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Review Article

sICAM as a Predictor of Outcome in Acute Spontaneous Intracerebral Hemorrhage

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Abstract

Background: Serum concentrations of adhesion molecules may be connected to the pathogenesis of secondary brain injury after spontaneous Intracerebral Hemorrhage (ICH). This study posits the hypothesis that levels of adhesion molecules substantially increase after ICH and are decreased thereafter, and that they can predict treatment outcomes.

Methods: Our study was conducted as a prospective study on 25 patients with acute spontaneous ICH presenting to ED of AL Sahel teaching hospital over a period of 19 months (May 2014 to November 2015) confirmed by patient history and brain CT scan. The studied population was divided into two groups; group 1(25 patients) with acute ICH and group 2(25) young volunteers. Patients in both groups were investigated with serial serum levels of sICAM during their hospital stay; the results of the 2 groups were compared. The case group was divided according to the outcome into two subgroups; bad outcome and good outcome by using the Modified Rankin Disability Scale (mMRS).

Results: Fifteen patients had bad outcome and 10 had good outcome. Cutoff point for the studied population for sICAM level on admission at 455 ng/ml could predict poor outcome with sensitivity 73% and specificity 80%, at 680 ng/ml could predict clinical seizures at sensitivity 100% and specificity 81% and at 505 ng/ml could predict non survivors with sensitivity 89% and specificity 88%.

Conclusion: Persistent increase in sICAM level implies a danger of poor therapeutic outcome for the treatment of spontaneous ICH during hospitalization. These findings are important because they offer a potential therapeutic target for patients with spontaneous ICH.

Keywords: ICAM; Modified rank in disability scale; GCS; Intraventricular hemorrhage

Introduction

Adhesion molecules sICAM-1 and Soluble Vascular Cell Adhesion Molecule-1 (sVCAM-1) are pro-inflammatory parameters for the activation of the immune system [1]. Their physiologic role is the regulation of cell-to-cell contacts [2]. Recruitment of activated peripheral blood mononuclear cells across endothelial cells of the blood brain barrier seems to be an essential step in the initiation of brain inflammation [3]. This step of immune cell entry into the brain tissue is regulated by adhesion molecules and leads to a complex cascade of events [2,4]. Moreover, adhesion molecules play a patho-physiologic role in cerebrovascular diseases [5].

Aim of the work

The aim of our study is to evaluate the role of sICAM as a predictor of outcome after acute spontaneous intracerebral hemorrhage.

Patients and Methods

Our study was conducted as a prospective case/control study on 25 patients with acute spontaneous intracerebral hemorrhage as confirmed by patient history and brain Computed Tomography (CT) scan, who were investigated with serial Serum Levels of Adhesion Molecules (sICAM) during their hospital stay compared to levels in volunteers. We have excluded patients who are/have:

a) Near death.

b) Central nervous system infection acquired during hospitalization.

c) Major systemic disease like end-stage renal disease, liver cirrhosis, or CHF.

The studied population was divided into two groups

Group 1 (Case group): Consisted of twenty five patients with acute spontaneous intracerebral hemorrhage.

Group 2 (Control group): Consisted of twenty five healthy volunteers.

Outcome in the case group (Group 1) was assessed upon discharge by using the Modified Rankin Disability Scale (mMRS). Good outcome was defined as an mMRS score of 0 or 1, whereas poor outcome was an mMRS score of at k least 2 or death.

Imaging

1. CT scan soon after arrival at the emergency room as well as serial follow-up brain CT every 3 days concurrently with the sampling for sICAM during hospitalization.

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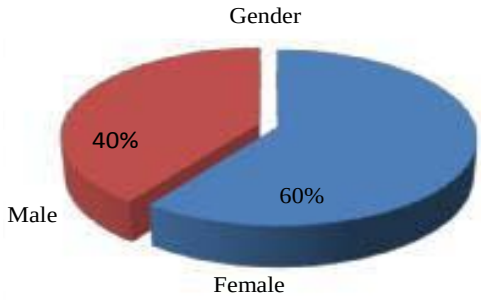

Figure 1: Demographic data of the case group on admission (Gender).

