The incidence and impact of lupus anticoagulants among patients in the intensive care unit

Abdulaziz S. Aldawood, *FRCPC, FCCP,*
Mark Crowther, *MSc, FRCPC,* ***Roman Jaeschke,*** *MSc, FRCPC,*
Ousama Dabbagh, *MD, FCCP,* ***Khalid Alkhairy,*** *MD, FRCPath,*
Salim Baharoon, *MD, FRCPC,* ***Nazir Ahmed,*** *MD.*

Coagulation abnormalities are commonly encountered in critically ill patients. Thus, intensivists are often challenged by the finding of prolonged activated partial thromboplastin time (APTT) in the setting of a normal international normalize ratio (INR). Potential causes of this presentation include heparin, a specific coagulation factor inhibitor, or a non-specific inhibitor, also known as a lupus anticoagulant (LA). Lupus anticoagulants are one of the 2 cardinal types of antiphospholipid antibodies. The presence of an antiphospholipid antibody (APA) in concern with venous or arterial thrombosis or recurrent pregnancy loss defines the antiphospholipid antibody syndrome (APS).[1] Antiphospholipid antibody syndrome is either identified using a coagulation assay for LA or by detection of an anticardiolipin antibody using a specific enzyme-linked immunosorbent assay.[1] Lupus anticoagulants are antibodies that interfere with one or more phospholipid-dependent activated partial throm-boplastin assays.[2] Other APA have been identified; these include antibodies directed against pro-thrombin or one a variety of anionic cell surface glycoproteins. Despite their name LA antibody are associated with thromboembolic events rather than clinical bleeding.[1] Approximately one third of individual with LA suffers with arterial or venous thrombosis or recurrent pregnancy loss. Lupus anticoagulant can be either primary (occurring without precipitant) or secondary to infections or medication.[3] As the intensive treatment of critically ill exposes patients to a variety of stimuli capable of triggering an immune response,[4] this prospective study was performed to determine the incidence of LA in such patients with isolated unexplained prolonged APTT. We also wanted to identify potential precipitating factors and the time course and outcome of patients with LA. The purpose of this prospective study was to investigate the incidence of isolated unexplained prolonged APTT in patients admitted to ICU and to screen such patients for LA.

All patients admitted to the Medical Surgical Intensive Care Unit (ICU) in Riyadh, Saudi Arabia, between November 2002 and November 2003 were considered enrolled in the study. Eligible patients were those with an unexpected, isolated prolongation of their APTT. We excluded patients if they have, preexisting coagulopathy (INR) of >1.5, therapeutic anticoagulation or expected need for such therapy, elective admission for post-surgical monitoring, immunosuppressive therapy within the last 4 weeks, hematological malignancy, auto-immune disease, and pregnancy. Consent for the study was not obtained, as we performed the investigation of a prolonged APTT as a component of standard clinical practice on all patients identified to have an isolated prolongation of their APTT. We reported the result of the investigation for LA to the clinical team caring for the patient; we made no other attempt at systematic follow-up. We treated all patients according to standards of care at the time of the study. If not contraindicated, all patients received prophylaxis against thromboembolism with low molecular weight heparin (LMWH) or unfractionated heparin at the discretion of the treating physician. In majority of patients, daily

Table 1 - Events while in the intensive care unit (ICU).

Events while in ICU	Number of patients (%)		*p*-value
	With positive lupus anticoagulant (n=13)	With normal activated partial thromboplastin time (n=142)	
Inotropic support	12 (93)	88 (62)	0.029
Sepsis	8 (92)	45 (32)	0.03
Mechanical ventilation	12 (92)	105 (74)	0.14
Blood transfusion	3 (23)	22 (15)	0.47
Platelet transfusion	0	5 (4)	
FFP transfusion	1 (7)	4 (3)	
ARDS (SD)	8 (5.64)	2 (15.38)	0.3760
Deep venous thrombosis	0	0	
Hemodialysis	1 (7.69)	14 (9.86)	0.8000

ARDS - adult respiratory distress syndrome, FFP - fresh frozen plasma, SD - standard deviation.

complete blood count, APTT, INR and renal function were determined. Liver function tests were measured on admission. In patients with an APTT above the upper limit of normal, studies for LA, we carried out a mixing study and thrombin time.

