Potential of Trimetazidine in Protecting the Myocardium on Coronary Artery Bypass Grafting Surgery: A Systematic Review and Meta-Analysis

Muhammad Sabri[1], Annisa Tria Fadilla[2], Hariadi Hatta[3], Brilliant[4], Moch Habib[5]

[1,3,4] Division of Cardiothoracic Vascular Surgery, Arifin Achmad Hospital, Pekanbaru, Indonesia
[2] *General Practitioner, Madani General Hospital, Pekanbaru, Indonesia*
[3,5] Division of Surgery, Arifin Achmad Hospital, Pekanbaru, Indonesia
[3,4,5] Faculty of Medicine, University of Riau, Pekanbaru, Indonesia

ABSTRACT

Aims: Increased biochemicals such as Troponin T, CKMB, and CK from myocardial injury are side effects of CABG. Trimetazidine is an anti-ischemic agent that can also have a cardioprotective. We conducted a systematic review and meta-analysis to analyse the role of trimetazidine therapy on postoperative myocardial preservation in CABG.

Methods: The research instrument used was RCT test articles that have been published in the PubMed, Cochrane, and Google Scholar databases in 2013 and 2023. We were classified into two group analyses based on sampling time (at least ≤12 or >12 hours after CABG).

Results: Five RCTs were finally included in the meta-analysis. Significant differences in TnT, CK-MB, and CK were found between trimetazidine-treated CABG patients and control CABG patients ($p < 00001$) in the subgroup examinations conducted ≤12 and >12 post-CABG, indicating significantly lower postoperative TnT, CK-MB, and CK levels in trimetazidine-treated CABG patients compared with control CABG patients.

Conclusion: Myocardial preservation of CABG by comparing the effects of trimetazidine and placebo by assessing several levels of myocardial damage such as TnT, CK-MB, and CK was significantly lower in CABG patients treated with trimetazidine compared with control CABG patients.

Keywords: Trimetazidine, Protecting the Myocardium, CABG, Systematic Review and Meta-Analysis

INTRODUCTION

CABG is an effective surgical treatment for coronary artery disease. However, during and after CABG, there can be ischaemic reperfusion injury resulting in myocardial damage, decreased cardiac output or even arrhythmias(1,2). Increased biochemicals such as Troponin T, CKMB, and CK from myocardial injury are side effects of CABG (3). So, the role of myocardial preservation is an essential issue for patients undergoing CABG.

Trimetazidine is an anti-ischemic agent that can also have a cardioprotective effect as it can alter the metabolic function of the myocardium without affecting cardiac haemodynamics, such as heart rate, systolic blood pressure, and myocardial oxygen consumption (4,5). By selectively inhibiting mitochondrial 3-ketoacyl CoA thiolase, TMZ reduces fatty acid oxidation and increases intracellular glucose and lactate consumption. As a result, the adverse effects of free fatty acid-related oxidative stress are reduced (6).

Therefore, we conducted a systematic review and meta-analysis of RCTs to analyse the role of trimetazidine therapy on postoperative myocardial preservation in CABG patients by assessing several biochemical markers of myocardial injury, including troponin T (TnT), creatinine kinase-myocardial band (CK-MB), creatine kinase and (CK). The Role of Trimetazidine in Protect the Myocardium on Coronary Artery Bypass Grafting Surgery.

METHODS

Eligibility critertia

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 (PRISMA) guidelines for systematic reviews and meta-analyses (7). The main outcome was the effectiveness of trimetazidine therapy on myocardial preservation in postoperative patients by assessing several blood biochemical markers of myocardial injury, such as troponin T (TnT), creatine kinase-myocardial band (CK-MB), and creatine kinase (CK), which were included in the study. Our systematic reviews are screened by two independent reviewers to ensure that relevant papers are included.