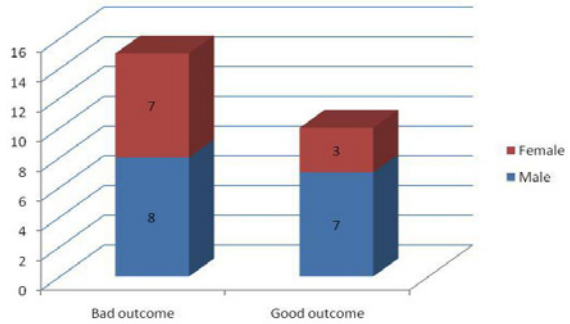

Figure 2: Gender difference between the two outcome subgroups.

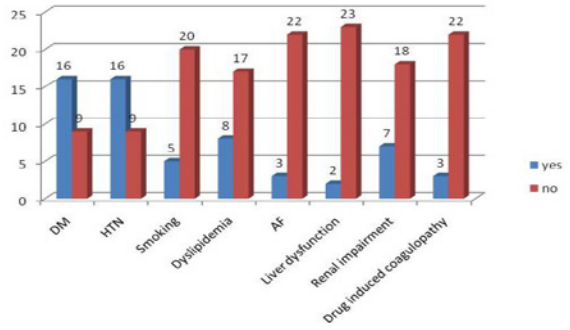

Figure 3: Other demographic data of the case group.

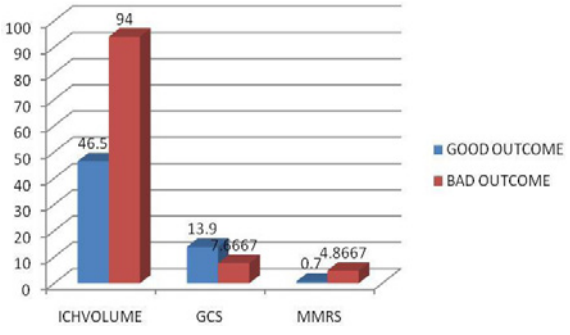

Figure 4: ICH volume and Scores in the two outcome subgroups.

2. Emergency brain CT scan was performed if there is clinical deterioration.

Serum ICAM: Levels of serum ICAM on admission (ICAM0), day 4 (ICAM1) and day 7 (ICAM2) will be assessed. One blood sample from each patient will be taken within 24 hours after the onset of ICH, then additional blood samples will be obtained on days 4 and 7 after the onset of ICH regardless of clinical deterioration.

Table 1: Demographic data of the case group on admission (Age).

	Number	Mean	Std Deviation
Age	25	60.04	12.0847

Table 2: Age difference between the two outcome subgroups.

	Outcome	N	Mean	Std. Deviation	P value
Age	**Good outcome**	10	59.7	11.04	0.911
	Bad outcome	15	60.2667	14.11	

Table 3: Other demographic data of the case group.

	Number	Percent
DM	16	64%
HTN	16	64%
Smoking	5	20%
Dyslipidemia	8	32%
AF	3	12%
Liver dysfunction	2	8%
Renal impairment	7	28%
Drug induced coagulopathy	3	12%

Table 4: ICH volume and Scores in the two outcome subgroups.

	Outcome	N	Mean	Std. Deviation	P value
ICH Volume	Good outcome	10	46.5000	9.14391	0.0001
	Bad outcome	15	94.0000	28.48559	
GCS	Good outcome	10	13.9000	0.73786	0.0001
	Bad outcome	15	7.6667	3.92186	
mMRS	Good outcome	10	0.7000	0.48305	0.0001
	Bad outcome	15	4.8667	1.64172	

Statistical analysis

Data will be expressed as mean ± standard deviation. Categorical variables will be compared by using the chi-square test or Fisher exact test, when appropriate. Serum levels of adhesion molecules will be compared by unpaired Student t test. Repeated measures of analysis of variance will be used to compare adhesion molecules at three different time points (days 1, 4 and 7). All continuous variables will be correlated by Pearson correlation coefficient. Receiver Operating Characteristic (ROC) curves will be generated for soluble adhesion molecule levels to determine cut off point for prediction of bad outcome. P value will be considered to be significant if ≤ 0.05.

