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Original Article

The effectiveness of olmesartan on inflammation at cardiopulmonary bypass

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Abstract

Aim: Systemic inflammatory response syndrome may develop after coronary artery bypass graft surgery that performed by cardiopulmonary bypass technique. It is known that olmesartan, an angiotensin II receptor blocker, has anti-inflammatory effects. The antiinflammatory efficacy of olmesartan treatment was investigated in patients undergoing cardiopulmonary bypass.

Materials and Methods: The study included 50 patients (14 female, 36 male) between 30-80 years of age were underwent CABG surgery. Patients were randomly assigned to control (Group C) and olmesartan (Group O) gruoups. Group O were treated with a single dose of 10 mg per day; 5 days preoperatively and 35 days postoperatively, 30 mg at the operation day. Samples were taken before the induction of anesthesia (T1), 5 minutes before cross clamping (T2), 5 minutes after cross clamping (T3), after protamine infusion (T4), postoperative day 3 (T5) and postoperative day 35 (T6) for total serum levels of IL-6, IL-10 and IL-18; for h-CRP levels preoperative (T1) and postoperative day 35 (T2).

Results: Statistically significant decrease of CRP levels were observed on the postoperative 35th day in Group O ($p<0.05$). Statistically significant decrease of IL-6 levels were observed in the Group O after protamine infusion (T4) and postoperative 3rd day (T5) ($p <0.05$).There was a statistically significant increase at 5 min. after the cross declamping time (T3) for IL-10 levels ($p<0.05$).

Conclusion: Although the anti-inflammatory efficacy of olmesartan has been proven, it can be accomplished by combining it with drugs that have anti-inflammatory effects like statins or dose increasing.

Keywords: Bypass; inflammation; interleukines; olmesartan

INTRODUCTION

Systemic inflammatory response syndrome (SIRS) is a complication of cardiac surgery after cardiopulmonary bypass (CPB). During the CPB, contact of the blood elements with the heart-lung pump system that provides extracorporeal circulation, ischemia/reperfusion injury (I/R), hypothermia, endotoxemia, surgical stress and anesthesia are possible causes of systemic inflammatory response syndrome (SIRS) (Table 1). Cytokines and the release of free oxygen radicals, activation of the complement system, arachidonic acid metabolites, endothelin and platelet activating factors play major role in SIRS (1). This inflammatory response may be the cause of complications such as myocardial dysfunction, respiratory failure, renal disorders, neurological disorders, bleeding diathesis, liver dysfunction and multiple organ failure (MOF), especially in the postoperative period (2-5).

The balance between the inflammatory and anti-inflammatory responses is important for the clinical course of the patient (6). On the other hand, the release of anti-inflammatory cytokine IL-10 during CPB plays a protective role against inflammation by inhibiting the production of proinflammatory cytokines (7). In vitro datas are supporting the anti-inflammatory efficacy of ARBs and increased inhibition of the production for monocyte chemotactic protein-1 (MCP-1) by human monocytes by irbesartan and losartan (8). In human body, the most important cytokine against the above-mentioned inflammatory cytokines is IL-10 that known as cytokine synthesis inhibitory factor (CSIF) (9-11).

Table 1. Releasing times of the cytokines after cardiac surgery

Cytokine	Beginning Time	Peak Time	Time
TNF	After the CPB	2-18 h later	24 hours
IL-1	After CPB finished	24 h	-
IL-6	2 h after CPB	4 h	3-5 days
IL-8	At the rewarming period	1-3 h later	24 hours
IL-10	End of the CPB	1 h after CPB	1-5 hours

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Cytokine secretion begins to increase at the onset of CPB and continues 12-24 hours postoperatively to the peak level. CPB and aortic cross clamp times are the most important parameters for affecting the cytokine secretion (12).

IL-6 involves in the adjustment of the immune response as a multifunctional pleotropic cytokine, in the acute phase response, hematopoiesis and inflammation (13). It is directly effective in leukocyte traffic and activation (14).

IL-10 is a key regulator in the inflammatory response and expresses both early and advanced atherosclerotic plaques in vascular pathologies where inflammation is important and limits the local inflammatory process (15,16).

IL-18 is a proinflammatory cytokine from the IL-1 superfamily and was first described as an IFN-inducing factor and it is converted into the pro-IL-18 mature form through the TLR pathway than release from the cells (17). A wide range of cells as macrophages, kupffer cells, keratinocytes, osteoblasts, astrocytes and DCs release IL-18 (18).

