30 درصد تخفیف نوروزی ویژه کارگاه‌ها و فیلم‌های آموزشی

اصول تنظیم قراردادها
پروپوزال نویسی
آموزش مهارت‌های کاربردی در ندوین و چاپ مقاله
Comparison of the Effects of Enoxaparin and Heparin on Inflammatory Biomarkers in Patients with ST-segment Elevated Myocardial Infarction: A prospective Open Label Pilot Clinical Trial

Somayyeh Nasiripour\textsuperscript{a}, Kheirollah Gholami\textsuperscript{b}, Sarah Mousavi\textsuperscript{c}, Abbas Mohagheghi\textsuperscript{d}, Mania Radfar\textsuperscript{a}, Mohammad Abdollahi\textsuperscript{a}, Zahra Khazaeipour\textsuperscript{a} and Mojtaba Mojtahedzadeh\textsuperscript{a,e,*}

\textsuperscript{a}Clinical Pharmacy Department, Faculty of Pharmacy, Tehran University of Medical Sciences and Health Services, Tehran, Iran. \textsuperscript{b}Clinical Pharmacy Department, Faculty of Pharmacy, Tehran University of Medical Sciences and Health Services and Research Center for Rational Use of Drugs, Tehran, Iran. \textsuperscript{c}Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran. \textsuperscript{d}Department of Cardiology, Shariati Hospital, Tehran University of Medical Sciences, Tehran 14114, Iran. \textsuperscript{e}Faculty of Pharmacy, and Pharmaceutical Sciences Research Centre, Tehran University of Medical Sciences, Tehran, Iran. \textsuperscript{f}Brain and Spinal Cord Injury Research Center, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran.

Abstract

Heparin and enoxaparin possess anti-inflammatory properties. We compared the effects of these drugs on inflammatory biomarkers in patients with ST-segment Elevated Myocardial Infarction (STEMI).

Thirty four patients with STEMI randomly separated in two groups and received standard doses of heparin and enoxaparin. The serum concentration of Serum Amyloid A (SAA), C-Reactive Protein (CRP), Interleukin (IL)-6, ferritin and Myeloperoxidase (MPO) were measured at baseline, 12, 24 and 48 hours after drug administration.

Serum concentrations of SAA (P: 0.02), CRP (P: 0.02) and ferritin (P: 0.01) significantly reduced in heparin group during measurements compared to baseline, circulating levels of IL-6 (P: 0.002), SAA (P: 0.009), CRP (P: 0.01) were significantly decreased in enoxaparin group. The overall difference in inflammatory biomarkers between heparin and enoxaparin group was not significant.

Both heparin and enoxaparine reduced serum levels of inflammatory biomarkers in patients with STEMI. This effect may provide additional clinical benefit of these drugs in the treatment of STEMI patients.

Keywords: Heparin; Enoxaparin; Acute coronary syndrome; STEMI; Inflammatory biomarkers.

Introduction

Inflammation has a key role in the pathogenesis of coronary artery plaque destabilization and rupture leading to Acute Coronary Syndrome (ACS) (1). Leukocyte activation, monocyte and neutrophil infiltration result in local and systemic inflammatory responses (2, 3). High circulating levels of inflammatory markers...
aged >18 years were considered for inclusion if they exhibited 1) Continuous chest pain upon presentation, refractory to nitrates and lasting ≥ 30 min; 2) ST-segment elevation of ≥ 0.2 mv in ≥2 contiguous precordial leads, or ≥ 0.1 mv in ≥2 contiguous limb leads, or new left bundle branch block on admission electrocardiogram 3) Elevated serum levels of cardiac markers.

The main criteria for exclusion were: pregnancy, treatment with heparin or enoxaparin for >24 hours before enrollment, treatment with a glycoprotein IIb/IIIa inhibitors, dipyridamole within the previous 2 weeks, treatment with an oral anticoagulant within previous 5 days, acute inflammatory disease (acute arthritis or acute infection) at the time of randomization, massive hemorrhage or blood transfusion, weight > 120 or < 40 Kg, acute renal failure, sepsis, hemoglobin < 8g/dl, patients receiving high dose of corticosteroids and thrombocytopenia within treatment period.