Correlation refers to a process for establishing whether or not relationships exist between two variables whereas correlation coefficient (r) means a single number that gives a good idea about how closely one variable is related to another variable [6].

Receiver Operating Characteristic (ROC) curves are a useful way to interpret sensitivity and specificity levels and to determine related cut scores. ROC curves are a generalization of the set of potential combinations of sensitivity and specificity possible for predictors [7]

ROC curve analysis not only provide information about cut scores, but also provide a natural common scale for comparing different predictors that are measured in different units, whereas the odds ratio in logistic regression analysis must be interpreted according to a unit increase in the value of the predictor, which can make comparison between predictors difficult [7]. An overall indication of the diagnostic accuracy of a ROC curve is The Area Under the Curve (AUC). AUC values closer to 1 indicate the screening measure reliably distinguishes among students with satisfactory and unsatisfactory reading performance, whereas values at. 50 indicate the predictor is no better than chance [8].

Results

Demographic data of the case group on admission

Age: The mean age of the case group was 60.04 years with standard deviation 12.08 (Table 1).

Comparing the two outcome subgroups as regards the age revealed no significant difference with P value 0.911 (Table 2).

Gender: Group 1 enrolled 15 (60%) males and 10(40%) females (Figure 1).

As regards the gender, there was a non significant difference between the two outcome subgroups with P value 0.678 (Figure 2).

Other demographic data of the case group are illustrated in Table 3 and Figure 3.

ICH volume and Scores: Table 4 shows the distribution of the two outcome subgroups as regards the ICH volume, GCS and mMRS. ICH volume and mMRS were significantly higher in bad outcome subgroup (94.00±28.48), (4.87±1.64) respectively than in good outcome subgroup (46.50±9.14), (0.70±0.48) respectively with P value 0.0001, whereas GCS was significantly lower in bad outcome subgroup (7.67±3.92) than in good outcome subgroup (13.900±0.74) with P value 0.0001 (Table 4 and Figure 4):

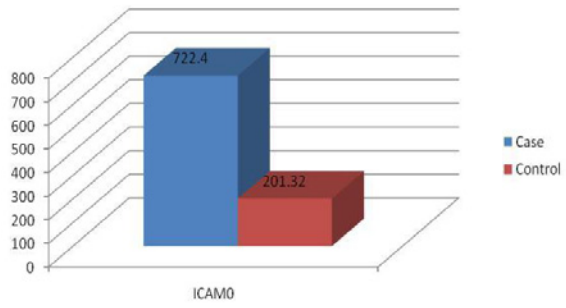

Figure 5: The mean ICAM level of both groups.

Table 5: The mean ICAM level of both groups.

	Group	N	Mean	Std. Deviation	P value
ICAM0	Case	5	22.4000	699.90642	0.001
	Control	5	1.3200	56.62208	

Table 6: ROC analysis for prediction of seizure with ICAM0 in group 1.

AUC	Cutoff value	P value	Sensitivity	ICAM0 Specificity
0.911	680	0.011	100%	81%
0.911	680	0.011	100%	81%

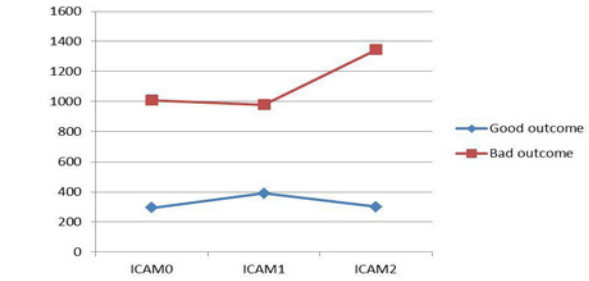

Figure 6: The mean ICAM levels of the two outcome subgroups.

