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ORIGINAL ARTICLE

THE ROLE OF PLASMA D-DIMER LEVELS IN PATIENTS WITH ACUTE MESENTERIC ISCHEMIA

By
Abd-Elazeem Ali,[1] Tarek Selim[2]
[1]Department of General Surgery, [2]Department of Clinical Pathology, Faculty of Medicine, Mansoura University-Egypt

Aim: *We designed this study to determine whether the fibrinolytic marker D-dimer is a useful early marker of acute mesenteric ischemia.*
Methods: *We measured plasma D-dimer levels in 25 patients presenting with severe abdominal pain, in addition to 10 healthy controls. Based on laparotomy findings, patients were categorized into those with acute mesenteric ischaemia (AMI)(15 patients) and those without acute mesenteric ischaemia (NAMI) (10 patients).*
Results: *We demonstrated significant increase of plasma D-dimer level in AMI group compared to NAMI group (P < 0.01). Furthermore, plasma D-dimer level was significantly elevated in NAMI group compared to controls (P < 0.001).*
Conclusion: *Plasma D-dimer > 3.8 ug/ml combined with relevant clinical variables has a high positive predictive value for early identification of patients with AMI. However, plasma D-dimer < 0.53 ug/ml has a high negative predictive value for AMI and could be used as an exclusion test. This strategy could aid in the decision for urgent surgery with subsequent improvement of the surgical outcome.*

Keywords: *fibrinolytic marker, intestinal ischaemia, prediction.*

INTRODUCTION

Intestinal ischemia has been classified into three major categories based on its clinical features, namely, acute mesenteric ischemia (AMI), chronic mesenteric ischemia (intestinal angina) and colonic ischemia (ischemic colitis). AMI is not an isolated clinical entity, but a complex diseases, including acute mesenteric arterial embolus and thrombus, mesenteric venous thrombus, and nonocclusive mesenteric ischemia (NOMI). These diseases have common clinical features caused by impaired blood perfusion to the intestine, bacterial translocation, and systemic inflammatory response syndrome. Unfortunately, AMI is associated with high mortality rate despite advances in surgical techniques and perioperative care.(11)

The diagnosis of AMI is suspected in elderly patients with sudden severe abdominal pain and minimal abdominal signs initially vomiting and/or diarrhaea with bloody stools, and a potential source of emboli such as atrial fibrillation. This combination of symptoms and signs is referred to as the clinical trial of acute mesenteric ischemia.(5,6) Laboratory signs such as increased white blood cell count or serum lactate concentration are non-specific, whereas C-reactive protein (CRP) levels are insensitive early in the course of the disease and non-specific at later stages.(14)

The unacceptably high mortality of AMI is mainly due to delay in diagnosis. The only strategy to reduce mortality is to diagnose the condition as early as possible before irreversible bowel damage occurs. Therefore, the development of a rapidly elevating marker for early identification of patients with AMI continues to be a major challenge in surgical practice.

D-dimer is a fibrinolytic marker that has been used in the diagnosis of thromboembolic events. A recent clinical pilot study shows that d-dimer could also be useful in identifying patients with acute mesenteric ischemia and

could be a practical aid in the decision for urgent surgery.[1,7] We designed this study to determine whether the fibrinolytic marker D dimer is a useful early marker of acute mesenteric ischemia.

PATIENTS AND METHODS

Selection of patients: The present study was conducted on 25 patients selected from those presenting to Al-Mansoura University Emergency Hospital with severe abdominal pain in addition to 10 healthy subjects as controls. Based on exploratory laparotomy findings, patients were categorized into those with acute mesenteric ischemia (AMI) and those without (NAMI).

The study subjects were categorized into the following groups:

Group I (Controls): Included 10 healthy subjects. They were 6 males and 4 females. Their ages ranged from 25 – 70 years (mean 40.8 ± 11.8).

Group II (NAMI): Included patients without acute mesenteric ischemia. They were 10 patients (6 with acute appendicitis, 2 with perforated duodenal ulcer, 1 with acute cholecystitis and pancreatitis and 1 with pelvic abscess). They were 6 males and 4 females. Their ages ranged from 21-80 years (mean 40.6 ± 19.3).