Search Strategy

This study was a systematic review with meta-analysis using scientific literature sources from PubMed, Embase Cochrane, and Google Scholar databases obtained systematically based on PRISMA recommendations (7). Literature sources were searched using the keywords ('coronary artery bypass graft' OR 'CABG' OR 'coronary bypass surgery') AND ('trimetazidine') AND ('myocardial protection') AND ('randomized controlled trial' OR 'RCT'). The time period was restricted from 2013 and 2023, and the languages were restricted to English. Further research was located by searching through all of the references in the relevant reviews and publications.

Study Selection

References of included studies were also screened to identify any other trials. Titles and abstracts were used to assess search results across all databases at first. For inclusion in the review, pertinent articles found during the first screening were further reviewed through to the end. Hand searches were conducted for any undiscovered studies in the field's past reviews and metaanalyses. By talking with the third author (H.H.), disagreements between the two reviewers were finally settled. We performed this review in accordance with the Cochrane Handbook for Systematic Reviews of Intervention and the PRISMA declaration (Preferred Reporting Items for Systematic Reviews and Meta-analyses).

Inclusion Criteria

Studies that were included in this review were chosen based on the PICOS (Population, Intervention, Comparison, Outcome, and Study design) framework. We only included randomized controlled trials (RCTs) conducted on patients post-CABG surgery (Population). The patients were divided into two

groups: trimetazidine in addition to conventional drugs (Intervention) or a placebo group receiving only conventional drugs (Comparison). Outcomes were to include any marker of myocardial injury (eg, cTnI, creatine kinase-MB [CK-MB] and creatine kinase [CK]). RCTs were classified into two analysis groups based on sampling time (either ≤12 or >12 hours after CABG).

Exclusion Criteria

This study excluded literature that was not published in English, reviews, editorials, commentaries or case reports, literature without full-text and statistical data, and literature that did not include the effect of Trimetazidine in post-CABG patients.

Data Extraction

The literature obtained from the database was then collected through the Mendeley Desktop application, extracted based on title and abstract, and then we developed the results of the literature data analysis that we obtained using Microsoft Excel (Microsoft® Corp., Redmond, WA). Two independent reviewers extracted the data using an Excel sheet.

Quality and Risk of Bias Assessment

One impartial reviewer assessed each included study's risk of bias. A bias risk assessment tool developed using the Cochrane Risk of Bias tool was used to assess the quality of the included studies.
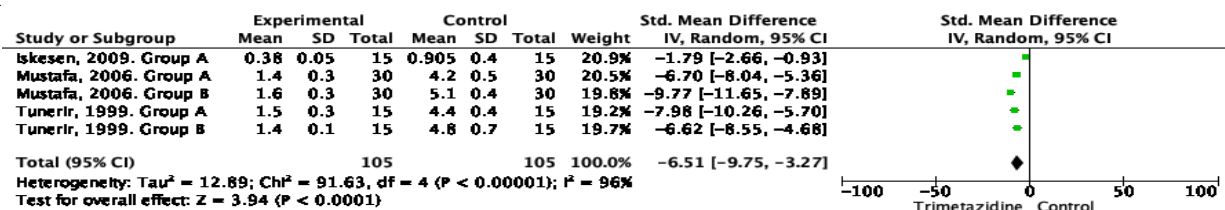
Results of Synthesis

Each author conducts his or her own review of the research included in the title and abstract of the publication before making a decision about which publication to review further. The next step is to evaluate all articles that are suitable for inclusion in the review, as they match the criteria set out in the review. After that, we will determine which articles to include in the review based on the findings we have found. This criterion is used in the process of selecting papers for further assessment. to simplify the process as much as possible when selecting papers to evaluate. Which initial investigations have been conducted, and what elements of the study make it appropriate for inclusion in the review, are discussed here.
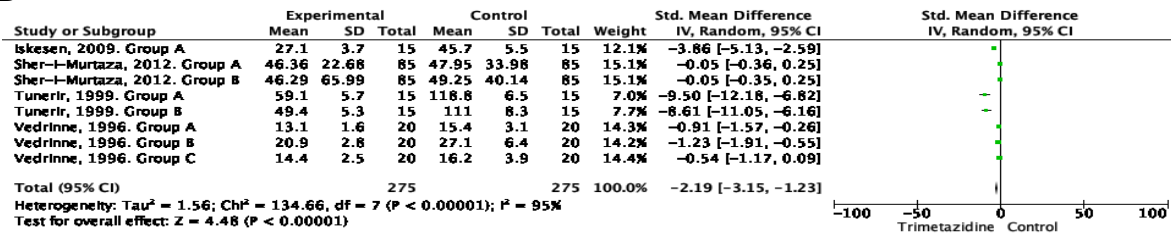
Data Analysis