**Treatment protocol**

Patients selected and randomized (simple randomization) to 2 treatment groups. Both groups received standard treatment for STEMI based on our hospital protocol. First group received weight adjusted enoxaparin (1 mg/Kg subcutaneously at 12 hours interval). Second group received heparin (initial bolus 60 unit/Kg, followed by a continuous infusion at 12 units/Kg/h). The infusion of heparin was dose adjusted according to the activated partial thromboplastin time (a PTT). The target a PTT being 1.5 to 2.5 times control, streptokinase was the thrombolytic agent used (1.5 MU IV over 60 min).

All patients received aspirin orally in a dose of 325 mg upon presentation and it was continued as a daily dose (100-325 mg) indefinitely. Further medical therapy including clopidogrel, beta blockers, nitrates, Ca channel blockers, angiotensin converting enzyme inhibitors and statins was prescribed based on hospital protocol.

Patient’s demographic, medical history and laboratory data were collected on pre-designed questionaries. Patient’s clinical and paraclinical characteristics were recorded at baseline as the following: Blood urea Nitrogen (BUN), Creatinin (Cr), WBC count, Platelet count, hemoglobin, Blood pressure, Heart rate,
Blood sugar, Ejection Fraction (EF), Electrolyte (Na⁺, K⁺, Ca²⁺, Mg²⁺), Creatin kinase MB, Prothrombin Time (PT), a PTT and international Normalization Ratio (INR).

Collection of blood samples and biologic measurements
Venous blood samples were taken at baseline (T0), 12(T1), 24(T2) and 48(T3) hours after drug administration. Blood samples were spun at 1500*g for 10 minutes and then was stored at -80°C until the time of analysis. Hs-CRP concentrations were analyzed by an immunoturbidimetric assay (Pars azmun, Tehran, Iran). Ferritin was measured by a chemiluminescence assay (Diasorin-lialison, Stillwater, MN, USA). SAA and MPO were analyzed using commercially available enzyme-linked immunosorbent assay kit (USCN Lifescience Inc, Wuhan, China). IL-6 was determined by an enzyme-linked immunosorbent assay kit (Abcam, Cambridge, UK).

Statistical analysis
The distribution of quantitative data was assessed for normality by one sample Kolmogorov-Smirnov test. t-test was used, for comparing quantitative variables in two groups. Qualitative variables were compared by Chi square test or Fisher’s exact test when appropriate. Repeated measurement analysis was conducted for serial comparisons of quantitative variables and comparisons between groups in different times of treatment. Qualitative variables were recorded by frequency and percent and quantitative variables by Mean ± SD (Standard Deviation). All statistical analysis were conducted using SPSS version 11.5 (SPSS Inc., Chicago, IL, USA) and significance was defined as p-value of <0.05.

Results
Baseline characteristic
During the recruiting period 34 patients with STEMI were enrolled in the study, 17 in each group. There were no statistically significance differences between groups in regard to clinical characteristics and laboratory data. Baseline inflammatory biomarkers were not significantly different in both groups (Tables 1, 2).

Changes of inflammatory biomarkers in four steps of measurements are presented in Table 3. Circulating levels of SAA (P: 0.02), CRP (P: 0.02) and ferritin (P: 0.01) significantly reduced in heparin group during measurement, however circulating levels of IL-6 (P: 0.002), SAA (P: 0.009), CRP (P: 0.01) were significantly decreased in enoxaparin group. MPO levels had variable changes during measurement (Figure 1), however the levels were lower in enoxaparin group (P: 0.5). The overall difference in inflammatory biomarkers between heparin and enoxaparin group were not significant.

Discussion
The current study has shown that both heparin and enoxaparin reduced serum levels of...
Table 2. Clinical characteristics of quantitative variables in groups of intervention.

