Original Article

Effects of Doxycycline on Left Ventricular Remodeling in Patients With Acute Anterior Myocardial Infarction Undergoing Primary Angioplasty: A Randomized Clinical Trial

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ABSTRACT

Background: Inflammatory mechanisms can cause left ventricular (LV) remodeling. These mechanisms include increased matrix metalloproteinases and the tissue inhibitors of metalloproteinases. Doxycycline is an antibiotic (macrolide) and a broad inhibitor of matrix metalloproteinases. This study evaluated the effects of early short-term doxycycline treatment on LV remodeling in patients suffering from ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI).

Methods: In the present double-blinded randomized control trial, 68 post-MI patients who underwent primary PCI for STEMI were assigned to 2 groups, each consisting of 34 volunteers. Over a 7-day period, all these volunteers took 100 mg of Doxycycline twice a day. A placebo with the same order was prescribed for the control group. The cardiac function, the LV diameter, the left atrial diameter, and the LV torsion were measured at baseline and 40 days afterward.

Results: The mean age of the control and experimental groups was 53.7 years and 56.1 years, respectively. The averages of the left atrial volume (P = 0.03), the LV end-diastolic volume (P = 0.03), and the LV end-systolic volume (P = 0.01) in the experimental group rose less significantly than those in the control group. However, the LV torsion such as basal rotation (P = 0.03), apical rotation (P = 0.02), twist (P = 0.02), and torsion (P = 0.002) increased more substantially in the experimental group than in the control group.

Conclusions: Early administration of doxycycline attenuated LV remodeling measured by speckle-tracking echocardiography in our patients with anterior STEMI after primary PCI, vs. our control group subjects, who were on a placebo diet. (Iranian Heart Journal 2019; 20(4): 22-30)

KEYWORDS: Left ventricular remodeling, ST-segment elevation, Torsion, Twist

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Myocardial infarction (MI) is one of the main causes of death in the world. ST-elevation myocardial infarction (STEMI) causes molecular, structural, and functional changes in the heart, termed “left ventricular (LV) remodeling”. LV remodeling is one of the important causes of heart failure in patients with acute MI, which eventually increases mortality and morbidity. MI can cause the migration of neutrophils, macrophages, and other cells into the infarct zone, leading to intracellular signaling and neurohormonal activation and subsequently resulting in the inducement of the inflammatory response. Post-MI remodeling has been divided into an early phase (within 72 h) and a late phase (beyond 72 h). Inflammatory mechanisms play a critical role in the early phase. Late remodeling induces the LV spherically and is associated with time-dependent dilatation, the distortion of the ventricular shape, and hypertrophy. The failure to normalize wall stress creates progressive dilatation and a decline in the contractile function; consequently, more recent studies have focused on anti-inflammatory treatment for LV remodeling.

According to previous studies, important parameters in primary LV remodeling and inflammation are the degradation of the intermyocyte collagen struts by serine proteases and the activation of matrix metalloproteinases (MMPs), which are released from neutrophils. Research has demonstrated that MMP levels in acute STEMI increase and that the inhibition of MMPs and the tissue inhibitors of metalloproteinases promotes LV remodeling in the wake of STEMI.

The expression of MMP-2 and MMP-9 increases in pressure overload (LV hypertrophy), and the increased MMP expression and activation has been shown to initiate heart failure progression in various experimental models and in humans. The data regarding MMP inhibition are, however, somewhat controversial. Several studies have shown that MMP inhibition or gene inactivation reverses LV remodeling and dysfunction. Doxycycline is a broad MMP inhibitor and improves LV remodeling. A chemically modified and semisynthetic tetracycline, doxycycline is used for its antibacterial properties and its ability to inhibit the transformation of pro-MMPs to active MMPs. Various animal studies have shown that not only are anti-inflammatory agents crucial in stabilizing the vulnerable plaques of the aorta but also they can prevent the firm rupturing of cerebral aneurysms. MMP-9 is known both for its predictive value in the cardiac complications of LV remodeling and for its use as a risk stratification marker. Moreover, some studies have claimed that doxycycline can decrease oxidative stress.

