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Investigating soluble thrombomodulin (sTM) as a predictor for major adverse cardiac events (MACE) after PCI in patients without current risk factors

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ABSTRACT

Prediction of major adverse cardiac events (MACE) has recently been a focus of biomedical researches. Identification of the predictors can be useful to select at risk patients for preventive treatment and healthy-life maintenance. The aim of this study was to evaluate the role of soluble thrombomodulin (sTM) to predict the development of MACE after PCI and stent placement. A total of 140 patients (aged 40-70 Years) undergoing percutaneous coronary intervention (PCI) and stent placement who's had inclusion craiteria were enroled. Personal information and medical history were recorded in a form. Blood samples were collected 24 hours after PCI and serum level of sTM was measured. Patients were followed up for 18 months. Coronary angiography was done for patients with chest pain or positive results of non- invasive tests. End point of the study was MACE including death, MI, early or late stent Thrombosis, Target vessel revascularization (TVR) and target lesion revascularization (TLR). mean age of patients was 55.61 and most of them were male (65%)-most common risk factor was dislipidemia (46%) and LAD was most common vessel (69%)- in follow up time coronary angiography was done for 39 patients That 29 of Them (20.7) had MACE 13 target. Lesion restenosis, 10 target vessel restenosis, 2 MI and 3 Thrombosis and one patient dead. There was signification association between, Reference vessels diameter with MACE (2.56 ± 0.25 VS 3.28 ± 0.39 mm P < 0/001). Mean Blood level of sTM in patients who had MACE was lower than mean sTM in other patient but there was not statistically significant (13.99 ±2.65 VS 15.11 ±3.25 ng/ml P=0.070). But among patients who had not current risk factors, mean blood level of sTM in cases with MACE was significantly lower than mean of sTM in cases without MACE.(11.84 ± 1.92 VS 16.46 ± 3.38 ng /ml P= 0.019) but only 4 patients were in first group (patients without current risk factors who had MACE). Despite the result of our study indicate that in patients who had not current risk. Factors, development of MACE after PCI and stent placement associate with low blood level of sTM but introduce of sTM as a predictor, need to supplementary investigations with more number of the patients.

Keywords: MACE, sTM, Restenosis, Thrombosis, PCI Complications

INTRODUCTION

Despite advanced techniques of stent placement which cause fewer vessel walls injury as well as introduction of drug-eluting stents which results in the least induction of immune response, stent restenosis and thrombosis are still the most common complications after PCI and stent placement [1-5]. Also, the results of a study determined that development of drug-eluting stents has Reduced The Target Lesion restenosis however The number of MACE did not decrease [6]. Therefore identification of markers as predictors of MACE can be useful to select at risk patients for aggressive preventive treatment. There are several markers representing endothelial activation including TM, Von willebrond factor and Tissue Plasminogen activator [6-8].

Thrombomodulint (CD 141 or BD -3) is a cell surface glycoprotein which originally identified on vascular endothelium as a natural anticoagulant. Major function of TM is thrombin receptor.

The binding of thrombin to TM significantly decrease the thrombins effect in conversion of fibrinogen to fibrin and activation of coagulation factors V, Vш and platelet [9-10]. TM-Thrombin complex also catalyze the protein C activation 1000 times faster than free thrombin. Activated protein C proteolytically inactivates the coagulation cofactors Va, and Vша. Thereby inhibiting the amplification of the coagulation system [11].

In addition, TM plays an important role in suppressing inflammation independent of anticoagulant activity [12]. Thrombin is a direct mediator of inflammation, acting as a chemoatractant for neutrophils and monocytes and stimulating endothelial cells to express monocyt chemoatractunt protein 1 (MCP-1) and other chemokines. Thrombin also induces endothelial cell expression of ICAM-1, VCAM-1, E-selectin and p-selectin as well as platelet activating factor [13].

TM regulats C3b inactivation by factor I [14]. The finding of different studies shown that TM decreases of neointhimal hyperplasia and TM gen polymorphisms are associated with CAD, Thrombosis and MI and high level of sTM signified protection and lower risk of CAD and reduced level of TM may contribute, to vascular damage and thrombosis in septicemia and cancer [15-20].

Objectives

In the present study we aim to evaluate the measurement of sTM in patients serum can be useful to predict development of MACE after PCI and stent placement.

MATERIALS AND METHODS

In a prospective study from Jan to Sep 2014, 140 patients (aged 40-70 years) who underwent PCI and stent placement in the Rajaie cardiovascular medical and research center, Tehran, Iran and didn't have any of the following criteria were included:

A - Inflammatory or auto immune disease.
B - History of CABG or PCI
C – History of angiography, surgery and cardiac events in the past 3 months.
D - History of fever or infection diseases 2 weeks before admission.

The personal information and medical history were recorded in a data collection form.
Blood samples were collected 24 hours after PCI and serum of samples were frozen at -70 until analysis.