C-reactive protein (CRP) is a major acute phase reactant in humans that rapidly elevates as response to infection and tissue injury. The results of many recent studies have shown that h-CRP is the strongest predictor of atherosclerosis and vascular deaths (19,20). When all of the inflammatory and lipid markers were compared in predicting cardiovascular events, CRP was found to be superior to all other biomarkers (including LDL) (21). Franke et al. state that cardiac operations produce a biphasic immune response (22).

Olmesartan is a recently developed angiotensine II (Ang II) receptor blocker. It decreases the blood pressure by blocking Ang II receptors like the other angiotensine receptor blocker (ARB)'s. It was determined that a single dose of 10 mg or more (10-40 mg) orally, olmesartan medoxomil reduces the blood pressure 75% of the patients (23).

MATERIALS and METHODS

The total of 50 patients who aged between 30 and 80 years were enrolled in a prospective randomized study after the approval of the Medical Faculty Clinical Research and Ethics Committees (No:17.02.2011-04.04). Informed voluntary consent form was obtained from all of the patients who accepted the study. Patients with thyroidal disease, arrhythmias, emergency operations, reoperations, need for an additional surgical procedure, over 80 years of age, chronic renal failure, chronic obstructive pulmonary disease, liver failure, heart rates were less than 60/min, ejection fraction (EF) was less than 30% and active infected were excluded from the study. Patients were randomly divided into two groups: 25 patients in Group C: Control group, 25 patients in Group O: Olmesartan group. Group C patients were used natural drug capsules as placebo. The patients in Group O were given 10 mg/day olmesartan medoxomil for preoperative 5 days and postoperative 35 days. 30 mg peroral olmesartan was given on the day of operation only one time.

Surgical procedures and grafts that were used in bypass surgery were same in both groups. All of the surgery performed with cardiopulmonary bypass technique and firstly left anterior descending artery (LIMA) was harvested firstly for left anterior descending artery (LAD) in all of the patients. Saphenous vein was harvested for the other vascular bypasses at the same time.

Blood samples were taken at basal (T1) and postoperative 35th days (T2) to determine serum h-CRP levels and for IL-6, IL-10 and IL-18 prior to induction of anesthesia (T1), 5 minutes after cross-clamping (T2), 5 min after cross declamping (T3), after protamine infusion (T4), postoperative 3rd day (T5) and on the postoperative 35th days (T6). All the blood samples were centrifuged at 3000 rpm for 5 minutes and stored at -85^{o}C. BOTEK washer (ELX 50TM Microplate, 40710000, Winooski, USA) and BIOTEK reader with enzyme-linked immunosorbent assay (ELISA) method that uses standard ELISA kits (BOSTER, Wuhan, CHINA) for serum IL-6, IL-10 and IL-18 levels (ELX 800TM 733310000, Winooski USA). Serum h-CRP levels were measured by using the nephelometer device (SIEMENS BN II MODEL, 282951, Germany) with the SIEMENS (Muenchen, Germany) commercial kit.

Statistical analysis

SPSS program versions were used for statistical evaluations. The datas were given as mean (±) standard error. Independent Sample t test was used for groups analysis. In order to determine the time-dependent difference between Independent Sample t test and intra-group measurements, the variance analysis test was used to the repeated measurements and $p < 0.05$ ratio was considered as significance.

RESULTS

Demographic datas of the patients are shown in Table 2. There was no difference between the characteristics of the two groups (Table 2).

Table 2. Groups Characteristics

	Group C (n=25)	Group O (n=25)
Male	18 (% 79.2)	18 (% 79.2)
Age	60.64 ± 10.53	63.36 ± 10.73
Weight (kg)	71.16 ± 8.52	71.56 ± 8.45
Length (cm)	168.4 ± 7.69	168.36 ± 7.53
Grafts	3.2 ± 0.86	3.08 ± 0.9
CPB time (min.)	80.2 ± 12.58	80.72 ± 12.34
Cross clamping time (min.)	50.12 ± 4.24	50.40 ± 4.60

The evaluation of the h-CRP levels; there was a significant increase in the control group on the postoperative 35th day and a statistically significant decrease was observed on the postoperative 35th day in the olmesartan group compared to the control group ($p<0.05$), (Table 3, Figure 1).