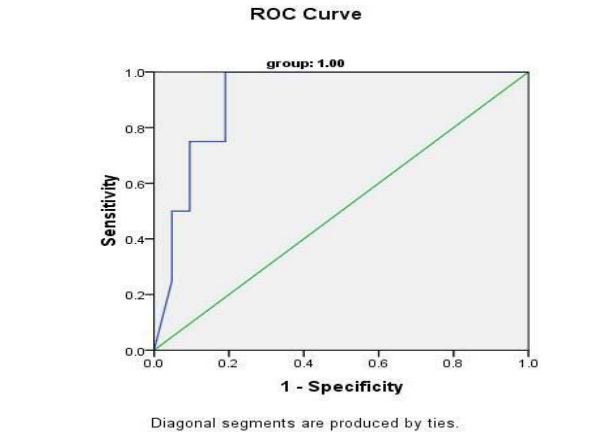

Figure 7: ROC analysis for prediction of seizure with ICAM0 in group 1.

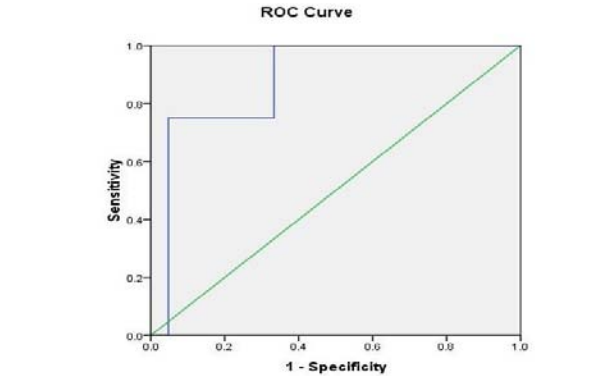

Figure 8: ROC analysis for prediction of seizure with ICAM1 in group 1.

ICAM levels the mean ICAM level of both groups (Case and Control) is illustrated in Table 5 and Figure 5: ICAM level on admission was significantly higher in the case group in comparison to the control group with P value 0.001.

The mean ICAM levels of the two outcome subgroups (good and bad outcome): The ICAM 0, 1and 2 were significantly higher in bad outcome subgroup and continued in rising for serum level as compared to good outcome subgroup which declined by the third reading, as shown in Figure 6.

ICAM and seizure

ICAM0 and seizure: The predictivity of ICAM0 for seizure was assessed to have sensitivity 100% and specificity 81% at the level of

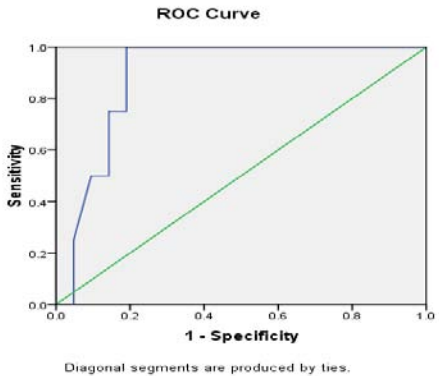

Figure 9: ROC analysis for prediction of seizure with ICAM2 in group 1.

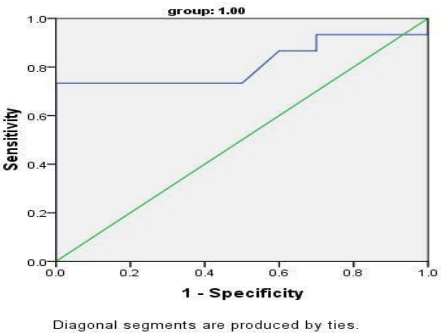

Figure 10: ROC analysis for prediction of outcome with ICAM0 in group 1.

