Benefit of Doxycycline Therapy in Acute St segment Elevation myocardial Infarction with Left Ventricular Dysfunction treated with primary percutaneous coronary intervention (PPCI)

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Abstract

Background: Several randomized trials performed in the era of doxycycline showed reduction in myocardial remodeling when compared with control therapy. **Methods:** This prospective study included 100 consecutive patients with first time acute anterior ST segment elevation myocardial infarction and left ventricular ejection fraction less than 40%.All patients underwent primary PCI and were divided into two groups; Group I who received bolus dose 100 mg of doxycycline immediately after PPCI then a maintenance dose 100 mg b.i.d for 7 days and group II who received standard treatment. Left ventricular end diastolic volume index (LVEDVI) was measured at baseline and six months by transthoracic echocardiography. **Results:** The 6-month LVEDVI significant decreased in the doxycycline group than in the control group [-13.2 ± 14.2 ml/m^2 (26%) versus 7.4 ± 14.35 ml/m^2(14%) respectively p= 0.001]. Left ventricular remodeling was reported in 60 % of all patients (42 % in group I versus 78 % in group II, P = 0.01). **Conclusion:** The result of current study suggests that doxycycline reduces the adverse LV remodeling in patients with acute anterior STEMI and LV dysfunction.

Key words: STEMI, remodeling, echocardiography

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Introduction

Prevention of cardiac remodeling and progressive dysfunction is a major goal after myocardial infarction (MI). However, current anti-remodeling therapies are clearly limited, as many ventricles enlarge after MI and mortality and morbidity remain significantly high[1]. Increased expression and activation of matrix metalloproteinase (MMPs) have been identified in myocardial remodeling processes associated with myocardial infarction. The MMPs are a family of enzymes that contribute to ventricular remodeling and heart failure by promoting extra cellular matrix (ECM) degradation[2]**.** The integrity of the original ECM is thought to play an important role in determining the extent of remodeling after MI which may serves to limit local and global ventricular remodeling and improves the function of the scar region and normal myocardium[3]. The possibility of using doxycycline antibiotic as MMP inhibitor in heart failure patients is attractive as doxycycline is a common tetracycline antibiotic, and has a unique property of broad spectrum MMP inhibition and amelioration of ischemia/reperfusion injury in the setting of MI[4]**.** Recent reports have showed that pretreatment with tetracycline derivative doxycycline before MI attenuate cardiac dilatation and improve endothelial function and treatment of coronary heart disease patients with reduction of serum inflammatory markers as well as circulating concentrations of MMP-9[5]. This study was designed to test the impact of doxycycline on left ventricular remodeling after STEMI.

Patients and methods

Study design

This prospective, controlled, non randomized study enrolled 100 consecutive patients with first time STEMI .The study was performed at the National Heart Institute, Cairo, Egypt in the period from September 2013 to September 2014. All patients were treated with primary percutaneous

coronary intervention (PPCI).We aimed to explore the clinical effect of doxycycline started early after STEMI and its therapeutic effect upon left ventricular dysfunction. All patients signed an informed consent and the study was approved by the local ethics committee. Key inclusion criteria were: Patients who were presented with first time anterior STEMI and left ventricular ejection fraction (LVEF) less than 40% (characteristic chest pain lasting for at least 30 minutes, not responsive to nitrates, with a new, or presumed new ST segment elevation in 2 or more contiguous leads of at least 2mm at the J point in leads V2-V3 or 1mm in other leads, or those with new LBBB). Key exclusion criteria were: patient with hypersensitivity to doxycycline, pregnancy, age under 18 years old, prior myocardial infarction, valvular heart disease, congestive heart failure.

Methods

Baseline evaluation

All patients had review of medical history on admission to emergency department including analysis of demographic data (age, sex), presence of risk factors of coronary atherosclerosis, associated co morbidities, general and cardiac examination, 12 leads ECG which was performed immediately on admission and every 6 h during the first 24 h, and once daily until discharge, routine laboratory investigations including cardiac biomarkers (Troponin I & CK-MB).

Coronary angiography and PPCI

Aspirin (300 mg loading ,then 75 mg maintenance) and clopidogrel (600 mg loading, then 150 mg/day maintenance for one week, then 75 mg/day for one year) were given on admission and after PPCI. Un-fractionated heparin (UFH) of 10000 units bolus dose was given after sheath insertion. The procedure was done according to the standard technique for coronary angiography and PCI. Trans femoral approach was done in all patients using 6 Fr sheaths. Diagnostic coronary angiography was done to explore non-infarct related artery. XB or Judkin left guide catheters used during PPCI. Aspiration catheters and glycoproteins inhibitors (GPI) were used in lesions with heavy thrombus burden and or impaired TIMI flow after PPCI. Bare metal or drug eluting stent were used, its size and length was detected by the operator.