|             | Enoxaparin N=17 | Heparin N=17 | p* |
|-------------|-----------------|--------------|----|
| Age         | 56.6 ± 13.3     | 56.5 ± 12.5  | 0.9|
| BMI         | 25.3 ± 3.3      | 24.9 ± 2.5   | 0.7|
| WBC         | 13317.0 ± 3030.9| 13141.2 ± 1757.8 | 0.4|
| RBC         | 4.8 ± 0.5       | 4.8 ± 0.5    | 0.8|
| Hb          | 14.6 ± 1.4      | 14.3 ± 1.4   | 0.5|
| PLT         | 214823.5 ± 58314.0| 223352.9 ± 50131.0 | 0.6|
| BUN         | 19.1 ± 4.5      | 18.4 ± 4.2   | 0.6|
| BMI         | 25.3 ± 3.3      | 24.9 ± 2.5   | 0.7|
| WBC         | 13317.0 ± 3030.9| 13141.2 ± 1757.8 | 0.4|
| RBC         | 4.8 ± 0.5       | 4.8 ± 0.5    | 0.8|
| Hb          | 14.6 ± 1.4      | 14.3 ± 1.4   | 0.5|
| PLT         | 214823.5 ± 58314.0| 223352.9 ± 50131.0 | 0.6|
| BUN         | 19.1 ± 4.5      | 18.4 ± 4.2   | 0.6|
| BMI         | 25.3 ± 3.3      | 24.9 ± 2.5   | 0.7|
| WBC         | 13317.0 ± 3030.9| 13141.2 ± 1757.8 | 0.4|
| RBC         | 4.8 ± 0.5       | 4.8 ± 0.5    | 0.8|
| Hb          | 14.6 ± 1.4      | 14.3 ± 1.4   | 0.5|
| PLT         | 214823.5 ± 58314.0| 223352.9 ± 50131.0 | 0.6|
| BUN         | 19.1 ± 4.5      | 18.4 ± 4.2   | 0.6|
| BMI         | 25.3 ± 3.3      | 24.9 ± 2.5   | 0.7|
| WBC         | 13317.0 ± 3030.9| 13141.2 ± 1757.8 | 0.4|
| RBC         | 4.8 ± 0.5       | 4.8 ± 0.5    | 0.8|
| Hb          | 14.6 ± 1.4      | 14.3 ± 1.4   | 0.5|
| PLT         | 214823.5 ± 58314.0| 223352.9 ± 50131.0 | 0.6|
| BUN         | 19.1 ± 4.5      | 18.4 ± 4.2   | 0.6|

♦t-test
BMI: Body Mass Index, Hb: Hemoglobin, PLT: Platelet, BUN: Blood Urea Nitrogen, Cr: Creatinine, BP: Blood Pressure, CKMB: Ceratin Kinase MB, AST: Aspartat aminotransferase, Alk Ph: Alkaline phosphatase, PTP:Prothrombin Time, PTT:Partial Thromboplastin Time, INR:International Normalization Ratio, SAA: Serum Amyloid A, MPO: Myeloperoxidase, CRP: C-Reactive Protein, IL-:Interleukin , T0:measurement at baseline(before intervention)
P: Level of significance (<0.05)

Table 3. Changes of inflammatory biomarkers in 4 steps of measurements in heparin and enoxaparin group.

| Group | T0               | T1               | T2               | T3               | P(changes in 4 steps) | P(comparing 2 groups) |
|-------|------------------|------------------|------------------|------------------|------------------------|------------------------|
| SAA   | Heparin 51.3 ± 14.1 | 43.1 ± 16.0      | 40.7 ± 12.4      | 42.2 ± 12.6      | 0.02                   | 0.5                    |
|       | Enoxaparin 50.9 ± 14.5 | 48.4 ± 13.7      | 43.6 ± 14.7      | 42.5 ± 12.9      | 0.009                  |                        |
| MPO   | Heparin 61.3 ± 29.4 | 56.1 ± 29.1      | 53.8 ± 35.9      | 58.6 ± 36.1      | 0.6                    | 0.5                    |
|       | Enoxaparin 53.7 ± 20.0 | 58.5 ± 25.3      | 46.3 ± 21.1      | 52.1 ± 16.8      | 0.5                    |                        |
| CRP   | Heparin 99.9 ± 111.3 | 89.6 ± 89.1      | 86.4 ± 50.2      | 85.4 ± 30.4      | 0.02                   | 0.8                    |
|       | Enoxaparin 115.7 ± 148.4 | 82.5 ± 112.5     | 50.2 ± 80.7      | 45.9 ± 50.0      | 0.01                   |                        |
| IL-6  | Heparin 29.2 ± 28.4 | 28.4 ± 23.6      | 20.9 ± 18.3      | 17.9 ± 17.2      | 0.08                   | 0.9                    |
|       | Enoxaparin 34.6 ± 28.8 | 27.0 ± 24.9      | 20.4 ± 24.2      | 18.6 ± 21.4      | 0.002                  |                        |
| Ferritin | Heparin 275.8 ± 136.3 | 263.2 ± 117.9    | 247.4 ± 107.8    | 229.1 ± 89.5     | 0.01                   | 0.1                    |
|       | Enoxaparin 213.3 ± 97.8 | 189.1 ± 82.9     | 187.2 ± 76.4     | 181.3 ± 72.7     | 0.2                    |                        |