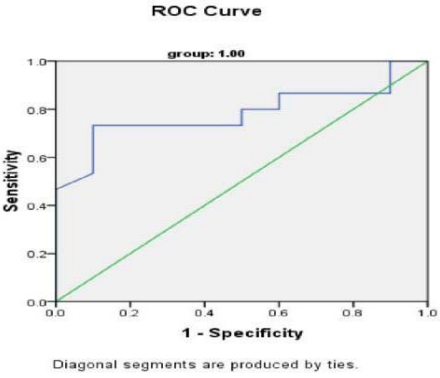

Figure 11: ROC analysis for prediction of outcome with ICAM1 in group 1.

680 ng/ml with AUC 0.911 and P value 0.011 (Table 6 and Figure 7).

ICAM1 and seizure: The predictivity of ICAM1 for seizure was assessed to have sensitivity 100% and specificity 67% at the level of 615 ng/ml with AUC 0.881 and P value 0.018 (Table 7 and Figure 8).

ICAM2 and seizure: The predictivity of ICAM2 for seizure was assessed to have sensitivity 100% and specificity 81% at the level of 970 ng/ml with AUC 0.88 and P value 0.016 (Table 8 and Figure 9).

ICAM and outcome: By analysis of ROC curve; ICAM level on admission at 455 ng/ml predicted a poor outcome with AUC 0.813, sensitivity 73% and specificity 80% with P value 0.009, for ICAM level

Table 7: ROC analysis for prediction of seizure with ICAM1 in group 1.

AUC	Cutoff value	P value	Sensitivity	ICAM0 Specificity
0.881	615	0.018	100%	67%

Table 8: ROC analysis for prediction of seizure with ICAM2 in group 1.

7	Cutoff value	P value	Sensitivity	ICAM0 Specificity
0.88	970	0.016	100%	81%

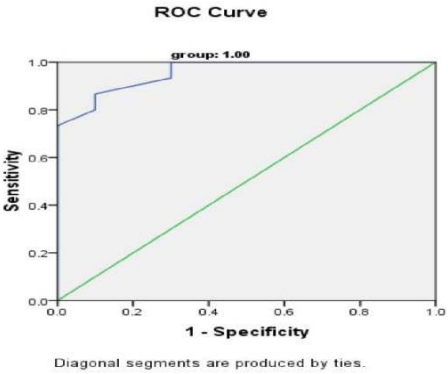

Figure 12: ROC analysis for prediction of outcome with ICAM2 in group 1.

Rankin Modified Scale Score	Description
0	No symptoms
1	No significant disability. Able to carry out all usual activities, despite some symptoms
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities
3	Moderate disability. Requires some help, but able to walk unassisted
4	Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent
6	Dead

(1, 2 and 5).

Graph 1:

on day 4 level of 460 ng/ml predicted a poor outcome with AUC 0.78, sensitivity 73% and specificity 90% with P value 0.018. Also, despite of lacking clinical value ICAM2 at day seven at 430 ng/ml predicted a poor outcome with AUC 0.957, sensitivity 90% and specificity 70% with P value 0.0001 as shown in Figures 10-12.

Discussion

By taking ICAM as a chemical biomarker for early inflammatory process that correlates to ICH, we compared the two studied groups (case and control groups) and we found that ICAM levels on admission were significantly higher in case group with P value 0.001 and the ICAM levels showed progressive increase at day four and day seven in the case group.

In other studies that compared cases of ICH with volunteers, plasma sICAM-1 and sVCAM-1 levels were elevated significantly

after the onset of ICH and peaked on days 10 (sICAM-1) and 4 (sVCAM-1) and then slightly decreased thereafter [9].

Same data were obtained in different types of intracranial hemorrhage, Kaynar et al. [10] studied ICAM and VCAM levels in CSF and sera of patients with acute subarachnoid hemorrhage and found that their levels were elevated in case group compared to those of healthy controls.