Echocardiography

Transthoracic echo was done at baseline, 30 days, and at 6 month. Using General Electric System Vivid-3machine with (2.5-5) MHZ probe. Two dimensional echo, M-Mode, Doppler and Simpson's methods were performed to obtain measurements of LV volumes, ejection fraction, segmental wall motion abnormality and mitral regurgitation according to recommendation of American society of echocardiography[6].The following measures were obtained; LVEDV (normal value (95±18 mL), LVESV (normal value (39±11 mL), LVEDVI (normal Value (45±10ml/ m^2), LVESVI (normal value (21±9ml/ m^2), and LVEF. Measurements were done using modified Simpson method. All data were analyzed by an independent investigator.

Study protocol

After PPCI, patients were subsequently divided into 2 group; Group (I) which included 50 patients in whom bolus of 100 mg doxycycline was given immediately after PPCI then 100 mg b.i.d for 7 days. Group (II) which included 50 patients in whom standard treatment was given.

Study end points

a) Primary end point was 6-month LVEDVI and LV remodeling. Remodeling was defined as > 20% increase in LVEDVI from baseline[7].

b) Secondary end point was 6 month mortality, re-infarction and heart failure.

Statistical analysis

Data are presented as mean± SD for continuous data and as number (%) for categorical data. Between groups analysis was done using student t-test for continuous data and by Chi-square test for qualitative data. Level of evidence was detected to be significant at P value <0.05. Data were collected and analyzed by SPSS (version 17, USA, IL).

Results

Study population

The mean age was 57 ± 11.4 years (58.1± 11.5 y versus 56.7 ± 11.0 y in group I and II respectively, P = 0.55), 67% were males (62% versus 72% in group I,II respectively P = 0.28), 33%had diabetes (28% versus 38% in group I,II respectively P = 0.28), 38% had hypertension (38 % in each group P = 1.0), 29 % had dyslipidemia (30% versus 28% in group I,II respectively P = 0.82), 47 % were smokers (50% versus 44% in group I,II respectively P = 0.54), 20% had positive family history of CAD (18% versus 22% in group I,II respectively P = 0.40). Between groups analysis showed no statistical significant differences in baseline characteristics.

Time from symptom onset to admission

The mean time was 7.07 ± 2.7 hours (6.45 ± 2.39 hours in group I versus 7.7 ± 2.97 hours in group II, P = 0.16), 10 % of patients were presented less than 3 hours (4 % versus 6 % in group I, II respectively, P = 0.5), 21 %were admitted between 3-6 hours from onset of symptoms (11 % in group I versus 9% in group II, P = 0.5). 69% were admitted after 6 hours from onset of symptoms (68% versus 70% in group I, II respectively, p= 0.5).

Door to balloon time

The mean time was 80.2 ± 38.5 minutes in all patients (73.5 ± 31.1 minutes in group I, versus 87 ± 44.49 minutes in group II, P =0.3).

Coronary angiography before PPCI

The culprit artery was LAD in 100% of patients.Single vessel disease was reported in 44% in all patients (44% in group I, II respectively, P = 0.81). 2 vessel disease was reported in 38% of all patients (20% versus 18% in group I, II respectively, P =0.81). 3 vessel disease was reported in 18% (16% in group I versus 20% in group II, P=0.81). TIMI flow pre PCI was zero in 68% of all patients (70%versus 66% in group I, II respectively P =0.66), while TIMI flow I was present in 32% of all patients (30%versus 34% in group I, II respectively P =0.66).

Table 1. Baseline characteristics of study population.