T0: baseline, T1: 12 h after intervention, T2:24 h after intervention, T3: 48 h after intervention
SAA: Serum Amyloid A, MPO: Myeloperoxidase, CRP: C-Reactive Protein, IL-:Interleukin
P: Level of significance (<0.05)
Heparin, enoxaparin and inflammatory markers in patients with STEMI. This effect may provide additional clinical benefit in the treatment of STEMI patients.

Release of Acute Phase Reactant proteins (APR) play a causative role in ACS. Elevated circulating levels of inflammatory biomarkers have prognostic value (4). High levels of hs-CRP increased risk of long term cardiovascular mortality in STEMI patients (33) and American Heart Association (AHA) recommend it as a biomarker for risk stratification in cardiovascular disorder (34). SAA had higher values in STEMI patients and together with hs-CRP had been associated with a major number of complicated lesions in patients with ACS (6, 35). Some of the commonly used drugs can reduce the inflammation process in ACS (36-38). The potential of heparin as an anti-inflammatory drug is supported by several clinical trials in various models of inflammatory disease (13-29). Heparin inhibits the function, expression or synthesis of adhesion molecules, cytokines, angiogenic factors and complements (39, 40). Also some in-vitro and in-vivo studies show that LMWHs possesses anti-inflammatory effects (18, 20, 22, 41-43). Based on our result, both drugs significantly reduced serum levels of CRP, SAA which regard to the role of these APR proteins worthy to be considered.

The ARMADA study The ARMADA study compared effects of unfractioned heparin (UFH), enoxaparin and dalteparin in 141 patients with unstable angina or non- STEMI. In this study enoxaparin decreased level of von willberand factor (an APR protein) significantly compared to heparin. The authors concluded that enoxaparin had superior and equivalent efficacy over UFH in unstable angina (31). James et al., evaluated the safety and efficacy of treatment with glycoprotein IIb/IIIa inhibition in addition to aspirin, low molecular-weight heparin and its influence on coagulation and inflammation in patients with unstable angina. Baseline levels of creatinine, C-reactive protein (CRP), troponin T (TnT) and N-terminal pro-brain natriuretic peptide (NT-proBNP) were analysed, but non of the drugs or combination of them reduced in flammatory markers in this study (44). Oldegren et al., evaluate the prolonged effect of dalteparine in unstable coronary artery disease, patients were received dalteparin 120 IU Kg (-1) s.c. twice daily for 5-7 days and randomized to placebo (n=285) or gender and weight-adjusted doses of dalteparin (5,000 or 7,500 IU) twice daily (n=270) for 3 months. Dalteparin persistently depressed coagulation activity but
Interleukin-6, C-reactive protein and fibrinogen levels were unaffected by dalteparin treatment (45). Our study was conducted in STEMI patients and in this setting both drugs was successful in reducing levels of inflammatory biomarkers. Although it is mentioned that pattern of activation of inflammation is different in non-STEMI and STEMI patients (46) and it is possible that heparin and enoxaparin have different mechanism of actions and work in a dissimilar way in ACS.

IL-6 is a well-known cytokine that have important role in inflammatory response (47, 48). High levels of IL-6 also increase the risk of mortality in STEMI patients (8), however both drugs reduced levels of IL-6 but the reduction was significant in enoxaparin group. Why enoxaparin is more effective than heparin on IL-6 is question to be answered in future studies.

Myeloperoxidase is a hemoprotein that abundant in rupture plaques and useful as a clinical tool in coronary artery disease (CAD) (49), however it is inferior to CRP as a marker for risk stratification. The levels of MPO had variable changes during our measurements, recent study shows for the first time the existence of diurnal variations in MPO levels in STEMI patients (higher at night), so time of blood sampling is important and it could be the reason of fluctuation of MPO levels in our study.

Conclusion

Heparin and enoxaparin are one of the important parts of ACS treatment, based on the role of inflammatory process in STEMI patients and potential of these drugs to suppress inflammatory biomarkers. It is probable that part of the benefit of these drugs in STEMI patients is because of their anti-inflammatory properties. Due to the small sample size conducted a similar study with a larger sample size is recommended.

