

**The Effect of Trimetazidine on Left Ventricular Function
and Hospitalisation in Ischaemic Heart Failure Patients in
Hospital Universiti Sains Malaysia**

DR ROBERTO ANGELO MOJLOU

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LIST OF ABBREVIATION

ACEI	Angiotensin converting enzymes inhibitor
ARB	Angiotensin receptor blocker
BB	Beta Blocker
CAD	Coronary artery disease
DM	Diabetes mellitus
HPT	Hypertension
HPL	Hyperlipidemia
EF	Ejection fraction
LV	Left ventricle
MPK	Makmal Perubatan Kardiologi
TMZ	Trimetazidine

ABTSRAK

Latar belakang : Trimetazidine digunakan terutamanya untuk pesakit yang menghidap penyakit jantung iskemia yang masih mengalami sakit angina yang berterusan. Beberapa kajian telah dilakukan bagi membuktikan kebaikan atau kesan trimetazidine terhadap pesakit lemah jantung. Pesakit ini kebanyakannya berumur dan menghidap kencing manis. trimetazidine dibuktikan mampu menambah-baikkan fungsi pam jantung dan kemasukkan ke hospital turut berkurangan. Walaubagaimanapun, trimetazidine belum lagi digunakan sebagai ubat utama bagi mengubati masalah penyakit lemah jantung iskemia. Objektif kajian ini adalah untuk menguji kesan trimetazidine terhadap fungsi pam jantung pesakit lemah jantung iskemia dan kesan terhadap kemasukkan ke hospital.

Kaedah : Ini adalah kajian keratan rentas perbandingan untuk menilai kesan trimetazidine jika ditambahkan pada rawatan konvensional bagi pesakit lemah jantung disebabkan iskemia. Kajian ini dijalankan dari November 2020 hingga Mac 2021. Persampelan mudah digunakan dan sampel dibahagikan kepada kumpulan trimetazidine dan tanpa trimetazidine. Pesakit direkrut dari klinik kardiologi di HUSM. Data asas seperti EF, usia, jantina, komorbiditi dan ubat-ubatan pada awal diperoleh secara retrospektif dari folder pesakit. Selepas itu, echocardiography susulan akan diperoleh setelah sekurang-kurangnya 6 bulan selepas rawatan. LVEF akan dikemukakan sebagai median + IQR dan dibahagikan kepada kumpulan trimetazidine dan bukan trimetazidine. Perbezaan nilai median antara kumpulan bebas dinilai menggunakan Ujian Mann-Whitney dan pemboleh ubah kategori dibandingkan dengan ujian chi-square. Untuk dua pemboleh ubah bersandar, kami menggunakan Ujian Peringkat Bertanda Wilcoxon. Sementara itu, regresi Poisson digunakan untuk meramalkan jumlah kemasukan ke hospital dalam tempoh 2 tahun selepas rawatan trimetazidine.

Keputusan : Di antara 139 pesakit, 73 pesakit menggunakan trimetazidine dan 66 pesakit tidak menggunakan trimetazidine. Data-data asas seperti ubat-ubatan dan tempoh terapi tidak

berbeza signifikan secara statistik. Terdapat perbezaan yang signifikan secara statistik dari pecahan ejeksi semasa tindak lanjut dengan atau tanpa rawatan trimetazidine (36% (IQR 6.5%) vs 33% (IQR 13%), $p < 0,001$). Terdapat juga perbezaan yang signifikan secara statistik dari peratusan pecahan pelepasan pada peringkat awal dan setelah menerima rawatan trimetazidine (33% (IQR 9%) to 36% (IQR 6.5%), $p < 0,001$). Pesakit yang menerima trimetazidine mempunyai risiko 0.78 (95% CI, 0.41 hingga 1.45) lebih sedikit untuk dimasukkan ke hospital, tetapi hasilnya tidak signifikan secara statistik, $p = 0.43$.

Kesimpulan : Penambahan trimetazidine di atas rawatan sedia ada bagi penyakit lemah jantung telah meningkatkan LVEF secara ketara dan menunjukkan risiko yang lebih rendah untuk dimasukkan ke hospital walaupun keputusan tidak ketara secara saintifik. Oleh itu, trimetazidine sememangnya mempunyai peranan dalam rawatan pesakit yang mengalami kegagalan jantung namun, kajian lebih besar diperlukan untuk membuktikan perkara tersebut.