Table 3. h-CRP levels (mg/dL). (Mean ± SD)		
Groups / Time	T_1	T_2
Group C	17.90±3.27	26.15±3.83
Group O	16.92±2.27	9.92±1.82*
*p<0.05 Compared with Group C at the same time		

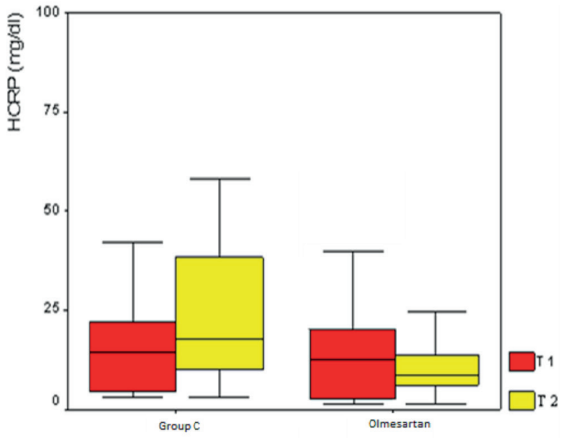

Figure 1. h-CRP levels (mg/dL). (Median ± SD)

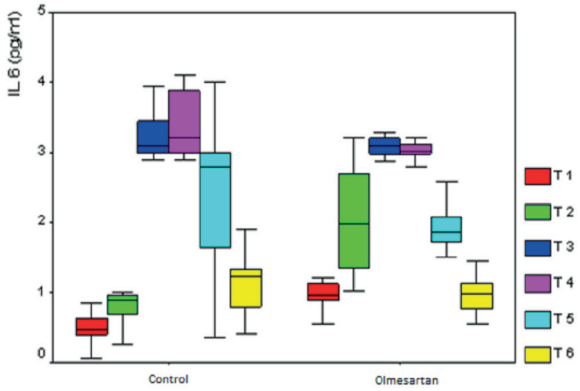

Figure 2. IL-6 levels (pg/ml). (Median± SD)

IL-6 levels were compared to Group O and Group C; statistically significant decreases were observed in the Group O after protamine infusion (T4) and postoperative 3rd day (T5) (p <0.05). Interestingly in Group C, 5 minutes after cross declamping a stastistically significant increase was seen. (Table 4, Figure 2), (p <0.05).

IL-10, an antiinflammatory cytokine levels were compared to Group O and Group C; In group O, there was a statistically significant increase at 5 min. after the cross declamping time (T3) (p<0.05). Interestingliy a statistically significant decreases were seen at postoperative 3rd and 35th days (p<0.05). (Table 4, Figure 3).

Table 4. IL-6, IL-10 and IL-18 levels (pg/ml). (Mean ± SD)							
Cytokine	Groups / Time	T_1	T_2	T_3	T_4	T_5	T_6
IL-6	Group C	0,50±0,04	0,93±0, 12[a]	2,99±0,17[a]	3,36±0,09[a]	2,34±0,21[a]	1,25±0,15[a]
	Group O	1,16±0,11*	2,01±0,13[a]*	3,04±0,05[a]	3,01±0,06[a]*	1,90±0,10[a]	0,99±0,05
IL-10	Group C	0,37±0,06	0,67±0,15[a]	2,08±0,20[a]	2,77±0,17[a]	1,25±0,15[a]	0,61±0,07[a]
	Group O	0,23±0,01*	0,49±0,17	2,50±0,17[a]	2,61±0,17[a]	0,54±0,04[a]*	0,29±0,02*
IL-18	Group C	1,36±0,10	1,85±0,15[a]	2,04±0,15[a]	1,97±0,12[a]	1,86±0,12[a]	1,54±0,09[a]
	Group O	1,94±0,14*	1,60±0,07	1,67±0,14	1,90±0,12	2,60±0,13*	2,85±0,09[a]*
*p<0. 05 Group C compared with Group O at the same time [a]p<0. 05 Compared with T1 at the same group							