Acknowledgment

We would gratefully like to thank specialist and nurses of the Cardiac Care Unit of Shariati Hospital for participating in this study. Likewise we like to thank SANOFI Company which partially supported this study.

References

(1) Hansson GK. Inflammation, atherosclerosis and coronary artery disease. *N. Engl. J. Med.* (2005) 352: 1685-95.
(2) Epstein FH, Fuster V, Badimon L, Badimon JJ and Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes. *N. Engl. J. Med.* (1992) 326: 242-50.
(3) Libby P. Current concepts of the pathogenesis of the acute coronary syndromes. *Circulation* (2001) 104: 365-372.
(4) Armstrong EJ, Morrow DA and Sabatine MS. Inflammatory biomarkers in acute coronary syndromes. *Circulation* (2006) 113: 152-155.
(5) Lindahl B, Toss H, Siegbahn A, Venge P and Wallentin L. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. *N. Engl. J. Med.* (2000) 343: 1139-147.
(6) Kosuge M, Ebina T, Ishikawa T, Hibi K, Tsukahara K and Okuda J. Serum amyloid A is a better predictor of clinical outcomes than C-reactive protein in non-ST-segment elevation acute coronary syndromes. *Circulation J. Off. J. Japanese Circulation Socie* (2007) 71: 186.
(7) Morrow DA, Rifai N, Antman EM, Weiner DL, McCabe CH and Cannon CP. Serum amyloid A predicts early mortality in acute coronary syndromes: a TIMI 11A substudy. *JACC.* (2000) 35: 358-362.
(8) Ikeda U, Ito T and Shimada K. Interleukin-6 and acute coronary syndrome. *Clin. Cardiol.* (2001) 24: 701-704.
(9) Gil M, Zarębiński M and Adamus J. Plasma fibrinogen and troponin I in acute coronary syndrome and stable angina. *Int. J. Cardiol.* (2002) 83: 43-46.
(10) Wang Y, Che S and Ma A. Clinical significance of serum cytokines IL-1beta, sIL-2R, IL-6, TNF-alpha, and IFN-γ in acute coronary syndrome. *Chinese med. Sci. J.* (2002) 19: 120.
(11) Morrow DA, Sabatine MS, Brennan ML, De Lemos JA, Murphy SA and Ruff CT. Concurrent evaluation of novel cardiac biomarkers in acute coronary syndrome: myeloperoxidase and soluble CD40 ligand and the risk of recurrent ischaemic events in TACTICS-TIMI 18. *Eur. Heart J.* (2008) 29: 1096-1102.
(12) Wollert KC, KempfT, Peter T, Olofsson S, James S and Johnston N. Prognostic value of growth-differentiation factor-15 in patients with non-ST-elevation acute coronary syndrome. *Circulation* (2007) 115: 962-971.
(13) Ang Y, Mahmud N, White B, Byrne M, Kelly A and Lawler M. Randomized comparison of unfractionated heparin with corticosteroids in severe active inflammatory bowel disease. *Aliment. Pharmacol. Ther.* (2000) 14: 1015-1022.
(14) Baram D, Rashkovsky M, Hershkoviz R, Drucker I, Reshef T and Ben-Shitrit S. Inhibitory effects of low molecular weight heparin on mediator release by mast cells: preferential inhibition of cytokine production...
and mast cell-dependent cutaneous inflammation. Clin. Exp. Immunol. (1997) 110: 485-491.

(15) Bowler SD, Smith SM and Lavercombe PS. Heparin inhibits the immediate response to antigen in the skin and lungs of allergic subjects. Am. J. Respir. Crit. Care. Med. (1993) 147: 160-163.

(16) Carr J. The anti-inflammatory action of heparin: Heparin as an antagonist to histamine, bradykinin and prostaglandin E1. Thromb. Res. (1979) 16: 507-516.

(17) Ceyhan B and Celikel T. Effect of inhaled heparin on methacholine-induced bronchial hyperreactivity. Chest. (1995) 107: 1009-1012.

(18) Deepa P and Varalakshmi P. Favourable modulation of the inflammatory changes in hypercholesterolemic atherogenesis by a low-molecular-weight heparin derivative. Int. J. Cardiol. (2006) 106: 338-347.