A variety of procedures are drawn upon to evaluate LV remodeling such as magnetic resonance imaging, perfusion scan, speckle-tracking echocardiography (STE), and stress echo with dobutamine. Given the safety and availability of echocardiography, today STE is deemed a new approach to the assessment of myocardial function. This imaging modality is based on an evaluation of torsion and deformation factors and may be able to detect exact degrees of functional impairment in ischemic tissues such as those discovered by myocardial perfusion imaging. Global and regional strains have been shown to associate well with visual wall motion abnormalities in patients with acute MI, non-coronary chest pains, or dilated cardiomyopathy. Many studies have recommended STE over other procedures for the measurement of LV remodeling; in addition, recent investigations have introduced torsion parameters as a sensitive approach for anticipating LV remodeling.

It has been proven that LV twist is a highly sensitive and specific procedure for the measurement of LV remodeling in a variety of cases. Cerisano et al. showed improvement in the left ventricular end-diastolic volume (LVEDV)
parameters and the limitation of the infarcted area after 6 months due to a short (7 d) treatment with doxycycline. Some other studies have reported the positive effects of doxycycline in patients after coronary artery bypass graft surgery.\textsuperscript{17,18} Given the importance of LV remodeling, in the present study, we utilized STE—as a harmless and sensitive procedure—to measure the effects of doxycycline on the LV torsion parameters in patients undergoing primary percutaneous coronary intervention (PCI).

**METHODS**

From 2015 to 2016, a total of 60 patients were randomly selected (based on the inclusion and exclusion criteria) from among all patients (450 patients in 1.5 years) with STEMI undergoing primary PCI at Rajaie Cardiovascular, Medical, and Research Center. All the subjects received complete information regarding the study protocol and volunteered to participate in the current study on the understanding that they could quit at any point during the study. The study population was divided into 2 different groups: experimental and control.

The inclusion criteria were comprised of anterior STEMI, primary PCI performed on the left anterior descending artery, and a left ventricular ejection fraction (LVEF) > 30\%. The exclusion criteria consisted of old MI, cardiogenic shock, liver and renal diseases, doxycycline sensitivity, and poor echocardiographic views. This was a balanced block randomized clinical trial (by 4 blocks). Neither the doctors nor the patients were aware of the group classification in order for the study to be a double-blind clinical trial. The experimental group (n = 30) received doxycycline at a dose of 100 mg twice a day for 7 days, while the control group simultaneously received a placebo twice a day for 7 days. Figure 1 display a summary of the methodology in this study.

Upon hospitalization, all the patients were evaluated by STE and transthoracic echocardiography (TTE) as soon as possible. Conventional M-mode echocardiographic measurements for the LV and the left atrium (LA) were obtained from the left parasternal long-axis view at the basal level. The LVEF was calculated visually. Two-dimensional imaging (appropriate depth, gain, and pulse repetition \[ frequency = .40 \text{ f/s} \]) in the apical 4-, 3-, and 2-chamber views was used to assess torsion, basal rotation, apical rotation, and twist in the LV, and all these data were recorded precisely. After 40 days, STE was performed again for the patients, so that all the factors in 2D echocardiography and LV torsion were assessed for a second time. Finally, all the data were compared in order to determine the effects of doxycycline on LV remodeling during the trial. The echocardiographic data were analyzed on the first day and at the end of the 40-day period by an expert technician.

**Statistical Analysis**

The continuous variables were expressed as the mean \( \pm \) the standard deviation (SD). The conventional echocardiographic parameters at baseline and 40 days after the administration of doxycycline were analyzed using the paired \( t \)-test. The strain parameters of each group at baseline and 40 days after the administration of doxycycline were also analyzed using the paired \( t \)-test, the \( \chi^2 \) test, and the Mann–Whitney \( U \) test with SPSS, version 20. Likewise, multivariable analyses were implemented using logistic regression statistical samples.
RESULTS

Initially, 68 patients were recruited in the current study on the basis of the study inclusion and exclusion criteria; however, 8 of them quit the trial. Therefore, 60 patients (75% male) were analyzed. A history of hypertension was reported in 40% of the study population, diabetes in 38%, and dyslipidemia in 36%. The distribution of the patients’ history and clinical features is depicted in Table 1. There were no statistically significant differences in the demographic characteristics between the experimental and control groups \((P = 0.05)\).