ABSTRACT

Background : Trimetazidine is primarily used in persistent angina in ischaemic heart disease patients. A few studies showed the potential benefit of trimetazidine in heart failure patients. They were mainly in patients with IHD, DM, and/or elderly patients. Trimetazidine has shown to improve LVEF and hospitalization in this group of patients. Nevertheless, trimetazidine is yet to be used as a first line therapy for heart failure patients with IHD. Objective of this study was to see the effect of trimetazidine on LVEF in IHD patients with reduced EF and hospitalization as well.

Methods : This is a comparative cross-sectional study to assess the effect of trimetazidine if added to conventional treatment in patients with IHD with heart failure. This study was conducted from November 2020 until March 2021. Convenient sampling was used, and samples were divided into trimetazidine group and non-trimetazidine arm (control). Patients were recruited from cardiology clinic in HUSM. Baseline data such as EF, age, gender, comorbidities and medications at baseline were obtain retrospectively from patients' folder. The baseline echocardiography was taken during diagnosis or within one month after starting medications. Subsequently, a follow up echocardiography was obtained after at least 6 months of therapy. Results of LVEF changes were presented as median \pm IQR and divided into trimetazidine and control group. Differences in median values between independent groups were assessed using Mann-Whitney Test and categorical variables were compared by chi-square test. For two dependent variables, we applied the Wilcoxon Signed Ranks Test. Meanwhile, the Poisson regression was used to predict numbers of hospitalization within 2 years post trimetazidine treatment.

Results : Among 139 patients, 73 patients were on trimetazidine and 66 without. Baseline characteristics such as medications and duration of therapy was not statistically significant.

There was a statistically significant median difference of ejection fraction at follow up with or without trimetazidine treatment (36% (IQR 6.5%) vs 33% (IQR 13%) respectively, $p < 0.001$).

There was also statistically significant median difference of ejection fraction percentage at baseline and follow up post trimetazidine treatment (33% (IQR 9%) to 36% (IQR 6.5%), $p < 0.001$). Patient who received trimetazidine has OR of 0.78 (95% CI, 0.41 to 1.45) less risk of hospitalization, however it was not statistically significant ($p = 0.43$).

Conclusion : This small study suggests that trimetazidine addition to standard therapy had positive effect on LVEF after 6 months. However, there was no difference in risk of hospitalization. Trimetazidine may have some role in treatment of patient with heart failure however, further randomized control trial needs to be done to confirm these findings and evaluate on the risk of hospitalization.

Keywords :

Trimetazidine, heart failure, ejection fraction, hospitalisation

CHAPTER 1 : INTRODUCTION

Trimetazidine is conventionally an anti-anginal medication, a metabolic agent, which protects against cardiac ischaemia by up-regulating glucose metabolism relative to that of fatty acid. It is thought to be partly due to its cellular mechanism, in short, decreasing fatty acid oxidation at the level of 3-ketoacyl CoA thiolase (Kantor et al., 2000). Trimetazidine is conventionally used according to the guidelines for patients with persistent angina. However, does it have effect on the LV function? In patients who have heart failure with reduced ejection fraction due to ischaemic heart disease and still symptomatic of heart failure and angina, does trimetazidine usage improve the left ventricular function which translates to better symptoms and less hospitalization?

It has been shown that trimetazidine, were able to, when compared to placebo, reduce the number of angina attacks in a week, reduce the use of nitroglycerin for angina relieve, and improve the exercise time to 1mm ST segment depression (Ciapponi et al., 2017). The study done by Ciapponi was a meta analysis using the Cochrane Central database of controlled trials, where they compared and analysed trials using Trimetazidine and placebo. Most of them showed benefit towards Trimetazidine.

