Original Article

Efficacy of Trimetazidine and Ranolazine in Angina

Comparative Efficacy of Trimetazidine and Ranolazine in Patients with Angina

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ABSTRACT

Objective: To determine the relative efficacy of two newly available metabolically active drugs Trimetazidine and Ranolazine in a subset of patients whose angina symptoms were not ameliorated with optimum dose of conventional anti-anginal medications (B-Blockers, Calcium Channel Blockers and Nitrates), as further increment in their dosage was detrimental for the rate pressure product.

Study Design: Prospective / Descriptive / cross sectional study

Place and Duration of Study: This study was conducted at the Cardiology Department, DHQ Teaching Hospital Dera Ghazi Khan from November 2016 to December 2016.

Materials and Methods: A total of 106 patients with symptomatic angina from Dera Ghazi Khan urban area were divided into two equal groups each consisting of 53 patients. In group 1 Trimetazidine and in group II Ranolazine was added in addition to their routine optimum treatment. They were evaluated after six weeks through a questionnaire for angina symptoms.

Results: The relief of anginal symptoms was 39.6% in group 1 (Trimetazidine group) while it was 67.9% in group II (Ranolazine group).

Conclusion: The Ranolazine is more effective in controlling the angina symptoms as compared to Trimetazidine as early as six weeks.

Key Words: Chronic Angina, Trimetazidine, Ranolazine

Citation of articles: Rehman K, Saeed MA, Gull T, Khalil MJ. Comparative Efficacy of Trimetazidine and Ranolazine in Patients with Angina. Med Forum 2017; 28(8):59-62.

INTRODUCTION

Chronic angina is a debilitating illness with annual mortality of 1.6% to 3.2%. Anginal episodes are still experienced in about 26% of the patients despite receiving optimum anti-anginal therapy or have undergone percutaneous or surgical revascularization procedures.[1] Among these patients many are not suitable candidates for further revascularization or cannot tolerate additional dose of B-Blockers or calcium channel blockers as it adversely affects the rate pressure product (double product). Trimetazidine or Ranolazine donnot significantly alter the double product and are beneficial for many patients particularly those who cannot tolerate further reduction of the double product.[2,3,4]

Trimetazidine is partial inhibitor of oxidation of free fatty acids and shifts ischemic myocytes oxidation to utilize more carbohydrate than fatty acids as carbohydrate's faster metabolism needs less energy than fat metabolism. It is a well-tolerated drug without any absolute contra indications.[8-10]

The proposed anti-ischemic mechanism of Ranolazine is that it inhibits late sodium inward current. The late sodium current channels are upgraded during ischemia and heart failure[5]. Activation of these channels causes increased sodium influx into myocytes thereby the activation of sodium calcium mechanism increases intra cellular calcium which can lead to metabolic, functional and electrical dysfunction. So Ranolazine attenuates the adverse effect of calcium over load and improves myocardial mechanical, electrical and metabolic function.[3] The metabolic efficacy of Ranolazine for less ischemia has been demonstrated in a study named "Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction, (MERLIN-TIMI 36)" trial in which 6,560 patients were randomized to receive either placebo or Ranolazine.[4] The result showed treatment with Ranolazine was associated with significantly less episodes of recurrent myocardial Ischemia, non sustained VT and pre mature ventricular ectopics. MARISA trial (mono therapy assessment of Ranolazine with stable angina) was a placebo control trial which documented the role of Ranolazine in patients with stable angina.[6-7]

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Received: May 02, 2017; Accepted: June 08, 2017

MATERIALS AND METHODS

Patients of Dera Ghazi Khan urban area who were diagnosed cases of angina and complaining of increase in frequency of chest pain for the last 3 to 4 months were evaluated through a questionnaire.

- Age
- Sex
- Address
- Duration of symptoms

Characteristics of chest pain

- Number of episodes/week after walking one block
- Number of sublingual tablets used to relive pain
- Duration of chest pain
- Use of medicine

ECG, CBC, CUE, Renal parameters and Chest X-Ray were obtained for every patient.

