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"Heart Failure"

Short Communication

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Acute and Chronic Heart Failure Therapies in Patients With Takotsubo Cardiomyopathy

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ABSTRACT

The management of patients with Takotsubo cardiomyopathy consists of heart failure treatment with angiotensin converting enzyme inhibitors and β -blockers. There are no specific guidelines for managing patients with Takotsubo cardiomyopathy and such patients are treated with generic heart failure medications. Evidence surrounding the management of these patients with heart failure medications is conflicting. Furthermore, the use of aspirin or antiplatelets is controversial as some studies have not shown any benefit although one trial demonstrated a reduction in major adverse cardiovascular events. At present there are no randomized trials to assess outcomes in patients treated with heart failure therapies.

KEYWORDS: Heart failure; Antiplatelets; Thrombus.

INTRODUCTION

The incidence of Takotsubo cardiomyopathy is approximately 1-2% of patients presenting with ST segment elevation myocardial infarction (STEMI). These patients are usually commenced on a loading dose of dual antiplatelet therapy with aspirin and a P2Y12 receptor inhibitor and the decision to continue with these medications varies amongst physicians. Since the echocardiogram demonstrates left ventricular systolic dysfunction angiotensin converting enzyme inhibitors and β -blockers are commonly prescribed. The evidence surrounding the use of dual antiplatelet therapy, heart failure medications and statins is sparse.

DISCUSSION

Takotsubo cardiomyopathy tends to be precipitated by a stressful event and is most often seen in post-menopausal women. The symptoms are indistinguishable from an acute coronary syndrome as patients may present with chest pain, dyspnea and ST segment elevation may be evident on the electrocardiogram, with a rise in serum troponin T/I. The diagnosis needs to be established by performing a coronary angiogram and an echocardiogram. On echocardiography there is sparing of the basal segments with hypokinesia or akinesia of the mid and apical segments of the left ventricle. The pattern of left ventricular dysfunction does not fit with a single coronary distribution. In order to diagnose Takotsubo cardiomyopathy, there must be no significant obstructive atheroma or ruptured plaque angiographically in addition to the echocardiographic features as described. Multiple theories regarding the pathophysiology of Takotsubo cardiomyopathy exist, the commonest being an excess in catecholamine release leading to myocardial stunning.

Complications of Takotsubo cardiomyopathy include cardiogenic shock and arrhythmias. If left ventricular systolic function is significantly impaired then left ventricular thrombus may occur.¹ In one study, left ventricular thrombus was present in 5.3% of patients with Takotsubo cardiomyopathy. In such cases, anticoagulation is indicated until there is recovery of left ventricular function and thrombus is no longer present.² Anticoagulation maybe considered prophylactically in severe systolic dysfunction to reduce the risk of thromboembolism³

although this is not common practise.

Once the diagnosis of Takotsubo cardiomyopathy has been made antiplatelet agents and nitrates can be stopped. β -blockers ideally should be continued since the condition is driven by excess catecholamine release and β -blockers inhibit excess sympathetic drive. Angiotensin converting enzyme inhibitors should be prescribed until cardiac function resolves. If there is clinical evidence of fluid overload diuretics can be commenced.¹ Intra-aortic balloon pump insertion maybe required for unstable patients in the presence of cardiogenic shock to provide circulatory support.^{4,5} The use of inotropes is not recommended because of increased circulating catecholamines.⁵ If cardiac stimulants are required levosimendan a calcium sensitiser may be beneficial because of its inotropic action and vasodilator effect hence causing increased force of myocardial contraction with a reduction in preload and afterload.⁶

Takotsubo cardiomyopathy is generally a reversible condition with the use of heart failure medications. The prognosis is excellent, and recurrence occurs in <10% of patients.¹

A limited number of trials have assessed outcomes with medications used in patients hospitalized with Takotsubo cardiomyopathy. In a retrospective study the benefits of treatment with angiotensin converting enzyme inhibitors, β -blockers, aspirin and calcium channels blockers in 36 patients with Takotsubo cardiomyopathy was assessed. Drug therapy was started during the index admission and continued for 30 days. Improvement in left ventricular function was assessed. There was no statistical significant difference in the improvement of left ventricular ejection fraction assessed on admission, prior to discharge and after 30 days of treatment between each treated group and patients who did not receive any drug therapy. There was no significant differences in length of hospital stay between treated patients and non-treated controls. None of the patients had recurrence of Takotsubo cardiomyopathy during the duration of the study. Therefore chronic treatment with β -blockers, angiotensin converting enzyme inhibitors, calcium channels blockers and aspirin does not provide any benefit in patients with Takotsubo cardiomyopathy.⁷