The level of thrombomodulin was measured in samples by ELISA (Enzyme- Linked Immuno Sorbunt Assay) method with the R & D company kits. Patients were followed up at 1, 3, 9, 18 months after PCI and coronary angiography was done for cases who had chest pain or positive results of noninvasive tests. End point of the study was MACE including death, MI, Early and late stent thrombosis, target vessel revascularization (TVR) and target lesion revascularization (TLR).

Statistical methods

Fitness interval variables to normal distribution was assessed via one-sample Kolmogorov-Smirnov test. Data presented as meant ± standard deviation for interval and count (percent) for the categoriol variables. Association between the incidence of MACE and sTM or patients characteristics were investigated by students t or Pearson chi-square tests .Statistical analysis was performed by using IBM SPSS statistics 19 windows (IBM INC, Armonk, NY, USA). P values ≤ 0.05 were considered as statistical significant.

RESULTS

Baseline characteristics

140 patients (mean age = 55.61 ± 9.8) male / female 91/49 participated. dislipidemia was most risk factor (46%). The prevalence of hypertention and diabetes mellitus was 43% and 29%. Baseline characteristics of the patients are listed in table 1. Most Patients had SVD and LAD was most common vessel (69%). lesion characteristics and PCI results were shown in table 2. In the follow up time coronary angiography was done for 39 patients. 29 patients had MACE (13 Target lesion revascularization, 10 target vessel revascularization, 3 thrombosis, 2 MI and one Patient dead)

Association between MACE with reference vessls diameter

There was significant association between reference vessels diameter with development of MACE (2.56 ±0.25 VS 3.28 ±0.39 mm, $P<0.001$).

Association between MACE with blood level of sTM

The mean serum level of sTM in patients who had MACE was lower than mean sTM in patients who had not MACE but there was not statistically significant (13.99 ± 2.65 VS 15.11± 3.02ng/mL P=0.07).

Between 140 cases of this study 19 patients had not current risk factors. In this group mean blood level of sTM in the cases who had not MACE (n=15) was significantly higher than mean of sTM in patients who had MACE (n=4). (16.46 ± 3.38 VS 11.48 ± 1.92 ng/mL p=0.019) mean serum level of sTM in different groups were shown in table 3.

DISCUSSION AND CONCLUSION

Since TM discovery as a critical cofactor in the initiation of the protein C anticoagulant pathway, biochemical and structural investigation revealed that TM ,especially its lectin like domain has potent anti-inflammotory function independent of anticoaqulant, activity [10-11].

And also results of several studies determined that TM gene polymorphisms associated with human diseases and TM plays a role in thrombosis, strok, arteriosclerosis and cancer [15,19]. Previous study by the authors showed that there is a significant association between the down regulation of sTM and atherosclerosis [21] blann and MC collum introduced TM and von will brand factor as predictors of MACE [22]. wong et al showed that the stent grafts which coated with recombinant human TM significantly inhibited neointimal hyperplasia compared with uncoated grafts [16]. Results of our study determined that in patients who had not current risk factors, development of MACE after PCI and stent emplacement correlate with low Serum Level of sTM, but introduce of sTM as a predictor of MACE in the patients need to supplementary investigations with more cases.

Table 1: Comparison of baseline characteristics between patients with MACE and without MACE

	Patients With MACE n=29	Patients Without MACE n=111	P value
Age (years)	56± 11.4	56 ± 11.3	>0.99
Gender (F/M)	10/19	39/72	0.947
Hyperlipidemia	14(%48)	49(%45)	0.691
Hypertention	13(%45)	46(%42)	0.742
Smoking	11(%39)	42(%38)	0.993
Family history	6(%20)	19(%18)	0.655
Diabet melitus	8(%29)	33(%30)	0.821
Data presented as mean± SD or count (%)			

Table 2: Lesion characteristics, angiography and PCI results in patients With MACE and Without MACE

Patients with MACE (n=29)		Patients Without MACE (n=111)	P value
SVD	14(%45)	52(%47)	
2VD	11(%38)	45(%40)P= 0.964	
3VD	4(%14)	14(%13)	
PCI on LAD	18	72	
PCI on RCA	8	32	
PCI on Diag	3	8	
PCI on LCX	6	21	
Total lesion Underwent PCI P=0.931	35	133	
Lesion length	29.11 ± 8.31mm	28.65 ± 7.01mm	0.763
Stent length	31.48 ± 9.01 mm	30.48 ± 8.16 mm	0.566
Reference Vessel Diameter	2.56 ± 0.25 mm	3.28 ± 0.39 mm	<0.001

Table 3: Serum level of TM in different groups

	Patients with MACE	Patients without MACE	P value
Mean serum level of sTM (ng/ ml)	(n=29) 13.99 ± 2.65	(n=111) 15.11 ± 3. 2	0.070
Mean serum level of sTM in patients who had not current risk factor (ng/ml)	(n=4) 11.84 ± 1.92	(n=15) 16.46 ± 3.38	0.019

REFERENCES

[1] Mauri L , Hsieh WH , Massaro JM , Ho KK , Diagostino R , Cutlip DE Stent Thrombosis in randomized clinical trials of drug-eluting Stents, N Eng J Med, 2007; 356; 1020-1029.