	All patients n = 100	Group I Doxycycline group n = 50	Group II control group n = 50	P value
Age, years, mean ± SD	57.4±11.2	58.1 ± 11.5	56.7 ±11.0	0.5
Male gender, n(%)	67(67%)	31(62%)	36(72%)	0.2
Family history of CAD	20 (20%)	9 (18%)	11 (22%)	0.4
Diabetes	33 (33%)	14 (28%)	19 (38%)	0.2
Hypertension	38 (38%)	19 (38%)	19 (38%)	1.00
Smoking	29 (29%)	15 (30%)	14 (28%)	0.5
Dyslipidemia	29 (29%)	15 (30%)	14 (28%)	0.8

Primary PCI

All patients received 10000 units of UFH pre PCI, femoral approach was done in all patients using 6 Fr sheath, XB guiding catheter was used in 90% of all patients while JL was used in 10% of all patients, floppy wire was used in 88% of all patients, while coated wire in 12 % of patients, predilatation was done in 22% of all patients (24% in group I versus 20% in group II, P=0.32), aspiration devices were used in 15% patients (12% in group I versus 18% in group II, p=0.40), glycoprotein inhibitors were used in 61% of all patients (52% versus 70% in group I, II respectively, P =0.06). The stent number was one in 87% of all patients (82% versus 92% in group

I,II respectively, P =0.137), while two stents in 13% of all patients (18% versus 8%in group I,II respectively, p=0.137), the mean stent length was 26 ± 11 mm (27 ± 13 mm versus 25 ± 9 mm in group I and group II respectively, P = 0.277), the mean stent diameter was 2.9±0.45 mm (2.80 ± 0.57 mm versus 3.0 ± 0.34 mm in group I, II respectively, P=0.06), Bare metal stents were implanted in 67% (72%versus 62% in group I,II respectively, p=0.288), while BMS-DES were used 33% (28% versus 38% in group I,II respectively, p=0.288). TIMI flow post PPCI was III in 79% of all patients (40% versus 39% in group I,II respectively, p=0.2),while TIMI flow II in 18% of all patients (16% versus 20% in group I,II respectively, p=0.919), and TIMI flow 0 was 3% in all patients (4% versus 2% in group I,II respectively, p=0.919). Coronary artery dissection was reported in 3% of all patients (4% versus 2% of group I,II respectively, P =0.48), distal embolization was reported in 2% in group I, II respectively, P=0.28)

Echocardiographic data

The mean LVEDVI at baseline was 53.65 ± 15.05ml/m^2 (55.8 ± 16.0 ml/m^2 in group I versus 51.5 ± 14.1 ml/m^2 in group II, P = 0.153). At 30 days LVEDVI was 52.25 ± 15ml/m^2 (51.6 ± 14.4 ml/m^2 for group I versus 52.9 ± 15.6 ml/m^2 for group II, p < 0.14), After 6 month, LVEDVI was 50.75 ± 13.5 ml/m^2 (42.6 ± 12.4 ml/m^2 for group I versus 58.9 ± 14.6 ml/m^2 for group II, p < 0.001). In group I, LVEDVI decreased by -13.2 ± 14.2 ml/m^2 (26%), p < 0.001. However, LVEDVI increased by 7.4 ± 14.35 ml/m^2 (14%) in group II, p < 0.001. At 6 months, remodeling was reported in 60 % of all patients (42 % in group I versus 78 % in group II, P = 0.011) Table 2, Figure 1, 2. The mean LVESVI at baseline was 33.4 ± 12.25 ml/m^2 (33.8 ± 13.5 ml/m^2 in group I versus 33.0 ± 11.0ml/m^2 in group II, P = 0.759). At 30 days LVESVI was 30.75 ± 12.5ml/m^2 (30.6 ± 11.4 ml/m^2 in group I versus 30.9 ± 13.6 ml/m^2 in group II, p < 0.14), After 6 months, LVESVI was 24.35 ± 7.2 ml/m^2 (22.2 ± 5.4 ml/m^2 in group I versus 26.5 ± 9.0ml/m^2 for group II, p < 0.008). In group I, LVESVI decreased by -11.6 ± 9.45 ml/m^2 (28%), p < 0.046), LVESVI decreased by - 6.5 ± 10.0 ml/m^2 (19%) in group II, p < 0.046) Table 2, Figure 1, 2. The mean LVEF at baseline was 31.75 ± 6.05 % (31.1 ± 6.3 % in group I versus 32.4 ± 5.8 % in group II, P = 0.293). At 30 days LVEF was 36.15 ± 11.5 % (36.4 ± 9.4 % for group I versus 35.9 ± 13.6ml/m^2 for group II, p=0.14), After 6 month, LVEF was 53.5±11.8 % (55.3 ± 5.1 % for group I versus 51.7 ± 6.7 % for group II, p < 0.004). In group I, LVEF increased by 24.2 ± 5.7% (48%), p <

0.005). However, LVEF increased by 19.3 ± 6.25% (38 %) in group II, p < 0.005) Table 2, Figure 1, 2.