As of today, the current guidelines for management of stable angina aimed at reducing the intensity, frequency and hence improve quality of life of patients. This may be achieved by combination of strategies such as cessation of smoking, daily aspirin, prescription of exercise, and risk factor modifications such as dyslipidemia, hypertension and diabetes. These combined with anti-anginal therapies were advocated in guidelines. First line pharmacological therapy aimed at reducing ischaemia were beta bockers, nitrates, with other first line therapy such as ACEIs/ARBs, CCBs, statins, anticoagulants (aspirin, clopidogrel, novel oral anticoagulation and etc).

Trimetazidine is taken orally, thereafter it will be absorbed in the intestines. Absorption or bioavailability has no significant effect with food intake (Ozbay L et al. 2012).

A study by A.V. Fendrikova in 2011 was conducted, where patient who were resistant to generic trimetazidine (defined as having persistent chest pain), switched to Preductal MR and followed up until 3 months. In the study, they included 112 stable coronary heart disease patients. Improvement in chest pain symptoms were proven using original trimetazidine. Patients who were switched to Preductal MR have reported 63% reduction in angina symptoms and 65% reduction in number of nitroglycerin tablets ($p < 0.01\%$). The reduction in these symptoms and usage of medications translated into better pharmaco-economics of the original trimetazidine.

Heart failure is a clinical syndrome which is caused by abnormalities in cardiac structure or physiology. These in turn cause inability to meet the heart metabolic demand, or perhaps require a higher than normal pressure to meet its demands. It is reported that the prevalence of heart failure ranges from 3-20 per 1000 population (Davis et al BMJ, 2000). Worldwide, the number seems to be on the rise.

Majority of the cause of HF in Malaysia is ischaemic heart disease followed by valvular heart disease and non ischaemic causes (68%, 29%, 28% respectively) (Reyes et al 2016). For the past decade, a lot of new therapy is available for heart failure management. 5 year mortality for HF is estimated at around 48%, which is higher than some cancers such as colorectal, non Hodgkin's lymphoma and breast cancer (NEJM 1992).

Due to the advancement in medicine with new therapeutic agents approved, more patients end up in the other end of spectrum of the disease which is dilated cardiomyopathy. When the CV risks were not properly controlled, they become more symptomatic.

Trimetazidine is still not yet a medication used in the treatment of heart failure. Few supporting evidence is available but not strong enough to be taken into account.

According to Malaysian heart failure guidelines 2019, heart failure is an important cause of acute recurrent medical hospitalisation (6-10%). Heart failure costs around 1.8% of total health expenditure.

Efficacy of trimetazidine

Meta-analyses was done by Ciapponi et al included 23 studies which evaluated the use of trimetazidine in angina pectoris. There was a reduction of 40% of mean number of angina attacks comparing to placebo. It was also supported by the evidence of reduction in use of nitroglycerin tablets and increase in exercise time to 1mm ST depression.

Xu et al, 2014 studied the effect of trimetazidine in elderly multivessel population with diabetic. There was significant improvement of angina symptoms and LV function in intervention group ($p < 0.01$).

Therapy such as ACEI/ARB, beta blocker or the new ARNI has been shown in multiple studies to improve mortality and morbidity especially in heart failure patients. But the limitation that we have with this medication is the issue with blood pressure. Often in advanced heart failure patients the cardiac output is impaired which reduces the blood pressure and thus perfusion to other organs.

In Hospital University Sains Malaysia, we have a dedicated daycare clinic for our heart failure patients who were still slightly congested but compensated. These patients were seen more frequently and medications were titrated more vigorously. The number of patients in this cohort clinic is increasing from time to time.

Heart Failure and LV function

There were a few small studies done on primarily ischaemic dilated cardiomyopathy patients using trimetazidine. All of them showed good results. A study by Yilmaz et al (2009) done which investigated heart failure patients showed improvement of left and right ventricular functions.

Brottier et al 1990 evaluated NYHA and angina symptoms and LV function by LV angiography. There was downgrading of 1 stage of functional class NYHA in treatment arm comparing to placebo

Moreover, a study by Giuseppe et al (2003), which primarily looked at comparison between Trimetazidine to placebo in improving systolic and diastolic LV function in diabetic patients with CAD. In 6 months, the LV ejection fraction increased by $5.4 \pm 0.5\%$ ($p < 0.05$) in intervention group whereas remained unchanged in placebo group.