Data analysis in this study used RevMan 5.4 software. This analysis produces effect size, heterogeneity, and random effect models
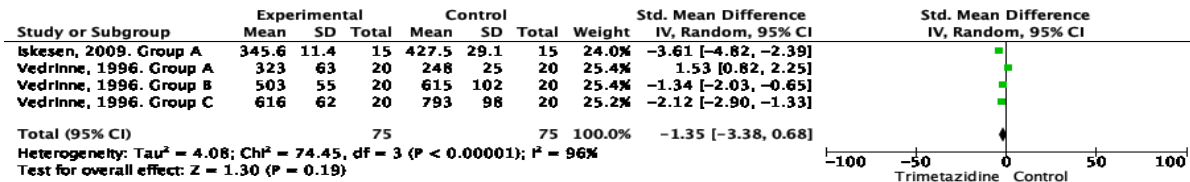
TnT

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Iskesen, 2009. Group A	0.38	0.05	15	0.905	0.4	15	20.9%	−1.79 [−2.66, −0.93]
Mustafa, 2006. Group A	1.4	0.3	30	4.2	0.5	30	20.5%	−6.70 [−8.04, −5.36]
Mustafa, 2006. Group B	1.6	0.3	30	5.1	0.4	30	19.8%	−9.77 [−11.65, −7.89]
Tunerir, 1999. Group A	1.5	0.3	15	4.4	0.4	15	19.2%	−7.98 [−10.26, −5.70]
Tunerir, 1999. Group B	1.4	0.1	15	4.8	0.7	15	19.7%	−6.62 [−8.55, −4.68]
Total (95% CI)			105			105	100.0%	−6.51 [−9.75, −3.27]

Heterogeneity: Tau² = 12.89; Chi² = 91.63, df = 4 (P < 0.00001); I² = 96%
Test for overall effect: Z = 3.94 (P < 0.0001)

CKMB

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Iskesen, 2009. Group A	27.1	3.7	15	45.7	5.5	15	12.1%	-3.86 [-5.13, -2.59]
Sher-i-Murtaza, 2012. Group A	46.36	22.68	85	47.95	33.98	85	15.1%	-0.05 [-0.36, 0.25]
Sher-i-Murtaza, 2012. Group B	46.29	65.99	85	49.25	40.14	85	15.1%	-0.05 [-0.35, 0.25]
Tunerir, 1999. Group A	59.1	5.7	15	118.8	6.5	15	7.0%	-9.50 [-12.18, -6.82]
Tunerir, 1999. Group B	49.4	5.3	15	111	8.3	15	7.7%	-8.61 [-11.05, -6.16]
Vedrinne, 1996. Group A	13.1	1.6	20	15.4	3.1	20	14.3%	-0.91 [-1.57, -0.26]
Vedrinne, 1996. Group B	20.9	2.8	20	27.1	6.4	20	14.2%	-1.23 [-1.91, -0.55]
Vedrinne, 1996. Group C	14.4	2.5	20	16.2	3.9	20	14.4%	-0.54 [-1.17, 0.09]
Total (95% CI)			275			275	100.0%	-2.19 [-3.15, -1.23]