We studied 1035 patients admitted to ICU during the study period and we excluded 880. We included the remaining 155 patients in the study. At time of admission the mean APTT of patients subsequently found to have a LA was 42.3 (7.9) seconds, compared with 38.4 (13.2) in those not found to harbor a LA (p=0.11). Out of 155 patients, 17 patients (11%) developed unexplained prolongation of APTT. In 2 patients the elevation of the APTT was likely secondary to liver failure, and in 2 others it was due to heparin contamination. Thirteen remaining patients (8% of the total cohort, 77% of the patients with unexplained prolongation of their APTT) met our criteria for LA.[2] The mean time to the development of LA after admission to ICU was 3.2 ± 1.9 days. All those patients with positive LA who survived had complete resolution of LA after a mean of 7.4 ± 3.7 days of the initial positive testing. We carried out univariate analysis, which showed the patients admitted with infections, and those with sepsis were significantly more likely to manifest LA (p=0.003, p=0.03). There were no other differences in time-dependent variables apparent in our analysis. During ICU course, 6 (46%) patients who developed LA died versus 8 (5.6 %) among patients who did not develop LA (p=0.0004). There were no proven episodes of DVT or PE among evaluated patients, although we did not perform screening for these events (**Table 1**).

Out of 17 patients who developed unexplained prolonged APTT in the ICU, 13 had a LA as defined by our laboratory protocol. On follow-up coagulation testing, all these LA had resolved. Wenzel et al[4] studied 233 consecutive critically ill patients of whom only 51 (21.9%) were eligible for LA screening. Of these, 27 (53%) patients were positive for LA. Lupus anticoagulant resolved in most patients within 4 weeks of its initial diagnosis. We found sepsis and catecholamines use to be predictors of LA development. Our study failed to identify any baseline or time-dependent risk factors associated with LA development in multivariable modeling but the duration of inotropes was a trend to develop LA. We did confirm previous observations that LA presence is usually transient and it disappears when and if the triggering factor is resolved.[4] Why the catecholamines associated with development of LA, not clear, there is clear evidence that catecholamines alter endothelial cell function and composition. However, there is a considerable overlap in patients requiring catecholamines and developed sepsis.[5] One of the main observations in our study was the increased mortality among patients with LA presence. As none of the patients with LA developed clinically obvious thromboembolism or bleeding, and clinically the death of most of them was attributable to underlying condition. We believe, that the presence of LA was not the cause of death, but rather a marker of underlying severe condition. Confirmation of such hypothesis would require larger sample size. Lupus anticoagulant which develops critically can influence clinical care; thus, prolongation of the APTT might either suggest a coagulopathy (and thus reduce the likelihood that patients would undergo needed interventional procedures) or complicated unfractionated heparin therapy (requiring use of anti-Xa heparin levels to guide therapy). Our observation that LA are frequent, uniformly resolves and, although our analysis had limited power, were not associated with thrombosis suggests that these LA are of little clinical significance. Routine use of LA insensitive APTT reagents would likely completely eliminate these LA and thus improve the quality of care.

In conclusion, LA develops often in critically ill patients. Lupus anticoagulant is associated with risk factors for severe critical illness and predicted mortality LA resolves within a month of recovery from critical illness in surviving patients. In our study, patients with LA did not develop either bleeding or thromboembolism although they were not systematically screened for thrombosis.

Received 3rd July 2005. Accepted for publication in final form 28th August 2005.

From the Departments of Critical Care (Aldawood, Dabbagh, Ahmed, Baharoon), and Pathology (Alkhairy), King Fahad Hospital, Riyadh, Kingdom of Saudi Arabia, Department of Medicine (Crowther, Jaeschke), McMaster University, St. Joseph's Hospital, Ontario, Canada. Address correspondence and reprint requests to Dr. Abdulaziz S. Aldawood, Department of Critical Care, King Fahad Hospital, PO Box 1149, Riyadh 11322, Kingdom of Saudi Arabia. Tel. +966 504486550. Fax. +966 (1) 2253379. E-mail: aldawooda@ hotmail.com

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