Regarding ICH volume, there was a significant relation that larger hematoma volume than 57.5 CM^3 predicted bad outcome with a sensitivity of 86.7% and specificity 90% and this was in concordance with Pipat et al who conducted a study by the year 2009 over 131 non traumatic intra cranial hemorrhage, (81 of them ICH), and they concluded that the two variables on CT imaging, identified as significant as early mortality predictors, were hematoma volume more than 60 CM^3, and presence of intraventricular hemorrhage extension [11].

In our study, the incidence of IVH was significantly higher in the bad outcome subgroup with P value 0.051, that is consistent with the results of the study by Pipat et al in 2009 in which survived patients associated with absent intraventricular hemorrhage extension and death associated with presence of intraventricular hemorrhage (P value 0.003), also this result agrees with that reported by Hung-Chen Wang et al in 2011 in which patients with bad outcome had a significant incidence of intraventricular hemorrhage extension with P value 0.006.

In our study, the incidence of clinical seizures comprised 4/25 (16%) that was in acceptable frequency as reported by different studies within the first 2 weeks in ICH that ranged from 2.7% to 17%, with the majority occurring at or near onset [12,13].

In a large, single-center study, prophylactic antiepileptic drugs did significantly reduce the number of clinical seizures after lobar ICH [10]. However, in prospective and population-based studies, clinical seizures have not been associated with worsened neurological outcome or mortality [12,14].

The clinical impact of subclinical seizures detected on EEG is also not clear. A recent analysis from the placebo arm of an ICH neuroprotectant study found that patients who received antiepileptic drugs (primarily phenytoin) without a documented seizure were significantly more likely to be dead or disabled at 90 days, after adjusting for other established predictors of ICH outcome [13]. Another recent single-center observational study had similar findings, specifically for phenytoin [15]. Thus only clinical seizures or electrographic seizures in patients with a change in mental status should be treated with antiepileptic drugs. Continuous EEG monitoring should be considered in ICH patients with depressed mental status out of proportion to the degree of brain injury. The utility of prophylactic anticonvulsant medication remains uncertain [16].

In our study clinical seizures were accompanied with poor outcome and a higher ICAM level throughout the hospital course till day 7. By analysis of ROC curve; ICAM level at 680 ng/ml predicted clinical seizures at sensitivity 100% and specificity 81% that could be used in the future with concurrent EEG or alone to recommend prescription of prophylactic anticonvulsants in case of ICH.

The ROC curves analysis in the study by Hung-Cheng Wang et al revealed that the cutoff point of sICAM-1 on admission was 194.61 ng/mL could predict poor outcome with (sensitivity of 68.8%, specificity of 71.4%, AUC of 0.717) and there were no mortalities [4].

In our study by analysis of ROC curve different cutoff points for egyptian population for ICAM0 at 455 predicted poor outcome with AUC 0.81, sensitivity 73% and specificity 80%, ICAMI at 460 predicted poor outcome with AUC 0.78, sensitivity 73% and specificity 90% and ICAM2 at 460 predicted poor outcome with AUC 0.95, sensitivity 90% and specificity 70%. As regards the mortality, by analysis of ROC curve different cutoff points for Egyptian population for ICAM0 at 505 predicted non survivors with AUC 0.878, sensitivity 89% and specificity 88%, ICAMI at 460 predicted non survivors with AUC 0.938, sensitivity 100% and specificity 82% and ICAM2 at 475 predicted non survivors with AUC 0.924, sensitivity 100% and specificity 75%.

In the near future, additional strategies that target inflammation in the very early phase of hemostasis [17] could offer exciting new promise in the therapeutic approach to ICH.

Conclusion

1. An increase in sICAM level implies a danger of poor therapeutic outcome for the treatment of spontaneous ICH during hospitalization.

2. Further large-scale studies are needed to elucidate the relevance of serum concentrations of adhesion molecules and secondary brain injury after spontaneous ICH.

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