Table2. Echocardiographic data

	All patients n = 100	**Group I** n = 50	**Group II** n = 50	**P value**
LVEDVI at baseline, ml/m^2, mean ± SD	53.65±15.05	55.8±16.0	51.5±14.1	0.153
LVEDVI at 30 day, ml/m^2, mean ± SD	52.25± 15	51.6±14.4	52.9±15.6	0.14
LVEDVI at 6 months, ml/m^2, mean ± SD	50.75±13.5	42.6±12.4	58.9±14.6	<0.001
Change in LVEDVI, ml/m^2	-2.9±14.2	-13.2 ±14.2	7.4±14.35	<0.001
Change in LVEDVI, %	6%	26%®	14%	<0.001
Remodeling	60(60%)	21(42%)	39 (78%)	0.011
LVESVI at baseline ,ml/m^2, mean ± SD	33.4±12.25	33.8±13.5	33.0±11.0	0.759
LVESVI at 30 day, ml/m^2, mean ± SD	30.75± 12.5	30.6±11.4	30.9±13.6	<0.14
LVESVI at 6 months, ml/m^2, mean ± SD	24.35±7.2	22.2± 5.4	26.5± 9.0	0.008
Change in LVESVI, ml/m^2	-9.1±9.72	-11.6 ±9.45	-6.5±10.0	0.046
EF at baseline, %	31.75±6.05	31.1± 6.3	32.4 ±5.8	0.293
EF at 30 day, %	36.15± 11.5	36.4± 9.4	35.9±13.6	0.14
EF at 6 months, %	53.5±11.8	55.3 ±5.1	51.7± 6.7	0.004
Change in EF, %	21.75±5.9	24.2 ±5.7	19.3±6.25	0.005

®= significant changes from baseline

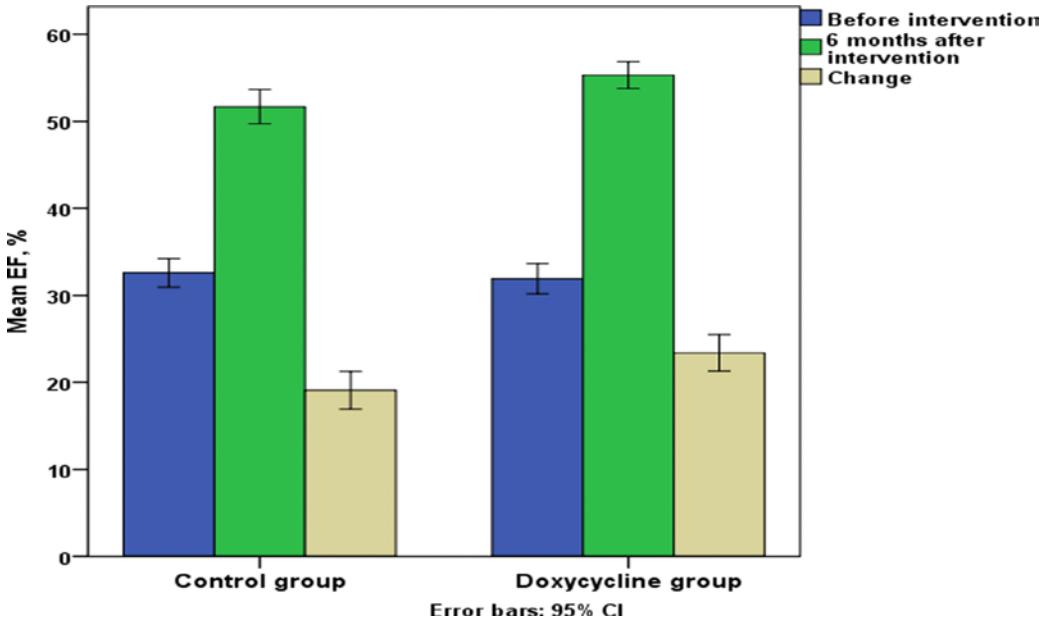

Figure 1: Mean LVEF at baseline and after 6 months.