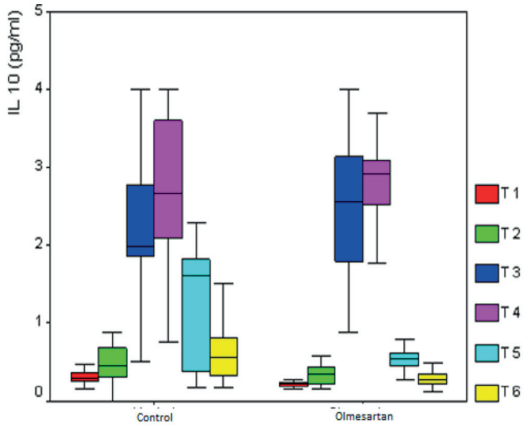

Figure 3. IL-10 levels (pg/ml). (Median± SD)

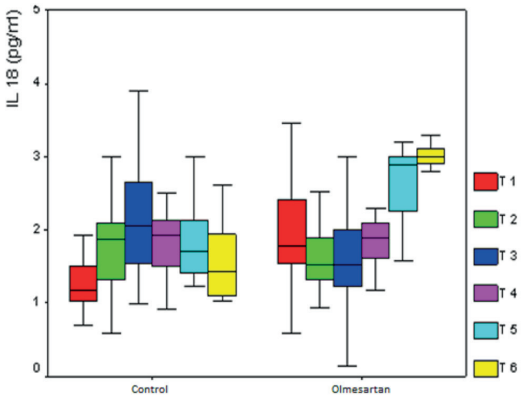

Figure 4. IL-18 levels (pg/ml). (Median± SD)

IL-18 levels were compared to Group O and Group C; Group O there were decreases at 5 min. after cross clamping (T2), 5 min. after cross declamping (T3) and after protamine infusion (T4), but these decreases were not enough to be

statistically significant. Interestingly at postoperative 3rd (T5) and 35th days (T6) there were statistically significant increases were seen (Table 4, Figure 4), ($p < 0.05$).

DISCUSSION

The average age of the patients with coronary artery surgery is increasing by the years. Therefore, increased problems in the myocardium and other organ function reserves were increased the importance of the surgery, anesthesia procedure and the other mechanical and pharmacological strategies too. Today, mortality is reported to be at 2-6% at cardiac surgery (24). Cardiac surgery with CPB technique triggers SIRS in the patient. Cytokines, arachidonic acid metabolites, endothelin and platelet activating factors play major role in SIRS (1). This inflammatory response may be the cause of complications such as myocardial dysfunction, respiratory failure, renal disorders, neurological disorders, bleeding diathesis, liver dysfunction, and even multiple organ failure, especially in the postoperative period (2-5).

This inflammatory system leads to the production of proinflammatory cytokines, such as IL-6, IL-18, and anti-inflammatory cytokines such as IL-10. There are also inhibitory mechanisms that prevent organ damage and suppress the inflammatory response after the cardiac surgery. Therefore, the balance between the inflammatory and anti-inflammatory responses is important for the patient's clinical condition and course. The release of anti-inflammatory cytokine IL-10 during CPB plays a protective role by inhibiting the production of the proinflammatory cytokines (7). Cytokine secretions begin to increase at early phase of CPB and reach the highest level postoperative 12-24th hours. CPB and aortic cross clamp times are the most important parameters for affecting the cytokine secretion (25).

In this study, all cytokines except the IL-18 levels in the olmesartan group reached the highest values after protamine infusion (T4). Since the next nearest sample was taken on the 3rd postoperative day, no datas could be obtained for the 12-24 hours peak. On the third postoperative day, the increase in the IL-18 levels were increased and reached the peak level at the postoperative 35th day ($p < 0.05$). these findings were proved that the proinflammatory cytokines such as IL-6, IL-8 and TNF-α, as anti-inflammatory IL-10 are highly valuable in the follow-up of the inflammatory response (26).

CRP is a nonspecific laboratory finding that triggers the hepatic production in various forms of infection, tissue damage and inflammation. In most normal subjects, the CRP level is 2 mg/dL or less. 3-8 mg/dL levels of CRP can be detected by standard methods; with h-CRP method, lower levels can be detected and used to determine the risks today. In this study, it was observed that h-CRP showed a significant increase in Group C and could be supressed by olmesartan in Group O. In a study, it was observed that angiotensine receptor blockers reduced hs-CRP levels in renal transplant patients when administered 2-4 months (27). In this study we showed that 35 days of using olmesartan may reduce CRP levels to repress the immunresponse depended adverse affects in coronary artery bypass patients as well.