Chunzeng Lu et al in 1998 evaluated the effect of trimetazidine in ischaemic heart failure patient and assessed changes of left ventricular function as early as 2 weeks. They concluded that the medications did not only improve ischaemic regional myocardial dysfunction at rest but also during stress induced via dobutamine stress echocardiography ($p < 0.02$).

All these trials also evaluated symptoms of angina and heart failure which did show significant improvement. They evaluated functional status using objective measures such as stress test and some with functional NYHA with patient reported symptoms.

Diabetes mellitus was diagnosed based on the guidelines by using glucose measurement, OGTT or HBA1c. Patient must be on treatment for DM with either oral or/and injectable medications.

Coronary artery disease was confirmed using coronary angiography or other modalities such as computed tomography of coronary angiography (CT coronary angiography).

CHAPTER 2 : OBJECTIVES OF STUDY

Main Objective

- (a) To determine the effect of trimetazidine in ischaemic dilated cardiomyopathy patient.

Specific objectives

(i) To study the effect of trimetazidine in improving the left ventricular ejection function (LVEF) in patient with heart failure due to ischaemic heart disease.

(ii) To evaluate frequency of hospitalization due to heart failure between patients who were on trimetazidine and without trimetazidine from starting of therapy to a maximum of 2 years duration.

CHAPTER 3 : MANUSCRIPT

JOURNAL : Malaysian Journal of Medical Sciences

TITLE : The Effect of Trimetazidine on Left Ventricular Function and Hospitalisation in Ischaemic Heart Failure Patients in Hospital Universiti Sains Malaysia.

Author : Roberto Angelo Mojolou

Department of Internal Medicine, School of Medical Sciences, Universiti Sains Malaysia,
16150 Kubang Kerian Kota Bharu, Kelantan, MALAYSIA

Corresponding author: Dr. W. Yus Haniff Bin W. Isa

Cardiology Unit, Department of Internal Medicine, School of Medical Sciences, Universiti
Sains Malaysia, 16150 Kubang Kerian Kota Bharu, Kelantan, MALAYSIA

Email :

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INTRODUCTION

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METHODOLOGY

This study was to assess the effect of trimetazidine in ischaemic dilated cardiomyopathy patients in improving LVEF and frequency of hospitalization. This was a comparative cross-sectional study to assess the effect of trimetazidine if added to conventional ischaemic dilated cardiomyopathy patients.

The list of patients was obtained from either physician clinic Cardiology, Heart failure MPK clinic, or echocardiography room. From physician clinic cardiology or heart failure clinic, during the clinic consultation, the case notes were reviewed and screened for inclusion or exclusion criteria. From echocardiography room, the lists were obtained from a folder that was kept as a reference for the echocardiographer. The inclusion criteria include patients with coronary artery disease, by which a coronary angiography was done, LVEF less than 40%, with risk factors for IHD (i.e HPL, HPT, DM), and on heart failure therapy. Patient who had recent ACS/stroke at diagnosis, renal impairment (egfr < 30), cardiac arrhythmia and uncontrolled hypertension were excluded. When the patient was diagnosed with ischaemic dilated cardiomyopathy, they were started on therapy including ACEI/ARB/ARNI, beta blocker and/MRA. The treatments were started after the diagnosis was made. Upon doing echocardiography, the patient would be started on therapy. However, some patients were started on therapy early based on clinical presentation, but echocardiography done and confirmed the findings. The echocardiography must be done within one month of starting therapy. Optimal therapy for heart failure refers to any heart failure medications started from time of therapy and titrated during subsequent review. Thus, during the recruitment, patient might not be on all heart failure medications yet e.g beta blocker followed by ACEI and later MRA added as tolerated.

Upon fulfilling the criteria, patients were contacted and reviewed in the clinic. The patients were given ample time to read the patient information sheet, thereafter written consents were obtained. After getting the consent, baseline data were obtained from the case note. Baseline data includes demography and echocardiography. The patients were divided into two groups, one cohort were patients on trimetazidine, and without trimetazidine which were the control group.