Heterogeneity: Tau² = 1.56; Chi² = 134.66, df = 7 (P < 0.00001); I² = 95%
Test for overall effect: Z = 4.48 (P < 0.00001)

CK

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Iskesen, 2009. Group A	345.6	11.4	15	427.5	29.1	15	24.0%	-3.61 [-4.82, -2.39]
Vedrinne, 1996. Group A	323	63	20	248	25	20	25.4%	1.53 [0.82, 2.25]
Vedrinne, 1996. Group B	503	55	20	615	102	20	25.4%	-1.34 [-2.03, -0.65]
Vedrinne, 1996. Group C	616	62	20	793	98	20	25.2%	-2.12 [-2.90, -1.33]
Total (95% CI)			75			75	100.0%	-1.35 [-3.38, 0.68]

Heterogeneity: Tau² = 4.08; Chi² = 74.45, df = 3 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.30 (P = 0.19)

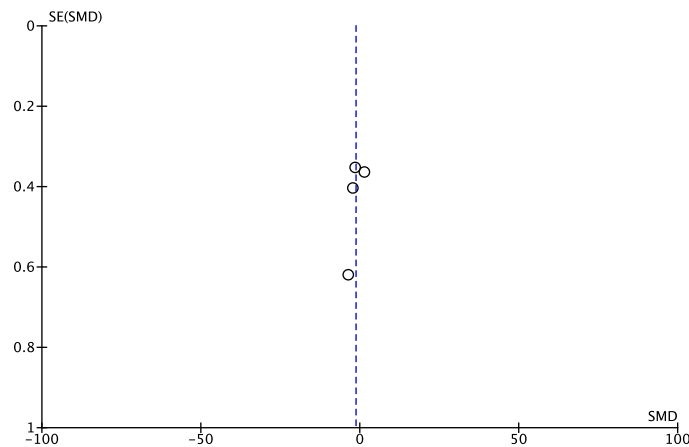**Fig 2.** *Forest plot* RCT meta-analysis of the effect of Trimetazidine on Markers of myocardial injury showing significant differences between Trimetazidine and control groups in terms of TnT, CKMB, and CK ≤12 hours postoperatively.

SULT
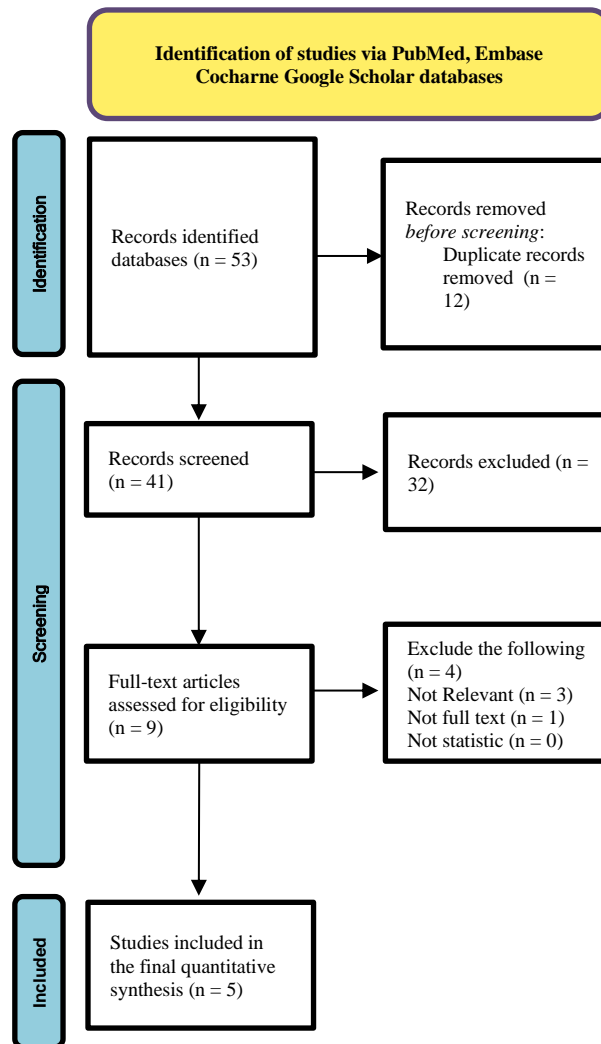
Fig 1. Scheme of article search using PRISMA guidelines

The results of the literature search are presented in Figure 1. A total of 45 potentially relevant articles were identified, of which 5 RCTs were suitable upon application of the inclusion criteria (8, 9, 10, 11, 12).