Group III (AMI): Included patients with acute mesenteric ischemia. They were 15 patients (6 with thromboembolic occlusion of the superior mesenteric artery and 9with mesenteric venous occlusio). They were 8 males and 7 females .Their ages ranged from 25 – 80 years (mean 51±15.0).

Operative procedures: Resection anastomosis for the gangrenous parts of the intestine was the surgical treatment for all cases of AMI. Thromboembolectomy was done for those with occlusion of the superior mesenteric artery. Appendectomy was done for acute appendicitis. Closure with omental patch was the operation done for perforated duodenal ulcer. Cholecystectomy was done for cholecystitis.

Laboratory Tests

Specimen collection: Blood samples were collected at operation within 6 hours of the onset of abdominal pain. 1 mL of venous blood was mixed with the dipotassium salt of ethylene-diamine-tetra-acetate (EDTA) at a concentration of 1.2 mg of the anhydrous salt per mL of blood and was used to carry out the complete blood count. 1.8 mL of venous blood were delivered into a plastic tube containing 0.2 mL of the anhydrous salt of trisodium citrate (3.2 %) and was used to perform the coagulation assays and the D-dimer assay. 3 mL of venous blood were allowed to clot and the serum was used for measurement of serum creatinine, serum albumin and total serum bilirubin.

Methods: Complete blood count was performed in a Cell Dyne 1700 automated hematology counter (Abbott Diagnostics, USA).

Prothrombin time was estimated according to the method of Quick (16), using DiaPlastin Kit (DiaMed AG,Switzerland)and reported as INR.

Activated partial thomboplastin time (APTT) was measured according to the method reported by Procter and Rapaport,[15] using Diacelin Kit (DiaMed AG, Switzerland). Fibrinogen assay was done according to the method of Clauss,[8] using Fibri-Prest Kit (Stago Diagnostica, france).

Serum creatinine, serum albumin and total serum bilirubin were assayed using kits procured from Human GmbH (Wiesbaden, Germany).

Plasma D- dimer concentration was measured using a quantitative Zymutest D-dimer ELISA assay kit (Hyphen BioMed, France).

Statistical Analysis of Data: Statistical analysis of data was performed using SPSS (Statistical package for social science) computer program version 10. Qualitative data were presented as numbers and Fisher exact test was used for group comparison Kolmogorov Smirnov test was used to evaluate the distribution of Quantitative data. For parametric variables, ANOVA was used to test for the significant difference between the three studied groups and Bonferroni test was used to test for the significant difference between each two groups. For non-parametric variables, Kruskal-Wallis test was used to test for the significance of differences between the three studied groups and Mann-Whitney test was used to test for the significance of differences between each two groups. Spearman rank correlation coefficient was used to study the linear relationship between variables. $P< 0.05$ was considered significant. Receiver operating characteristic analysis was used as a predictive value model to assess the diagnostic accuracy of D-dimer assay for AMI.

RESULTS

The results of this study are summarized in tables 1-4. and (Figs. 1, 2).

Table 1. Shows the clinical and laboratory data of the studied groups.

Table 2. Shows the comparison between plasma D-dimer levels in the studied groups. Statistically significant differences of D-dimer levels were demonstrated between the three studied groups ($P< 0.001$). The level in AMI

group was significantly increased median=17.90 compared to NAMI group median=1.39 (P< 0.01). Furthermore, plasma D-dimer was significantly elevated in NAMI group compared to controlsmedian=0.24 (P< 0.01).

(Fig. 1) illustrates dot plot.

For the D-dimer levels in the studied groups. The highest levels were encountered in AMI group. The estimated 97.5 percentile of D-dimer levels in controls was 0.53 ug/ml.

Table 3. Shows the sensitivities, specificities and likelihood ratios for positive test (LR+) of D-dimer for AMI at different cut off values. At a D-dimer level of 0.53 ug/ml, the sensitivity was 100% with specificity of 10% and a LR+ of 1.1. However, at a D-dimer level of 3.8 ug/ml, the sensitivity was 73% with specificity of 90% and a LR+ of 7.3.

Table 4. Shows the correlation between D-dimer level and each of fibrinogen and total leucocytic count in the studied groups. No significant correlations could be detected in any of the studied groups (P>0.05).

