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Review

The efficacy of trimetazidine on stable angina pectoris: A meta-analysis of randomized clinical trials

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ABSTRACT

This meta-analysis aimed to evaluate the efficacy of trimetazidine in combination with other anti-anginal drugs versus other anti-anginal drugs in the treatment of stable angina pectoris (SAP). Randomized controlled trials (RCTs) published in English and Chinese were retrieved from computerized databases: Embase, PubMed, and CNKI. Primary outcomes consist of clinical parameters (numbers of weekly angina attacks and nitroglycerin use) and ergometric parameters (time to 1 mm ST-segment depression, and total work (in Mets) and exercise duration (in seconds) at peak exercise) in stable angina pectoris treated by trimetazidine or not. The quality of studies was evaluated using Jadad score. Data analysis of 13 studies was performed using Stata 12.0 software. Results showed that treatment of trimetazidine and other anti-anginal drugs was associated with a smaller weekly mean number of angina attacks (WMD = −0.95, 95%CI: −1.30 to −0.61, Z = 5.39, P < 0.001), fewer weekly nitroglycerin use (WMD = −0.98, 95%CI: −1.44 to −0.52, Z = 4.19, P < 0.001), longer time to 1 mm ST-segment depression (WMD = 0.30, 95%CI: 0.17 to 0.43, Z = 4.46, P < 0.001), higher total work (WMD = 0.82, 95%CI: 0.44 to 1.20, Z = 4.22, P < 0.001) and longer exercise duration at peak exercise (WMD = 49.81, 95%CI: 15.04 to 84.57, Z = 6.38, P < 0.001) than treatment of other anti-anginal drugs for stable angina pectoris. Sensitivity analysis was performed. Sub-group analysis showed that treatment duration was not a significant moderator and patients treated within 8 weeks and above 12 weeks had no difference in the outcomes addressed in this meta-analysis. No publish bias was detected. This meta-analysis confirms the efficacy of trimetazidine in the treatment of stable angina pectoris, in comparison with conventional antianginal agents, regardless of treatment duration.

1. Introduction

Stable angina pectoris (SAP) is a clinical syndrome of temporary hypoxic ischemic status caused by persistent coronary stenosis induced heart load increase. Typical symptoms include burning sensation, pain, pressure, squeezing, or tightness. And atypical symptoms often described as fatigue, indigestion, lightheadedness, nausea, dyspnea and weakness in addition to pain. Moreover, these symptoms can vary from patient to patient across sexes and is present in different parts of the body, including chest, neck, jaw, shoulder, back and arms [1]. The annual mortality rate of stable angina pectoris is 1.6–3.7%, and the incidence of myocardial infarction is 1.2–3.1% [2,3]. The most important prognostic factors of stable angina pectoris are the left ventricular systolic function, comorbidity with other chronic medical conditions, especially coronary artery disease [4].

Traditional hemodynamic agents for the treatment of stable angina pectoris, including β-blockers, calcium antagonists, and nitrates, reduce angina attacks by reducing ATP consumption via lowering heart rate and blood pressure or increasing ATP production through enhancing coronary blood flow [5]. Metabolic agents such as trimetazidine (TMZ), which was officially quoted for the medical management of SAP in American and European guidelines, is a new class known as 3-ketoacyl-CoA thiolase (KAT) inhibitors, representing a new treatment of ischemic heart disease [6,7]. Through selective inhibition of long-chain KAT, trimetazidine promotes cardiac glucose metabolism through switching energy substrate preference from fatty acid oxidation to glucose oxidation [8]. Unlike conventional anti-angina drugs, trimetazidine restores myocardial oxygen supply and demand balance not by hemodynamic changes, but by selective inhibition of long-chain 3-ketoacyl coenzyme A thiolase, thus partially suppressing the oxidation of fatty acid β system, stimulating glucose metabolism and increasing myocardial ischemic tolerance [9,10].

Studies have shown that trimetazidine is associated with functional improvement and symptom relief in newly-diagnosed patients or in coronary patients resistant to hemodynamic agents [11]. The treatment of trimetazidine combined with hemodynamic agents offers full additional efficacy while preserving tolerability [9,10], whereas hemodynamic combination therapy demonstrates minimal or no benefit over monotherapy in the treatment of stable angina pectoris [12,13]. Since most clinical trials involved a limited number of patients, this study

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systematically combines a variety of randomized controlled trials (RCTs) to show the efficacy of trimetazidine in combination with other anti-anginal drugs versus other anti-anginal drugs in the treatment of stable angina pectoris using meta-analysis following MOOSE guidelines [14] for observational studies and the QUORUM guidelines for randomized controlled trials [15].

2. Materials and methods

2.1. Search strategy

We performed an extensive literature search using the keywords "trimetazidine", "stable Angina Pectoris" and "randomized controlled trials" in various combinations to identify randomized controlled trials published in English and Chinese from different computerized databases: Embase, PubMed and Chinese CNKI databases. We also searched the articles from the bibliographies of the retrieved studies and review articles. The corresponding authors in some studies were contacted because necessary information was lacking in their published articles.