IL-6 was originally found to be a B cell differentiating factor. In some studies, IL-6 does not have any IFN activity, but it plays a role in the adjustment of the immune response as a multifunctional pleotropic cytokine, in acute phase response, hematopoiesis and inflammation (13). In this study, after the cross-clamping (T2) it began to increase and reached the higher values at protamine infusion time (T4). Postoperative 3rd and 35th days it decreased gradually. When inspect the olmesatan's affect on IL-6 levels in CPB it could have seen that it is affective especially postoperative period. IL-6 levels were statistically significant decreased especially at pstoperative 3rd day (T5) in Group O. In a previous study it was observed that 12 weeks of olmesartan administration was reduced IL-6 and hs-CRP levels in hypertensive patients given in the dose of 20mg/per days (28).

IL-10 is the key regulator in the inflammatory response. The immunosuppressive effects of IL-10 protect the body from microbial infection and autoimmune diseases to over-stimulated inflammatory responses. IL-10 limits the production of the TLR agonist as a primary function. They secrete induced cytokines and chemokines in macrophages and DC's. It's direct effect on macrophage monocyte function with Class II major histocompatibility complex (MHC) molecules and auxiliary stimulator CD80/CD86 surface results as releasing for the down-regulatation of immune response (25). In this study, it was observed that IL-10 levels in Group C increased at 5 min. after cross declamping (T3) and protamine infusion time (T4). It could be seen that olmesartan only affects IL-10 levels as a statistically significant increase at 5 min. after cross declamping time (T3). It can be accepted as an antiinflammatory regulation of olmesartan.

As in the other members of the IL-1 family, the extracellular form of IL-18BP (IL-18 binding protein) is only as an immunoglobulin-like form and is linked to the IL-18Rα chain to which the amino acid sequences can bind (16). IL-18 plays an important role in the body defense. Increases in normal or activated immunity. Invitro neutralization of the IL-18 inhibits the secretion of TNF-α, IL-6, INF-γ by macrophages (29). In this study, IL-18 levels were began to increase at 5 min. after cross clamping (T2) and reaches the peak value at 5 min. after cross declamping (T3) in Gropup C. This period means that the patient is totally on CBP. In Group O, we can see decreases of the IL-18 levels at this time period but none of them were statistically significant. So we can say that Olmesartan couldn't affect IL-18 levels on CPB.

Recently, in a study that conducted with olmesartan and pravastatin on the inflammation and atherosclerosis, vascular inflammation with AT1R blockage was found to be significantly reduced in patients with essential

hypertension (28). In this study, the anti-inflammatory efficacy of olmesartan on h-CRP, TNF-α, IL-6, ICAM-1 and MCP-1 were evaluated. In conclusion a significant reduction was observed in biochemical markers of vascular inflammation by early treatment such as 6 weeks in patients with essential hypertension (28). Combination with Olmesartan and Statins or increase the treatment doses of olmesartan or prolong the treatment can be more effective on the inflammatory response after the CPB because there were many signs that anjiotensine receptors blockers can reduce inflammatory effects in coronary artery patients.

LIMITATIONS

The administration of olmesartan at 10 mg/day dose and 35 days may be insufficient to initiate anti-inflammatory effects. It may be sufficient but not enough to supress the extreme inflammation that arised in CPB. Times that the samples were taken could be changed to detect the inflammation circumstances more correctly. If more cases were studied maybe more detailed results could be measured and defined.

CONCLUSION

The application of olmesartan (10 mg/day) for the duration of 35 days postoperatively and 30 mg at operation day in the patients with coronary artery bypass graft surgery was not able to suppress the proinflammatory cytokines (IL-6, IL-18) according to the baseline values as unpredictably. In addition, the decrease of the h-CRP levels by olmesartan as an anti-inflammatory effects has been proven. IL-10 and IL-18 levels were also observed independently in both groups. It was concluded that olmesartan may reduce postoperative complications especially in postoperative period by decreasing the inflammatory response on h-CRP. We showed that Rosuvastatin 20 mg per day can reduce inflammatory effects on CPB patients in a similar study model in our clinic. We believe that antiinflammatory effect of olmesartan can be improved by combining with statins and a significant anti-inflammatory effect can be obtained together by incerasing IL-10 and decreasing IL-6 and IL-18 (30).

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Conflict of interest : The authors declare that they have no competing interest.

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