In a recent retrospective study of 206 patients with Takotsubo cardiomyopathy the use of aspirin, dual antiplatelet therapy with aspirin and clopidogrel, β -blockers, statin, or angiotensin converting enzyme inhibitor use were analysed to assess if there was any impact on major adverse cardiovascular events (MACE) during hospitalisation. MACE was defined as heart failure during hospitalisation, in hospital mortality, stroke or respiratory failure requiring mechanical ventilation. The incidence of in hospital heart failure was 26.7%, in hospital mortality was 7.3%, stroke occurred in 7.3% of patients and MACE rates were 42.3%. The use of aspirin and dual antiplatelet therapy at the time of hospitalisation were independent predictors of a lower incidence of MACE; aspirin $p=0.04$; dual antiplatelet therapy; $p<0.01$. Physical stressors were an independent pre-

dictor of worse MACE; $p<0.01$. Therefore, the use of aspirin and dual antiplatelet therapy were independent predictors of a lower incidence of MACE during hospitalisation for Takotsubo cardiomyopathy. Further, randomised clinical trials (RCT) however are required to confirm the findings of this study.⁸

In patients who have been treated for Takotsubo cardiomyopathy, it is unclear whether heart failure therapies should be continued once the patients left ventricular function has normalised. Physicians may consider discontinuation of these drugs once there is normalization of left ventricular function. There is limited data to support the continuous use of angiotensin converting enzyme inhibitors and β -blockers blockers for the prevention of Takotsubo cardiomyopathy recurrence or improvement in survival rate. There is discrepancy as to the use of dual antiplatelet therapy.

In a meta-analysis of chronic drug therapy in patients with Takotsubo cardiomyopathy there was no benefit of long term use of heart failure therapies and post-myocardial infarct drugs in patients with Takotsubo cardiomyopathy. In patients taking β -blockers the recurrence rate of Takotsubo cardiomyopathy was 1.81% *versus* 2.86% in the control group, 0.5% with angiotensin converting enzyme inhibitors *versus* 0% in the control group, 0.5% with aspirin *versus* 0% in control. There was no effect on recurrence with the use of statins. All the studies included in the meta analysis were either observational or non-randomized with low number of patients recruited in each trial consisting of approximately 100 patients or less.⁹

In a further meta-analysis by Singh et al¹⁰ the recurrence rate of Takotsubo cardiomyopathy was approximately 5% at 6 years with an annual rate of 1.5%. Recurrent chest pain was encountered in 14% of cases whilst 11% of patients reported dyspnea without evidence of recurrent Takotsubo cardiomyopathy. Discharge medications during initial admission included β -blockers in 66.8% and angiotensin converting enzyme inhibitors/angiotensin receptor blockers in 67.4% of patients. Recurrence rate was independent of the use of β -blockers, but was less with the use of angiotensin converting enzyme inhibitors/angiotensin receptor blockers. Recurrences of Takotsubo cardiomyopathy was often seen in patients who had previously had a severe episode of Takotsubo cardiomyopathy. Therefore, this study suggests that angiotensin converting enzyme inhibitors and angiotensin receptor blockers may reduce further episodes of Takotsubo cardiomyopathy whilst there is no role for β -blockers in preventing recurrences. Other trials have also supported the notion that β -blockers do not reduce future episodes of Takotsubo cardiomyopathy. However, studies carried out on animals have shown that β -blockers prevent the recurrence of Takotsubo cardiomyopathy.¹¹

The benefit of post-acute coronary syndrome drugs such as statins, aspirin, and clopidogrel, are of unknown benefit. Due to the lack of atherosclerotic plaques in coronary angiography, dual antiplatelet therapy with aspirin and P2Y12 receptor

blocker for a period of 12 months may not be required. However, in a study of 14 patients with Takotsubo cardiomyopathy atherosclerotic plaques were demonstrated on intracoronary ultrasonography with erosive plaques constituting 50% of all cases.¹² In this situation, the use of dual antiplatelet therapy together with a statin is justified.

CONCLUSION

The acute treatment of patients with Takotsubo cardiomyopathy generally consists of heart failure medications. The evidence regarding the use of these drugs both acutely and chronically is conflicting. In general the use of aspirin should be considered in patients who have evidence of coronary disease angiographically. Larger randomized and adequately powered studies are needed to establish whether there is any benefit from acute and long term use of heart failure therapies.

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