(Fig. 2) depicts a ROC analysis curve of D-dimer levels for AMI. The area under the curve represents the overall diagnostic accuracy of D-dimer for AMI estimated as 89.0%.

Table 1. Clinical and laboratory data of the studied groups.

Parameters	Control n=10 mean ±SD	NAMI N=10 mean ±SD	AMI N=15 mean ±SD	P1	P2	P3
Age (Y)	40.8±11.80	40.6±19.36	51.0±15.0	>0.05	-	-
Sex (M/F)	6/4	6/4	8/7	>0.05	-	-
Abd. Pain (+ ve)	-	10 (100%)	15 (100%)	-	-	-
Vomiting (+ ve)	-	2 (20%)	15 (100%)	-	<0.001	-
Ileus (+ ve)	-	0.0 (0.0%)	15 (100%)	-	<0.001	-
DVT (+ ve)	-	0.0 (0.0%)	1 (6.7%)	-	>0.05	-
Hb (g/dl)	12.95±1.03	11.69±2.09	10.91±1.50	<0.05	>0.05	>0.05
TLC (x109/l)	6.45±1.22	13.71±6.0	16.08±9.67	<0.01	>0.05	<0.05
Plat (x10 9/l)	264.0±77.77	254.0±95.78	292.2±168.88	>0.05	-	-
INR	1.02±0.04	1.19±0.33	1.41±0.21	<0.01	>0.05	>0.05
APTT (sec)	27.7±2.98	36.0±2.10	38.46±4.10	<0.001	>0.05	<0.01
Fibrinogen (g/L)	3.32±1.0	2.71±1.30	2.95±1.69	>0.05	>0.05	>0.05
Creatinine (mg/dl)	0.78±0.10	1.19±0.40	1.68±0.65	<0.001	<0.05	<0.01
Bilirubin (mg/dl)	0.69±0.09	1.28±0.55	1.46±0.65	<0.001	>0.05	<0.001
Albumin (mg/dl)	4.2 ±0.42	3.76±0.63	3.39±0.79	<0.05	>0.05	>0.05

AMI = patients with acute mesenteric ischemia
NAMI = patients without acute mesenteric ischemia
P1 = Significance of difference between the three studied groups.
P2 = AMI vs NAMI
P3 = NAMI vs Control
P<0.05 was considered significant

Table 2. Comparison between plasma D-dimer levels in the studied groups.

Parameters	Control n=10 median (Range)	NAMI n=10 median (Range)	AMI n=15 median (Range)	P1	P2	P3
D-dimer (ug/ml)	0.24 (0.11-0.53)	1.39 (0.42-4.9)	17.90 (1.0-28.5)	<0.001	<0.01	<0.001

AMI = patients with acute mesenteric ischemia
NAMI = patients without acute mesenteric ischemia
P1 = Significance of difference between the three studied groups.
P2 = AMI vs NAMI
P3 = NAMI vs Control
P<0.05 was considered significant

Table 3. Sensitivity, Specificity and LR+ of D-dimer for AMI at different cut off values.

Cut off value	Sensitivity (%)	Specificity (%)	LR+
0.53	100.0	10.0	1.1
0.71	100.0	20.0	1.3
0.89	100.0	30.0	1.4
1.18	93.0	40.0	1.6
1.51	86.0	50.0	1.7
1.89	86.0	60.0	2.2
2.40	86.0	70.0	2.9
2.57	86.0	80.0	4.3
3.82	73.0	90.0	7.3

LR+ = Likelihood ratio for positive test
AMI = patients with acute mesenteric ischemia

Table 4. Correlation between D-dimer level and each of fibrinogen and TLC in the studied groups.

	D-dimer			
	Fibrinogen		TLC	
Groups	r	P	r	P
Control	0.222	>0.05	-0.353	>0.05
NAMI	0.274	>0.05	-0.055	>0.05
AMI	-0.240	>0.05	0.188	>0.05

AMI = patients with acute mesenteric ischemia
NAMI = patients without acute mesenteric ischemia
TLC = total leucocytic count
P<0.05 was considered significant

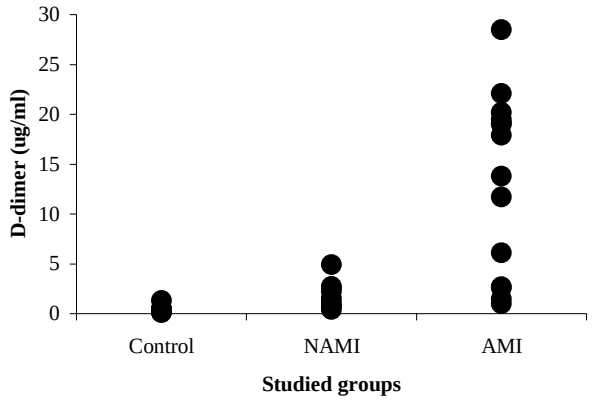

Fig 1. Plasma D-Dimer Levels in the studied group.