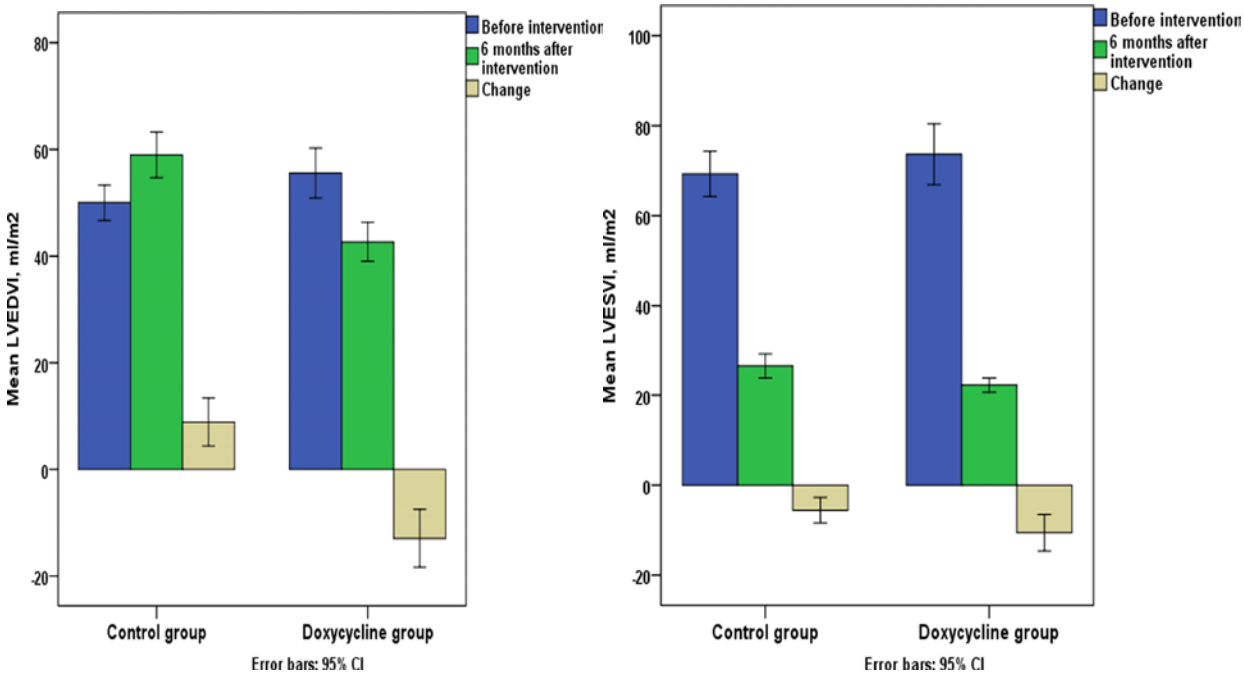

Figure 2: Mean LVEDVI and LVESVI at baseline and after 6 months.

Six month adverse events

Mortality was reported in 7% (8% in group I versus 6% in group II, P = 1.00). No reported cases of re-infarction in both groups. Heart failure was evident in 32% of patients (20% in group I versus 12% in group II, p = 0.067).

Discussion

Doxycycline is beneficial in reducing left ventricular remodeling in patients with acute anterior myocardial infarction undergoing primary PCI [7]. Several randomized trials some of them showed benefit in reduction in LV remodeling in the form of (% Δ LVEDVI) was significantly lower in the doxycycline group than in the control group by more than 20%, other one failed to show a treatment benefit in remodeling process[8].This study evaluated the short term outcome of doxycycline therapy started early after myocardial infarction associated with left ventricular dysfunction. Doxycycline significantly reduced left ventricular remodeling at 6 months. Remodeling was reported in 60 % of all patients (42 % in group I versus 78 % in group II, P = 0.011). In our study, from baseline to 6-months follow-up, the mean LVEDVI significantly decreased by -13.2 ± 14.2 ml/m^2 (26%) in doxycycline group, p < 0.001)However, the mean LVEDVI significantly increased by 7.4 ± 14.35 ml/m^2(14%) in control group, p < 0.001. In PREMIER trial,[9] the only phase II clinical trial in patients with AMI, the prevention of early remodeling, was performed on 250 patients with STEMI who were randomized to treatment with PG-116800 or placebo 48 h after reperfusion therapy. Patients underwent echocardiography at baseline and at 90 days to assess remodeling. The primary end point was change in left ventricular end diastolic volume index at 90 days after MI. Results showed that there was not difference between the two groups (LVEDVI change from base line to 3 months were 5 ml/m^2 in both groups, respectively, P = 0.51). In Tip top trial 2012,[10]change in LVEDVI from baseline to 6 months was significantly lower in doxycycline group than control group (- 5 ± 27 ml/m^2(4%) versus 25 ± 41 ml/m^2(15.5%)respectively, P = 0.001).In the study by Ceseriano et al., 2013,[11] from baseline to 6-month follow-up LVEDVI remained substantially unchanged in the doxycycline group, while it was significantly increased in the control group (0.3+12.5 ml/m^2

