPR were not sufficient to determine sustained ROSC (17). In another study, Lim et al. measured bispectral index (BIS) (an electroencephalography (EEG) parameter) values during CPR and concluded that this was also not sufficient for determining ROSC or sustained ROSC (18). Existing diagnostic tests cannot by themselves reliably determine survival or sustained ROSC in CA patients (17-19). The primary aim of our study was therefore to investigate the value of SCUBE1 levels investigated at the start of CPR in predicting patients in whom sustained ROSC could or could not be achieved following CPR. SCUBE1 is a novel cell surface protein secreted during early embryogenesis. It is stored inside the alpha granules of inactivated platelets, and is released from the cell surface in the form of small, soluble particles following activation by thrombin, and thus enters the thrombus. SCUBE1 accumulation has been determined in the subendothelial matrix of advanced atherosclerotic lesions using immunohistochemical methods. The general view is that SCUBE1 may be a novel platelet endothelial adhesion molecule and may play a pathological role in cardiovascular biology (13,20). Since thromboembolic events such as pulmonary embolism and acute coronary syndrome play a dominant role in the etiology of CA, changes may occur in SCUBE1 levels in CA patients. Ours is the first study to investigate SCUBE1 as a predictive biochemical marker for sustained ROSC in CA patients. We conclude that SCUBE1 levels are not significant as a marker in the establishment of sustained ROSC after CPR.

In addition to ACLS procedures, current guidelines also focus on post-resuscitative care (10). In addition to survival, the most important aim of post-CA care is to return patients to pre-arrest functional levels. Brain damage is one of the principal causes of mortality and morbidity in patients undergoing CPR following CA (21). Post-CA cerebral perfusion impairment concludes with compromise of the integrity of the blood-brain barrier glial and global hypoxic ischemic brain damage arising due to death of glial and neuronal cells (22). Neurological prognostic factors must be identified as early and accurately as possible in order to determine therapeutic strategies following successful CPR (7). Useful methods for predicting post-CA prognoses are rather limited (23). Several biochemical markers have been investigated in the context of predicting good and poor outcome post-CA, but none has been identified as sufficient by itself (10). In this context, the two most researched biomarkers are neuron-specific enolase (NSE) and S100B. In the meta-analysis published by Wang et al., They stated that NSE and S100B can be used for the prediction of patients with poor prognosis with multiple evaluations after CA (24). Chung-Esaki et al. argued that NSE can be used to predict patients with poor prognosis, but it is not sufficient to make a good and poor prognosis decision alone (25).

In the context of the secondary aim of our study, SCUBE1 levels investigated at the start of CPR were insufficient to predict patients with good prognosis. No previous studies have investigated SCUBE1 levels in the prognosis of CA. However, studies have reported that SCUBE1 can be used diagnostically in the course of different diseases. Dai et al. compared plasma SCUBE1 levels in patients with acute coronary syndrome and reported higher values than in a healthy control group. They reported that SCUBE1 began rising 6 h after onset of symptoms. However, they also reported that while SCUBE1 may not be a sensitive biochemical marker for acute coronary syndrome, it may be a good marker of platelet activation in acute thrombotic patients (26). Türkmen et al. compared SCUBE1 levels in rats with experimentally induced mesenteric ischemia with those of a control group. Higher SCUBE1 levels were observed in the mesenteric ischemia group at 2 and 6 h compared to the control group (27). The present study investigated the value of SCUBE1, a novel biochemical marker that contributes to the acceleration of platelet activation and aggregation in ischemic events, in predicting good and poor prognosis in the three-month period following CA. Although SCUBE 1 levels were approximately twice as high in the poor prognosis group than in the good prognosis group, the findings were not statistically significant in differentiating the two. We therefore think that measurement of SCUBE1 levels will not be useful in predicting prognosis in CA patients.

Recommendations for future research

In patients after CPR, various clinical outcomes can occur that may progress to death. When CPR will start, how long it will last and how it will end, are important problems in the management of these critical patients. Based on these problems, it is obvious that some biochemical markers may be useful at the beginning of CPR or during application and new studies should be done about them.

LIMITATIONS

Since our study involved a limited number of patients, the numbers of patients in the good and poor prognosis groups were very low. Due to the study design, both in- and out-of-hospital CA patients were enrolled. These two arrest groups differ significantly in terms of CPR success and prognosis, and this is reflected in our results. Since therapeutic hypothermia, one of the principal components of post-resuscitative care in the CRP AHA guideline, is not available in our center, our post-CPR success, survival and neurological outcome data are all affected.

CONCLUSION

We determined no dıfference in SCUBE1 levels in CA patients with and without sustained ROSC and with good or poor prognosis. We think that the use of SCUBE1 levels measured at start of CPR for predicting post-CPR survival and neurological outcome is not sufficient for that purpose, and that large series studies are now required.

Conflict of interest: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: All procedures performed in studies involving human

The study was approved by the Ethics Committee of the Regional Education and Research(Decision No. 2014/25).

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