[2] Shoji M, Koba S, Kobayashi; y,Roles of Bone-Marrow Drived cell and inflammation cytokines in neointimal hyperplasia after vascular injury. Biomed Res Int 2014.
[3] Michael S. Kim and lorry S. Dean In-Stent Restenosis, Cardiovascular Therapeutics, 2011; 29(3): 190-198.
[4] Otto S, Nitsche k, Jung C, Gassdorf J, Jania kF, Goebel B Figulla HR, Poerner TC. Determination of Neointimal Proliferation and stent Coverage after intracoronary Therapy With Drag- Eluting Devices in Stable coronary artery disease;J invasive cardiol, 2014; 26(12): 648-53.
[5] Loeffen R, Godschal k TC , Van Oerle R, Spronk HMH , Hackeng CM, Ten Berg JM, Ten cate H. The hypercoagulable Profile of Patients with Stent Thrombosis. Heart Journal 2015, 101: 1126-1132.
[6] Tomokozu ikemoto, yuribiro Hojo, Hideyuki kando NOZOMU Takahashi, Masahiro, Plasma endoglin as a marker To Predict cardiovascular events in Patients With chronic coronary Artery diseases. Heart and Vessels, Jul. 2012; 27(4): 344-51.
[7] Tuan D pham, Cuong C.To, Honghui wang and xiaobo Zhou, Analysis of MACE with entropy-Based complexity information, Technologies in biomedicine, Vol. 69; 261-72.
[8] Igor Mrdovic, Lidija savic, gordana Krljanac Milika asanin, jeva Perunicic, Predicting 30 day MACE after primary PCI. Inter J car. 2013; 20: 220-7.
[9] Martin FA, Murphy RP, Cummins PM, Thrombomodulin and the vascular endothelium; in sights in to functional, regulatory and therapeutic aspects. Am J physiol Heart Circ physiol 2013; 304(12): 1585-97.
[10] Weller H, Isermann BH. Thromobomduline. J thromb Haemost 2003 Jul; 1(7); 1515-24.
[11] Yi-Heng Li, Cheng-Hsiang Kuo , Guey-Yueh Shi, Hua-Linwu, the role of Thromobomduline Lectin Like domain in inflammation. Journal of Biomedical Sci. 2012; 19; 34.
[12] Van de Wouwer, Conway EM. Novel Function of Thrombomodulin in inflammation. Crit care Med 2004; 32(5S): 254-61.
[13] Wanxing cui, Julianty Angsana, Jing Wen, Elliot chaikaf Liposomal formulation of thrombomodulin increased engraftment after intraportal islet transplantation. Cell transplantation, 2010; 19(11): 1359-67.
[14] Verhagen HJ, Heijnen-Snyder GJ, Pronk A, Vroom TM, Elkelboom BC, Sixma JJ. Thrombomodulin activity on mesothelial cells. British Journal of Haematology, 1996; 542-49.
[15] Shuai Zhang, Zhe Zhang, Feng Zhang,Chuanxiang W, ying B. Association between Thrombomodulin Polymorphysms and CAD Risk, Medical SCI Monit. 2014; 20: 1407-14.
[16] Wong G, LI, JM, Hendricks G, Eslami; MH, Rohrer MJ, Culter BS. Inhibition of experimental neointimal hyperplasia by recombinant thrombomodulin coated (ep TFE) stent grafts. J Vasc Surg 2008; 47(3): 608-15.
[17] J.M Waugh, li Hawkins , E yuksel , M.D Kuo, P.N. Cifraba , P.R Hilfiker, Thrombomodulin over expression to limit neointima Formation, Circulation, 2000; 102: 332-7.
[18] Po-KU chen , Bi-Ing chang , cheng – Hsiang Kuo, Pin- shern chen , chia fong cho , chuan fa chang, Thrombomodulin Function as a Plasminogen rcceptor to Modulate angiogenesis, The faseb Journal 2013; 27(11): 4520-31.
[19] Kenneth K. Wu, Nena Aleksic, Chul Ahn, Eric Boer Winkle, Aaron R Folsom, Harinder Juneja thrombomodulin Ala 455 Polymorphism and risk of CHD. Circulation 2001; 108: 1886-89.
[20] Juan M Jimenez, Varesh Prasad, Michael Dyu, Christopher Kampmeyer, Abdul Hadi Koakur, Jiang Wang, Macro and micro scale variables regulate stent haemodynamics, fibrin deposition and thrombomodulin Expression. J R SOC Interface, 2014; 11(94): 1079-94.
[21] Nozar Givtaj, H.A.Bassiri, Nader Givtaj, B.V Behhnam. Correlation between Blood levels of Adhesion Molecules ICAM-1, VCAM-1 and Thrombomodulin with coronary, Artery disease. Iranian Heart J. 2010; 11(1): 24-29
[22] Blann AD, MC Collum CN, Von will brand Factor and sTM as predictors of Adverse events among subject with Peripheral or coronary atherosclerosis, Blood coagul fibrinolysis, 1999; 10(6): 375-8.