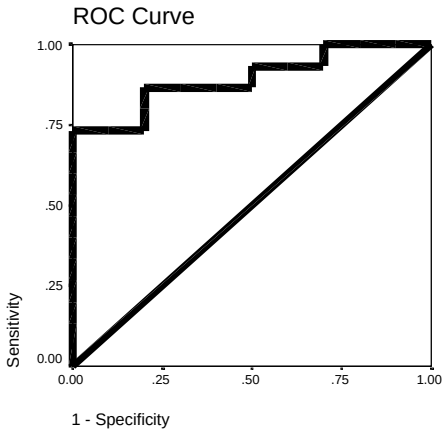

Fig 2. Figure 2: ROC analysis of D-dimer for AMI

DISCUSSION

Acute mesenteric ischemia is a life-threatening vascular emergency that requires early diagnosis and intervention to adequately restore mesenteric blood flow and to prevent bowel necrosis and patient death. The underlying cause is varied, and the prognosis depends on the precise pathologic findings. Despite the progress in understanding the pathogenesis of mesenteric ischemia and the development of modern treatment modalities, acute mesenteric ischemia remains a diagnostic challenge for clinicians, and the delay in diagnosis contributes to the continued high mortality rate reported to be 50% in a recent study. Early diagnosis and prompt effective treatment are consequently essential to improve the clinical outcome.[9,12] In the present study , we evaluated plasma D dimer as an early marker for acute mesenteric ischemia among patients presenting with severe abdominal pain. Patients were

Categorized into two subgroups namely, acute mesenteric ischemia (AMI) group and non-AMI (NAMI) group based on laparotomy findings. Additionally, a group of healthy subjects was enrolled to define the basal plasma level of D-dimer.

In the present study there was significant elevation of plasma D-dimer level in AMI group compared to NAMI group. Furthermore, plasma D-dimer level was significantly increased in NAMI group compared to controls. This is attributed to the ongoing activation of coagulation and fibrinolysis by the pathologic processes. These findings are consistent with previously reported data.[1,2,10] The 97.5 percentile of the D-dimer data in controls was 0.53 ug/ml. Furthermore, the receiver operating characteristic analysis of D-dimer levels have revealed that at a cut off value of 0.53 ug/ml the diagnostic sensitivity of D-dimer for AMI was 100% with specificity of 10%. These findings indicate that D-dimer has a low specificity for AMI at this cut off level (0.53 ug/ml). Therefore, as the D-dimer level was increased in all patients with AMI above this cut off value, a normal concentration may serve as an exclusion test. Interestingly, we had a case of acute cholecystitis and pancreatitis with manifestations similar to AMI, the D-dimer level of this case was found to be 0.098 ug/ml. This finding proves the high negative predictive value of D-dimer. In an attempt to increase the specificity of D-dimer for AMI we have selected a cut off value (3.8 ug/ml) at which the specificity was 90%, however, the sensitivity was reduced to 73%. Although the overall diagnostic accuracy of plasma D-dimer levels for AMI was estimated as 89%, a high index of clinical suspicion is required in combination with the selected cut off values to improve its diagnostic value. This is in agreement with Acosta et al. (2004),[2] who reported that a raised D-dimer concentration has a low specificity for AMI, however, in combination with clinical variables the diagnostic value could be improved. They demonstrated that the clinical triad for superior mesenteric artery occlusion (old age, severe abdominal pain, potential source of emboli) has the same LR+ of D-dimer level >1.5 mg/l according to their method of assay.