Meta-analysis: ≤12 hours postoperatively

Figure 2 and figure 3 shows the forest plot evaluating trimetazidine therapy on TnT, CKMB, and CK assessed ≤12 hours postoperatively from several reported data results. TnT consisted of three studies, Ezzeldin et al. and Tunerir et al. each reporting 2 data results, and Iskesen et al. reporting 1 data result, with high heterogeneity ($I2 = 96\%$, $p < 0.00001$); for CKMB, there were four studies, Iskesen et al. reporting 1 data result, Sher-i-Murtaza et al. Tunerir et al. reported 2 data results, and Vedrinne et al. reported 3 data results. With high heterogeneity ($I2 = 95\%$, $p < 0.00001$); in CK, there were two studies from Iskesen et al. reporting 1 data result, and Vedrinne et al. reporting 3 data results with high heterogeneity ($I2 = 96\%$, $p < 0.00001$); This all studies used a random effect model.

The pooled effect size differed significantly between the trimetazidine and control groups. In the TnT subgroup analysis ≤12 hours postoperatively (SMD = -6.51, 95% CI = -9.75 to -3.27, $p < 0.00001$). All three studies showed significant differences between trimetazidine and the control group. For the subgroup analysis of CKMB ≤12 hours postoperatively (SMD = -2.19, 95% CI = -3.15 to -1.23, $p < 0.00001$). Showed a significant difference between trimetazidine and the control group except in the study of Sher-i-Murtaza et al. subgroups A and B and the study of Vedrine et al. subgroup C. Furthermore, the subgroup analysis of CK ≤12 hours postoperatively (SMD = -1.35, 95% CI = -3.38 to 0.68, $p < 0.00001$). Showed a significant difference between trimetazidine and the control group except for Vedrinne et al. subgroup A.
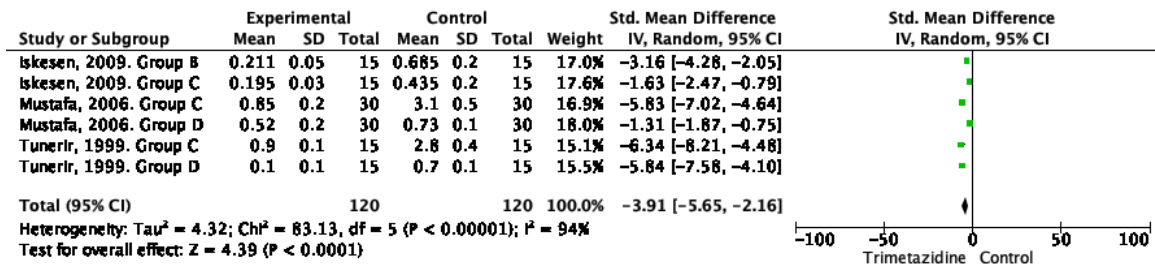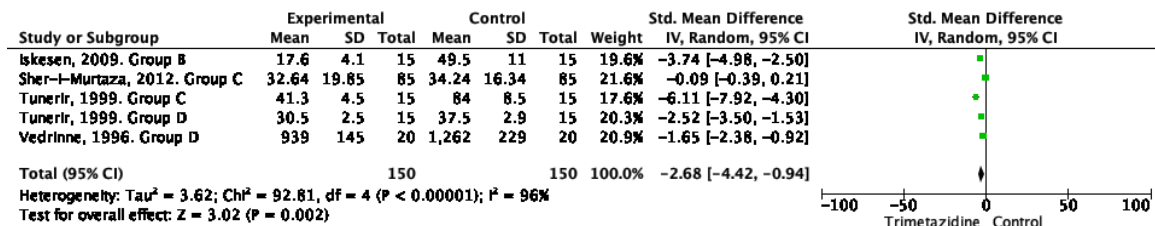