Table 1. Characteristics of the control and experimental groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control Group</th>
<th>Experimental Group</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>63</td>
<td>86</td>
<td>0.03</td>
</tr>
<tr>
<td>Age</td>
<td>53.7</td>
<td>56.1</td>
<td>0.07</td>
</tr>
<tr>
<td>Hypertension</td>
<td>36%</td>
<td>43%</td>
<td>0.6</td>
</tr>
<tr>
<td>Diabetes</td>
<td>36%</td>
<td>40%</td>
<td>0.79</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>40%</td>
<td>33%</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Echocardiographic Findings

Table 2 demonstrates the mean 2D echocardiographic findings in terms of the LVEF, the LVEDV, the left ventricular end-systolic volume (LVESV), and the left atrial volume (LAV) initially on hospitalization and then 40 days afterward.
Table 2. Echocardiographic alterations in the control and experimental groups

<table>
<thead>
<tr>
<th></th>
<th>First Day</th>
<th>Day 40</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control Group</td>
<td>Experimental Group</td>
</tr>
<tr>
<td>LAV (mL)</td>
<td>42.1±3.5</td>
<td>41.4±5.7</td>
</tr>
<tr>
<td>LVESV (mL)</td>
<td>79.1±9.1</td>
<td>76.2±8.9</td>
</tr>
<tr>
<td>LVEDV (mL)</td>
<td>128±19.1</td>
<td>122±14.3</td>
</tr>
<tr>
<td>EF (%)</td>
<td>35-40</td>
<td>35-40</td>
</tr>
<tr>
<td>Apical</td>
<td>6.7±1.6</td>
<td>7±1.6</td>
</tr>
<tr>
<td>Basal</td>
<td>8.5±2</td>
<td>8.9±1.9</td>
</tr>
<tr>
<td>Twist</td>
<td>15.2±3.6</td>
<td>16±3.5</td>
</tr>
<tr>
<td>Torsion</td>
<td>1.97±0.4</td>
<td>2.1±0.4</td>
</tr>
</tbody>
</table>

LAV, Left atrial volume; LVESV, Left ventricular end-systolic volume; LVEDV, Left ventricular end-diastolic volume; EF, Ejection fraction

The t-test results (Fig. A-2) revealed that the LAV was not statistically significantly different between the 2 study groups on the first day (42.1 mL in the control group vs 41.4 mL in the experimental group; P = 0.57). Conversely, 40 days later, the differences between the 2 groups in terms of the LAV increased (53.2 mL in the control group vs 50.2 mL in the experimental group; P = 0.03).
As is illustrated in Figure B-2, the 2 study groups were statistically significantly different from each other as regards the LVESV: the mean LVESV rose from 79.1 mL on day 1 to 89.9 mL on day 40 in the control group, while it increased from 76.2 mL on day 1 to 83.2 mL on day 40 (P = 0.21 on day 1 vs P = 0.01 on day 40).

As is demonstrated in Figure G-2, the mean LVEDV rose in both groups: from 128 mL on day 1 to 149 mL on day 40 in the control group and from 122 mL on day 1 to 140 mL on day 40 in the experimental group (P = 0.2 on day 1 vs P = 0.03 on day 40).

As is shown in Figure G-2, the mean LVEF was about 35%–40% on day 1 in both groups. However, on day 40, the mean LVEF was 35%–40% in the control group and 40%–45% in the experimental group (P = 0.008).

As is depicted in Figure 3-A, the mean LV apical rotation in the control group was 6.7° on day 1 and 7.2° on day 40, whereas the mean LV apical rotation changed from 7° on day 1 to 8.4° on day 40.

**Figure 3.** A) speckle-tracking echocardiography, B) apical rotation, C) basal rotation, D) twist, E) torsion

**STE**
Figure 2 depicts the mean LV apical and basal rotation, as well as the mean LV twist and torsion, measured by STE on day 1 and on day 40.
on day 40 in the experimental group ($P = 0.43$ on day 1 vs $P = 0.02$ on day 40).

As is illustrated in Figure 3-B, the mean LV basal rotation was $8.5^\circ$ in the control group and $8.9^\circ$ in the experimental group on the first day ($P = 0.36$). Nonetheless, on day 40, this value increased to $9.3^\circ$ in the experimental group, while it decreased in the control group ($P = 0.02$).