2.2. Criteria for selecting articles

All RCTs addressing the difference in the efficacy of trimetazidine in combination with other anti-anginal drugs versus other anti-anginal drugs in the treatment of stable angina pectoris were included. Two investigators (Fang Qi and Fang Dong) independently assessed the manuscripts generated for relevancy and manuscripts with the following criteria were excluded: (1) comparisons were not made between trimetazidine in combination with other anti-anginal drugs versus other anti-anginal drugs in the treatment of stable angina pectoris; (2) a standardized effect size could not be calculated. As this meta-analysis mainly involved data from published studies, an institutional review board approval was not required.

2.3. Quality assessment and data abstraction

The quality of each complete published trial was assessed by the following five criteria: (i) randomization, generation of allocation sequence (computer-generated

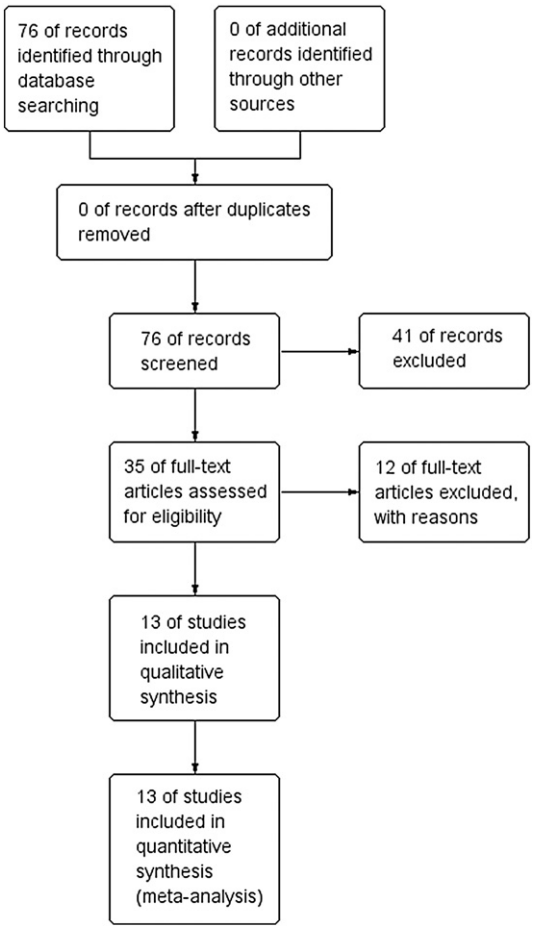

Fig. 1. Flowchart describing the article selection process.

Table 1
Study design and characteristics of studies included.

	Year	Number and sex of patients		Age (years)		Study drugs		Duration of angina		TMZ Dosage (mg/day)	Treatment duration (weeks)
		T (total/male)	C (total/male)	T	C	T	C	T	C		
Vitale	2012	249/225	136/120	59.9 ± 8.2	59.6 ± 8.2	TMZ + atenolol	atenolol	68.8 ± 74.5	58.2 ± 56.3	70	NR
Ribeiro	2007	5	5	62 ± 8		TMZ + hemodynamic antianginal therapy	hemodynamic antianginal therapy	NR		60	6
Szwed	2001	179/142	168/137	54.5 ± 8.1	54.2 ± 8.2	TMZ + Metoprolol	Metoprolol	57.6 ± 57.4	58.7 ± 52.9	60	12
Andreas	1997	26	23	NR		TMZ + propranolol	Propranolol	NR		60	8
Liang	2004	53/35		53.3 ± 8.7		TMZ + metoprolol	Metoprolol	NR		60	12
Zhang	2006	44/26	43/24	54.5 ± 8.1	54.2 ± 8.2	TMZ + metoprolol	Metoprolol	NR		60	8
Lin	2013	34/21	31/17	58.3 ± 10.3	60.2 ± 10.6	TMZ + conventional B receptor blocking or calcium channel blockers	Conventional B receptor blocking or calcium channel blockers	NR		60	12
Zheng	2010	50	50	60		TMZ + conventional B receptor blocking or calcium channel blockers	Conventional B receptor blocking or calcium channel blockers	NR		60	12
Xu	2005	40/27	40/29	61(54–71)	62(56–70)	TMZ + metoprolol + Diltiazem hydrochloride tablets	Metoprolol + diltiazem hydrochloride tablets	NR		60	24
Li	2013	129/75	129/73	60.45 ± 11.02	60.58 ± 10.95	TMZ + conventional B receptor blocking or calcium channel blockers	Conventional B receptor blocking or calcium channel blockers	25.8 ± 13.7	26.8 ± 13.1	60	NR
Zhou	2010	41/28	41/27	57 ± 8.5	58 ± 9.2	TMZ + Metoprolol	Metoprolol	NR		60	12
Yang	2011	31/21	31/19	50–75		TMZ + conventional B receptor blocking or calcium channel blockers	Conventional B receptor blocking or calcium channel blockers	24–60		60	4
Ren	2008	25	25	47–75		TMZ + metoprolol	Metoprolol	NR		60	12