Other medications were allowed during the study. Patient must be on standard therapy per guidelines requirement. A follow up echocardiography was obtained by looking at latest echocardiography done. The follow up data was taken after at least 6 months of trimetazidine therapy. Patient should be on the optimal medication for at least 6 months however they would not be necessary on all 3 medications (ACEI/ARB/ARNI, beta blocker, MRA) as well as variable medication dose were accepted. This would mean that the repeated echocardiography was obtained after the patients were on treatment for 6 months. Hospitalization rate were obtained from patient history and discharge summary by looking at retrospective data collection. Any hospitalization within period of after starting therapy to maximum of 2 years were recorded. The echocardiography was done by qualified cardiovascular technician.

Data were presented in median \pm inter quartile range (IQR) due to the skewed distribution as confirmed by normality testing. Difference in median values between independent groups were assessed using Mann-Whitney Test and categorical variables were compared using chi-square test. For two independent variables, we applied Wilcoxon Signed Ranks Test. Meanwhile, the Poisson regression was used to predict number of hospitalizations within 2 years post trimetazidine treatment.

Baseline demographics

The demographic at baseline includes age, gender, comorbidities, and medications. The diagnosis using coronary angiography were obtained as well. Other information such as imaging with myocardial perfusion scan, functional assessment were obtained.

LV ejection fraction

The echocardiographic assessment was done at rest. Cardiovascular technician will perform the measurement using the Philip's EPIQ machine (Phillips Healthcare, Selangor).

The measurement were taken according to recommendation from American Society of echocardiography (**ASE, updated 2018**). The LV endocardial border were traced at 2 views. At 4 chamber and 2 chamber views. (Simpson Biplane).

Study area

This study was conducted in Hospital University Sains Malaysia. Patient were recruited from specialist clinic or heart failure clinic. In heart failure clinic, these patients require more extensive monitoring with adjustment of medications. Hence, this data entry were frequent and latest.

Study population

Dilated cardiomyopathy with HFrEF due to ischaemic heart disease in specialist clinic or heart failure clinic in Hospital University Sains Malaysia. Ischaemic heart disease refers to patients who were diagnosed with coronary artery disease.

Ethical clearance was obtained from USM Human Research Ethics Committee (USM HREC). This study was approved by the Research Ethics Committee (Human) School

of Medical Sciences (PPSP) University Sains Malaysia. The study complied with acceptable international standards including the Declaration of Helsinki. Besides that, before obtaining the data and medical record review, permission from the hospital director and Secretariat Outcome Based Budgeting (OBB) were obtained.

RESULTS

In this study, among 139 patients, 73 patients were on trimetazidine (62 males, 11 females) and 66 were not on trimetazidine (50 males, 16 females). Male was significantly more in numbers (112 vs 27). Mean age were 59 years old for control and 62 for trimetazidine group. In the trimetazidine group, 46 (63%) had DM, 61 (83%) HPT, and 54 (74%) HPL whereas in control 39 (59%), 55 (83%) and 35 (53%) respectively. In regards of medications, in trimetazidine group, 34 (46%) were on ARNI, 34 (46%) on ACEI/ARB, 65 (89%) on BB, and 48 (65%) on MRA whereas 36 (54%), 18 (27%), 56 (84%), and 49 (74%) respectively in control group. The baseline characteristics of HPL was significantly different in this study ($p=0.01$). All patients underwent coronary angiography for diagnosis of coronary artery disease. For exercise stress test, 42 patients (57.5%) in trimetazidine and 28 (42.4%) in another arm. All the baseline characteristics were not significantly different except for HPL and myocardial perfusion scan.

1. Outcomes of the study population

Variable	Without		With		U-test	p-values*
	TRIMETAZIDINE		TRIMETAZIDINE			
	Median	(IQR)	Median	(IQR)		
EF Baseline	32.5%	11.0%	33.0%	9.0%	2112.5	0.21
EF Follow Up	33.0%	13.0%	36.0%	6.50%	1562.0	<0.001

*Mann-Whitney U-Test

There was no statistically significant median difference of ejection fraction at baseline with or without trimetazidine treatment ($p = 0.21$). However, there was a statistically significant median difference of ejection fraction at follow up with or without trimetazidine treatment ($p < 0.001$).