Fig. 3 *Funnel plot* RCT meta-analysis of the effect of Trimetazidine on Markers of myocardial injury showing significant differences between Trimetazidine and control groups in terms of TnT, CKMB, and CK ≤12 hours postoperatively.

Meta-analysis: >12 hours postoperative

Figure 4 and figure 5 shows the forest plot evaluating trimetazidine therapy on TnT, CKMB, and CK assessed >12 hours postoperatively.
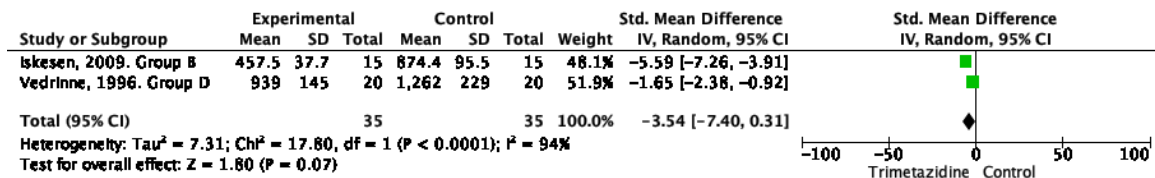
TnT

CKMB

CK

Fig 4. *Forest plot* RCT meta-analysis of the effect of Trimetazidine on Markers of myocardial injury showing significant differences between Trimetazidine and control groups in terms of TnT, CKMB, and CK > 12 hours postoperatively.

For TnT, studies from Ezzeldin et al. and Iskesen et al. each reported 2 data results, Tunerir et al. reported 2 data results with high heterogeneity (I2 = 96%, p < 0.00001); for CKMB, studies from Iskesen et al. Sher-i-Murtaza et al. and Vedrinne et al. with each reporting 1 data result, then Tunerir et al. reported 2 data results with high heterogeneity (I2 = 95%, p < 0.00001); in CK, studies from Iskesen et al. and Vedrinne et al. each reported 3 data results with high heterogeneity (I2 = 96%, p < 0.00001); Thus all studies used a random effect model.

The pooled effect size differed significantly between the trimetazidine and control groups. In the TnT subgroup analysis >2 hours postoperatively (SMD = -3.91, 95% CI = -5.65 to -2.16, p < 0.00001). All three studies showed significant differences between trimetazidine and the control group. Subgroup analysis of CKMB >12 hours postoperatively (SMD = -2.68, 95% CI = -4.42 to -0.94, p < 0.00001). Showed a significant difference between trimetazidine and the control group except in the Sher-i-Murtaza et al. subgroup C study. Furthermore, subgroup analysis of CK >12 hours postoperatively (SMD = -3.54, 95% CI = -7.40 to -0.31, p < 0.00001). Showed a significant difference between trimetazidine and control groups.
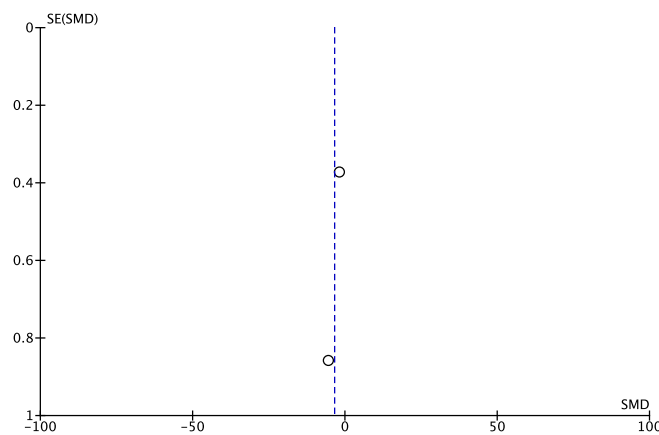
Fig. 5 *Funnel plot* RCT meta-analysis of the effect of Trimetazidine on Markers of myocardial injury showing significant differences between Trimetazidine and control groups in terms of TnT, CKMB, and CK >12 hours postoperatively.