In the present study there was no correlation between D-dimer and the inflammatory markers, fibrinogen and total leucocytic count in the studied groups. This suggests that D-dimer is not a non-specific marker of inflammation or necrosis, but rather is an early marker of acute vascular events. In agreement with these findings, It has been reported that the rise of D-dimer concentration in patients with AMI is consistent with that in patients with ruptured

aortic aneurysm[3] and acute arterial thrombosis of the leg.[13] Furthermore, D-dimer is a stable molecule and its plasma concentration does not fluctuate. Moreover, the molecule has a sufficiently long half life (4-8 hours in vivo) to attain higher plasma levels in situations where the generation of D-dimer is accelerated.[4] These properties make D-dimer an excellent marker For early identification of patients with AMI.

In conclusion, plasma D-dimer > 3.8 ug/ml combined with relevant clinical variables has a high positive predictive value for early identification of patients with AMI. However, plasma D-dimer < 0.53 ug/ml has a high negative predictive value for AMI and could be used as an exclusion test. Therefore, D-dimer testing should be performed as an integral part of the diagnostic work-up of patients with acute abdomen. This strategy could aid in the decision for urgent surgery with subsequent improvement of the surgical outcome of patients with acute vascular events in general and patients with AMI in particular.

REFERENCES

1. Acosta S, Nilsson TK, Bjorck M. Preliminary study of D-dimer as a possible marker of acute bowel ischaemia. Br J Surg. 2001;88:385-96.

2. Acosta S, Nilsson TK, Bjorck M. D-dimer testing in patients with suspected acute thromboembolic occlusion of the superior mesenteric artery. Br J Surg. 2004;91:991-1004.

3. Adam DJ, Ludlam CA, Ruckley CV, Bradbury AW. Coagulation and fibrinolysis in patients undergoing operation for ruptured and non-ruptured infrarenal abdominal aortic aneurysms. J Vasc Surg. 1999;30:641-56.

4. Amiral J, Fareed J. Thromboembolic diseases: Biochemical mechanisms and new possibilities of biological diagnosis. Semin Thromb Hemost. 1996;22:41-53.

5. Bjorck M, Acosta S, Lindberg F, Troeng T, Bergqvist D. Revascularization of the superior mesenteric artery after acute thromboembolic occlusion. Br J Surg. 2002;89:923-34.

6. Bradbury AW, Brittenden J, McBride K, Ruckley CV. Mesenteric ischaemia: a multidisciplinary approach. Br J Surg. 1995;82:1446-56.

7. Brill-Edwards P, Lee A. D-dimer testing in the diagnosis of acute venous thromboembolism. Thromb Haemost. 1999;82:688-97.

8. Clauss A. Rapid physiological coagulation method in determination of fibrinogen. Acta Haematologica. 1957;17:237-48.

9. Huang HH, Chang YC, Yen DH, Kao WF, Chen JD, Wang LM, et al. Clinical factors and outcomes in patients with acute mesenteric ischemia in the emergency department. J. Chin Med Assoc. 2005;68:299-306.

10. Kulacoglu H, Kocaerkek Z, Moran M, Kulah B, Atay C, Kulacoglu S, et al. Diagnostic value of blood D-dimer level in acute mesenteric ischemia in the rat: an experimental study. Asian J Surg. 2005;28:131-9.

11. Lange H, Jackel R. Usefulness of plasma lactate concentration in the diagnosis of acute abdominal disease. Eur J Surg. 1994;160:381-98.

12. Oldenburg WA, Lau LL, Rodenberg TJ, Edmonds HJ, Burger CD. Acute mesenteric ischemia: a clinical review. Arch Intern Med. 2004;164:1054-62.

13. Peltonen S, Lassila R, Rossi P, Salenius JP, Lepantalo M. Blood coagulation and fibrinolysis activation during sudden arterial occlusion of lower extremities-an association with ischemia and patient outcome. Thromb Haemost. 1995;74:1442-9.

14. Potts FE IV, Vukov LF. Utility of fever and leukocytosis in acute surgical abdomens in octogenarians and beyond. J Gerontol A Biol Sci Med Sci. 1999;54:M55.

15. Procter RB, Rapaport SI. partial thromboplastin time with Kaolin. Am J of Clin. Path. 1961;36:212-21.

16. Quick AJ. Hemorrhagic disease and thrombosis, Philadelphia, Lea and Febiger Co. 1966 P:354.