(19) Diamant Z, Timmers MC, Van der Veen H, Page CP, Van der Meer F and Sterk PJ. Effect of inhaled heparin on allergen-induced early and late asthmatic responses in patients with atopic asthma. Am. J. Respir. Crit Care. Med. (1996) 153: 1790-1795.

(20) Downing LJ, Strieter RM, Kadell AM, Wilke CA, Greenfield LJ and Wakefield TW. Low-dose low-molecular-weight heparin is anti-inflammatory during venous thrombosis. J. Vasc. Surg. (1998) 28: 848-854.

(21) Föwaczyn Z, Wiebecke B and Loeschke K. Unfractioned heparin in the therapy of patients with highly active inflammatory bowel disease. Am. J. Gastroenterol. (1999) 94: 1551-1555.

(22) Hochart H, Vincent Jenkins P, Smith OP and White B. Heparin, enoxaparin and inflammatory markers in acute coronary syndromes. Thromb. Haemost. (2003) 102: 823-828.

(23) Lane DA and Adams L. Non-antiagulant uses of heparin. N. Engl. J. Med. (1993) 329: 129-30.

(24) Li J and Vlodavsky I. Heparin, heparan sulfate and heparanase in inflammatory reactions. Thromb. Haemost. (2009) 102: 823-828.

(25) Mousa SA (ed.) Heparin, low molecular weight heparin, and derivatives in thrombosis, angiogenesis, and inflammation: emerging links 2007: New York: Straton Intercontinental Medical Book Corporation, (1974).

(26) Nelson RM, Cecconi O, Roberts WG, Aruffo A, Linhardt RJ and Bevilacqua MP. Heparin oligosaccharides bind L- and P-selectin and inhibit acute inflammation. Blood. (1993) 82: 3253-3258.

(27) Rumelt S, Stolovich C, Segal ZI and Rehany U. Intraoperative enoxaparin minimizes inflammatory reaction after pediatric cataract surgery. Am. J. Ophthalmol. (2006) 141: 433-437.

(28) SalibaRJ MJ. Heparin in the treatment of burns: a review. Burns. (2001) 27: 349-358.

(29) Zezos P, Papaioannou G, Nikolaidis N, Patsiaoura K, Papaeorgeiou A and Vassiliadis T. Low-molecular-weight heparin (enoxaparin) as adjuvant therapy in the treatment of active ulcerative colitis: a randomized, controlled, comparative study. Aliment. Pharmacol. Ther. (2006) 23: 1443-1453.

(30) Wang L, Brown JR, Varki A and Esko JD. Heparins anti-inflammatory effects require glucosamine 6-O-sulfation and are mediated by blockade of L- and P-selectins. J. Clin. Invest. (2002) 110: 127-136.

(31) Montalescot G, Bal-dit-Sollier C, Chibedi D, Collet JP, Soulat T and Dalby M. Comparison of effects on markers of blood cell activation of enoxaparin, dalteparin, and unfractionated heparin in patients with unstable angina pectoris or non-ST-segment elevation acute myocardial infarction (the ARMADA study). Am. J. Cardiol. (2003) 91: 925-930.

(32) Nallarantnam M, T, Kettle A, Smyth D, Winterbourn C, Elliott J, Richards M and McClean D. Heparin, But not bivalirudin, liberates endothelial myeloperoxidase in patients with ST Elevation Myocardial Infarction(STEMI). Heart Lung Circ. (2007) 16: 24-25.

(33) Zairis MN, Adamopolou EN, Manousakis SJ, Lyras AG, Bibis GP and Ampatzidou OS. The impact of hs C-reactive protein and other inflammatory biomarkers on long-term cardiovascular mortality in patients with acute coronary syndromes. Atherosclerosis (2007) 194: 397-402.

(34) Hlatky MA, Greenland P, Arnett DK, Ballantyne CM, Criqui MH and Elkind MSV. Criteria for evaluation of novel markers of cardiovascular risk: A Scientific Statement From the American Heart Association. Circulation. (2009)119: 2408-2416.

(35) Jousilahti P, Salomaa V, Rasi V, Vahtera E and Palosuo T. The association of c-reactive protein, serum amyloid a and fibrinogen with prevalent coronary heart disease-baseline findings of the PAIS project. Atherosclerosis (2001) 156: 451-456.