Fig 6. Results of the Cochrane bias assessment tool

DISCUSSION

During ischaemia, the blood supply to the heart is reduced and may even stop altogether, resulting in a reduced supply of oxygen, glucose and fatty acids. Ischaemia inactivates oxidative phosphorylation and causes loss of adenine nucleotides and cytochrome-C, accumulating free phosphates, fatty acids, lactic acid and increased cellular calcium, and intracellular acidosis. During reperfusion, oxygen interacts with the respiratory chain of damaged mitochondria to generate a cas0cade of oxygen-free radicals that cause damage (13, 14, 15).

Trimetazidine is an anti-ischemic agent that acts on several mechanisms. Firstly, by inhibiting mitochondrial 3-ketoacyl coenzyme A thiolase as β-oxidation. Thus, altering cardiomyocyte metabolism from fatty acid oxidation to glucose oxidation. Secondly, trimetazidine can reduce sodium accumulation in cardiomyocyte cytoplasm by improving energy insufficiency, reducing the formation of reactive oxygen species and reducing neutrophil infiltration. Third, trimetazidine can reduce collagen accumulation and cardiac fibroblast connective tissue growth factor expression. Fourthly during reperfusion after an acute ischaemic episode, trimetazidine can improve the mechanical resistance of the sarcolemma to oedema-

induced mechanical stress (16).

CABG is an effective surgical treatment for coronary heart disease. Ischaemic reperfusion injury during and after CABG can cause myocardial damage. Although several methods have been developed to reduce the adverse effects on myocardial tissue, cardiac dysfunction remains common (17, 18, 19).

A major issue in cardiac surgery is protecting the myocardium against ischaemic reperfusion injury during cardiac arrest. The primary purpose of cardioplegia during open-heart surgery is to protect myocardial function and metabolism, but there may be some injury to myocardial tissue that can be detected biochemically. Ineffective and inadequate myocardial protection may lead to myocardial dysfunction and even death despite good revascularisation.

Several studies have shown that trimetazidine can reduce the increase in biochemical markers due to myocardial damage during a heart attack. Therefore, in this systematic review and meta-analysis, we measured the combined effect, which showed that the <12 and >12 hours postoperative values of Troponin T, CKMB, and CK were significantly lower in the trimetazidine group than in the control group. This indicates a significant difference so that trimetazidine therapy after CABG surgery has a positive effect on the myocardial preservation of CABG patients. A systematic review and meta-analysis of 5 RCTs on postoperative myocardial preservation of CABG by comparing the effects of trimetazidine and placebo as a control group by assessing several levels of myocardial damage such as TnT, CK-MB, and CK were significantly lower in CABG patients treated with trimetazidine compared with control CABG patients. In summary, postoperative trimetazidine treatment positively affects myocardial preservation in CABG patients.

Limitation

There are some limitations to this systematic review and meta-analysis. The quality of the data at our disposal limits the scope of our review. Although we identified several well-conducted RCTs, most of the studies identified were observational studies, many of which were non-comparative in nature. Many of the studies included are also retrospective, with a high risk of reporting bias.

CONCLUSION

The study examined the effects of trimetazidine and placebo on myocardial preservation after CABG. The results showed that patients treated with trimetazidine had considerably reduced levels of myocardial damage, such as TnT, CK-MB, and CK, when compared to control CABG patients. In conclusion, myocardial preservation in CABG patients is positively impacted by postoperative trimetazidine medication.

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