(0.4%) and 8.7 + 15.5 ml/m^2 (13.4 %) respectively, P = 0.004). This discrepancy between our result and tip top 2012 and Ceseriano, 2013 could be explained by differences in study population. In Muhlestein 2014,[12] 6 months primary endpoint was only a 0.4% increase in LVEDVI in patients assigned to doxycycline compared with a 13.4% increase in the control patients (P = 0.012). In the study by Ceseriano et al., 2014, [6] from baseline to 6 months, LVEDVI decreased in group 2 (-3 ml/m^2), and increased in group 1 (6 ml/m^2), p = 0.001). In group 2, LVEDVI reduction was similar regardless of drug therapy, while in group 1 the LVEDVI was smaller in patients treated with doxycycline as compared to control (3 ml/m^2) versus (10 ml/m^2) p = 0.006. A similar pattern was observed also for LV end-systolic volume and ejection fraction. In STEMI patients at higher risk, as those with a baseline TIMI flow grade ≤ 1, doxycycline reduces LV remodeling. In our study, doxycycline significantly reduced left ventricular remodeling at 6 months. Remodeling was reported in 60 % of all patients (42 % in group I versus 78 % in group II, P = 0.011). In PREMIER[9]Trial, remodeling was reported in 92% of all patients (98% in doxycycline and control groups respectively, P = 0.51). This discrepancy between our result and those reported by PREMIER trial could be explained by dose of doxycycline that was four fold lower in PREMIER trial than effective dose of doxycycline in our study, also primary end point in PREMIER trial was 90 day follow up LVEDVI in both groups where in our study primary end point was 6 months follow up LVEDVI in both groups. In our study, 6 months mortality was 7%, 4 patients (8%) in the doxycycline group and 3 patients (6%) in the control group. No reported cases of re-infarction in both groups. Heart failure was evident in 32% of patients (20% in group I versus 12% in group II). In PREMIER trial, 3 months mortality was 5 patients (4 (3%) in PG-116800 group and 1 (1%) in control group, P = 0.21). Re-infarction was reported in 10 patients (7 (6%) in doxycycline group and 3 (2%) in control group, P= 0.21). Heart failure was reported in 10 patients (8%) in doxycycline group and 9 patients (7%) in control group, P = 0.82. In TIP TOP trial 2012, 6 months mortality was 5.5 % (6 patients), 2 patient (3.6%) in the doxycycline group and 4 patients (7.3%) in the control group. 6 patients in the doxycycline group (10.8%) and 9 patients in the control group (16.2 %) had congestive heart failure, P= 0.04). Ceseriano and his colleague 2013, reported that 6 months mortality was 4.6% (5 patients), 1 patient (1.8%) in the doxycycline group and 4 patients (7.3%) in the control group. 4 patients in the doxycycline group (7.4%) and 7 patients in the control group (13.7%) had congestive heart failure, P = 0.04). In the study by Ceseriano 2014,

6 months mortality was 5 patients 4.6 % [4 patients (5 %) with baseline TIMI flow grade ≤ 1 (one in the doxycycline group (2 %), and three in the control group (8 %), one patient (3 %) with baseline TIMI flow grade 2–3 in the control group died]. Ten patients with baseline TIMI flow grade ≤ 1 (13 %), three in the doxycycline group (7 %) and seven in the control group (19 %), and one patient with baseline TIMI flow grade 2–3 (3 %) randomized to doxycycline group had heart failure. Myocardial infarction was 19 % within the group with baseline TIMI flow grade ≤ 1 (30 %in the control group and 10 % in the doxycycline group, respectively, P = 0.04) and 9 % within the group with baseline TIMI flow grade 2–3 (11 % in the control group and 7 % in the doxycycline group, P = 1.0). This discrepancy between our results and those reported by PREMIER trial, Ceseriano 2012, TIP TOP 2013 and Ceseriano 2014 could be explained by differences in study population and difference in sample size.

Conclusion

Doxycycline significantly reduced left ventricular remodeling post myocardial infarction.

Recommendation

Further studies with larger sample size and different modalities are required to assess safety and efficacy of doxycycline in prevention the ominous progression of left ventricular dysfunction to adverse remodeling.

Study limitation

- Small sample size.
- Short follow up period.
- Lack of randomization.

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