(36) Kinlay S, Schwartz GG, Olsson AG, Rifai N, Leslie SJ and Sasiela WJ. High-dose atorvastatin enhances the decline in inflammatory markers in patients with acute coronary syndromes in the MIRACL study. Circulation (2003) 108: 1560-1566.

(37) Koskenkari J, Kaukoranta P, Rimpiläinen J, Vainioläppä V, Ohtonen P and Surcel HM. Anti-inflammatory effect of high-dose insulin treatment after urgent coronary revascularization surgery. Acta Anaesthesiologica Scandinavica. (2006) 50: 962-969.

(38) Patti G, Greico D, Dicouzno G, Pasceri V, Nusca A and Di Sciascio G. High Versus Standard Clopidogrel Maintenance Dose After Percutaneous Coronary Intervention and Effects on Platelet Inhibition, Endothelial Function, and Inflammation, Results of the ARMYDA-150 mg (Antiplatelet Therapy for the ARMYDA-150 mg (Antiplatelet Therapy for Unstable Angina and Non-ST-Elevation Myocardial Infarction(STEMI). J. Am. Coll. Cardiol. (2011) 57: 771-778.

(39) Elsayed E and Becker RC. The impact of heparin compounds on corticosteroid-induced cutaneous responses: a construct for future investigation and pharmaceutical development. J. Thromb. Thrombolysis (2003) 15: 11-18.

(40) Young E. The anti-inflammatory effects of heparin and related compounds. Thromb. Res. (2008) 122: 743-52.
(41) Manduteanu I, Voinea M, Capraru M, Dragomir E and Simionescu M. A novel attribute of enoxaparin: inhibition of monocyte adhesion to endothelial cells by a mechanism involving cell adhesion molecules. *Pharmacol.* (2002) 65: 32-37.

(42) Quartermain D, Li YS and Jonas S. The low molecular weight heparin enoxaparin reduces infarct size in a rat model of temporary focal ischemia. *Cerebrovasc. Dis.* (2003) 16: 346-55.

(43) Vignoli A, Marchetti M, Balducci D, Barbui T and Falanga A. Differential effect of the low-molecular-weight heparin, dalteparin, and unfractionated heparin on microvascular endothelial cell hemostatic properties. *Haematologica.* (2006) 91: 207-214.

(44) James S. Coagulation, inflammation and myocardial dysfunction in unstable coronary artery disease and the influence of glycoprotein IIb/IIIa inhibition and low molecular weight heparin. *Ups. J. Med. Sci.* (2004) 109: 71-122.

(45) Oldgren J, Fellenius C, Bomann K, Jansson JH, Nilsson TK, Wallentin L and Siegbahn A. Influence of prolonged dalteparin treatment on coagulation, fibrinolysis and inflammation in unstable coronary artery disease. *J. Intern. Med.* (2005) 258: 420-427.

(46) Di Stefano R, Di Bello V, Barsotti MC, Grigoratos C, Armani C and Delli-Omodarme M. Inflammatory markers and cardiac function in acute coronary syndrome: difference in ST-segment elevation myocardial infarction (STEMI) and in non-STEMI models. *Biomed. Pharmacother.* (2009) 63: 773-780.

(47) Panahi Y, Mojtabehzadeh M, Zekeri N, Beiraghdar F, Khajavi MR and Ahmadi A. Metformin Treatment in Hyperglycemic Critically Ill Patients: Another Challenge on the Control of Adverse Outcomes. *Irran. J. Pharm. Res.* (2011) 10: 913-919.

(48) Tabeeefar H, Beigmohammadi MT, Javadi MR, Abdollahi M, Mahmoodpoor A and Ahmadi A. Effects of Pantoprazole on Systemic and Gastric Pro- and Anti-inflammatory Cytokines in Critically Ill Patients. *Irran. J. Pharm. Res.* (2012) 11: 1051-108.

(49) Dominguez-Rodriguez A, Abreu-Gonzalez P and Kaski JC. Diurnal variation of circulating myeloperoxidase levels in patients with ST-segment elevation myocardial infarction. *Int. J. Cardiol.* (2010) 144: 407-409.

This article is available online at http://www.ijpr.ir
۳۰ درصد تخفیف نوروزی ویژه کارگاه‌ها و فیلم‌های آموزشی

اصول تنظیم قراردادها

پروپوزال نویسی

آموزش مهارت های کاربردی در ندوین و چاپ مقاله