The mean LV twist, calculated by subtracting apical torsion from basal rotation, was $15.2$ in the control group and $16$ in the experimental group on the first day, and it changed to $15.5$ in the control group and $17.7$ in the experimental group on the 40th day ($P = 0.38$ on day 1 vs $P = 0.02$ on day 40).

The difference in the mean LV torsion between the 2 study groups was calculated to be approximately $0.13$ ($1.97$ in the control group vs $2.1$ in the experimental group; $P = 0.027$). On the 40th day, this difference reached $0.34$ ($1.93$ in the control group vs $2.27$ in the experimental group; $P = 0.002$) (Fig. 3-D).

**DISCUSSION**

In the present double-blind randomized control trial, we demonstrated the effects of the early administration of short-term doxycycline therapy in patients undergoing primary PCI on TTE parameters (LV torsion and twist). Our results showed that prescribing $100$ mg of doxycycline twice a day for $7$ days to this group of patients makes significant differences in TTE parameters of LV torsion and twist on the 40th postprocedural day. Indeed, the mean values of the LAV, the LVESV, and the LVEDV in our experimental group increased more than those in our control group. Further, the LVEF increased more significantly in the experimental group than in the control group. Additionally, an assessment of LV torsion parameters in both groups demonstrated significant differences in LV apical/basal rotation and LV twist and torsion between the 2 groups: LV apical/basal rotation and LV twist and torsion in the experimental group increased more significantly than those in the control group.

The phenomenon of LV remodeling occurs after MI progressively. It causes an increment in the LV size (LVEDV and LVESV), although it diminishes the LV EF. Previous research has shown that a $20\%$ increase in the LVEDV and a $10\%$ increase in the LVESV are indices of LV remodeling. This phenomenon is prevented by treatments such as early revascularization, neurohormonal inhibition, and beta-blocker prescription. Nonetheless, according to recent studies, the effects of doxycycline on inflammatory parameters are not clear.

Echocardiography is a broadly used clinical method for noninvasive imaging, especially in cardiovascular medicine, and STE is considered to be more useful than conventional echocardiography insofar as a quantitative evaluation of myocardial deformation by tracking myocardial movements is less angle-dependent. STE can identify subtle changes in contraction, which visual segmental functional assessments may not detect. The TIPTOP study is a recent review that underscored the advantages of doxycycline in LV remodeling.

The TIPTOP study used a combination of modalities— including echocardiography and perfusion scans; however, we drew upon 2D echocardiography and STE as the most sensitive approach to the evaluation of LV remodeling and obtained compatible outcomes with the TIPTOP study. Different procedures are used to evaluate LV remodeling such as magnetic resonance imaging, perfusion scans, STE, and the echo stress test with dobutamine. STE is one of the safest approaches because it is harmless and lacks radiation through the patient’s body. Recent studies have selected LV torsion as a sensitive marker for the evaluation of LV systolic myocardial performance.

Given the proven effects of doxycycline on inflammatory reactions in MI, early remodeling, and prohibitive effects on MMP,
this agent is recommended over other treatments. Recent years have witnessed a growing interest in the effects of MMPs patients with MI, and MMP-8 is now regarded as a predictive factor for the diagnosis of cardiovascular diseases. Likewise, some investigations have proven that high levels of the tissue inhibitors of metalloproteinases can improve LV remodeling. In light of the results from this and previous studies specifically working on patients with STEMI, we highly recommend that the beneficial outcomes of doxycycline be appraised in patients with acute coronary syndromes (eg, NSTEMI) or other cardiovascular conditions in the future.

In the current study, pantoprazole was prescribed to the patients to prevent gastrointestinal complications due to the consumption of doxycycline.

Study Limitations

Although the quality of 2D STE was acceptable, higher resolution for cardiac borders was still lacking. Automated speckle-tracking analysis is possible only with special software. Furthermore, since border tracing needs manual work, interobserver error is unavoidable.

Be that as it may, STE is a rapidly progressing imaging modality and 3D speckle-tracking may overcome many of the 2D strain shortcomings in the future.

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