On clinical evaluation pulse, B.P, temperature and respiratory rate was noted along with the examination of cardiovascular system. In this way 106 male patients were enrolled and divided into two groups each consisting to 53 patients. Group 1 patients were given Trimetazidine 35mg twice daily while patients of Group 2 were given Ranolazine 750mg as an add on therapy. Both groups were having diabetic patients 25 in Trimetazidine group while 26 in Ranolazine group. The average blood sugar was 210 ± 8 in both groups. The common medicines used by both groups are given below:

- Tab. Isorbide5-Mononitrate 60mg x 1x OD/ Isosorbide mononitrate 20mg x BID.
- Tab. Metoprolol 100mgxOD/ Atenolol 50mg OD/ Bisoprolol 5mg to 7.5 mg x OD
- Tab. Diltazem 60mg x TID/ Sustained release preparation 60mg BD
- Aspirin 75mg to 150mg OD
- Clopidogrel 75mg OD
- Statin 10mg to 20mg OD

With these medications the titrated heart rate was around 50 beats per minute and blood pressure was around 100/70 mmHg.

RESULTS

After six weeks patients were evaluated for number of anginal episodes by a cardiologist who was blinded to the treatment regime and results are given below:

In Trimetazidine group, 3 patients got 100% relief (no angina episode in a week) while in 7 patients got 75% relief (1 episode in a week). 50% (2 episodes) relief was noted in 4 patients and 25% (3 episodes) relief was noted in 6 patients. 33 patients experienced no relief of their angina symptoms.

In Ranolazine group, 9 patients got 100% relief (no angina episodes) while 75% (1 episodes) relief was noted in 18 patients. 50% (2 episodes) relief in 10 patients while 4 patients had only 25% (3 episodes) relief.

Table 1 shows the detail of relief of angina episodes in both groups.

Table No.1: Relief of angina episodes in both groups

Percentage relief of angina episodes per week	Trimetazidine Group I (n=53)	Ranolazine Group II (n=53)
100%	3 (5.6%)	9 (16%)
75%	7 (13.5%)	18 (33.9%)
50%	4 (7.5%)	10 (18%)
25%	6 (11.3%)	4 (7.5%)
0%	33 (62.24%)	12 (22.6%)

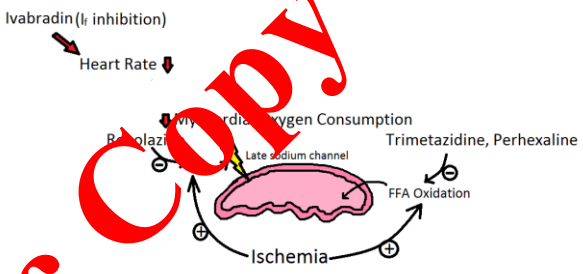

Figure No.1: FFA = free fatty acids, If = Pacemaker inward funny current

DISCUSSION

The management of patients with angina who are already on optimally titrated doses of nitrates, beta blockers and/or calcium channel blockers is challenging as further reduction in rate pressure products may be detrimental. So far them surgical revascularization or another alternative approach should be used. Courage trial included a large population with stable angina who were randomized to optimum medical management with or without PCI. There was no difference in cumulative rate of death and MI after 4.6 years. However in their management currently available metabolically active drugs like Trimetazidine, Ranolazine, Perhexilline and Ivabradine were not used. These metabolic drugs do not alter the rate pressure product and relieve angina by shifting cardiac myocytes metabolism from fatty acids to carbohydrate. [10-15]

Diagram 1 shows the mechanism of action of various metabolically.

Normally fatty acid oxidation is the major source of energy for myocardium up to 80% while glucose metabolism provides remaining quantity of energy. At rest, heart uses 15 to 20% of its maximum oxidative capacity while during ischemia this stressed myocardium surpasses its metabolic reserve and an aerobic limit is reached as a consequence anaerobic metabolism begins with further decline in ventricular

performance and worsening of angina.[15,16] We compared two metabolically active drugs (Trimetazidine and Ranolazine) whom efficacy is documented in various clinical trials that which drug is relatively more effective in our subset of patients and may be added first to standard regimen to save the money of the patients.[17-19] The literature revealed that the combination of Ranolazine when added to CCB's, BB's shows positive outcomes across all outcomes assessed while Trimetazidine when added to CCB's shows significant benefits for most but not for all outcomes. A prospective double blind study of 53 males with chronic angina were randomized to 12 weeks treatment of either Trimetazidine or Ranolazine and were assessed for flow mediated endothelium dependent or nitroglycerin induced dilatation of brachial artery using high resolution ultrasound. The results indicated that both drugs were effective in producing brachial artery dilatation in almost similar manner though Trimetazidine has better effect on flow dependent dilatation. While our study revealed better control of angina in patients who were using Ranolazine in addition to their standard anti-anginal regimen than those to whom Trimetazidine was given in addition to their anti-anginal medication (67.9% vs 39.6%) over a period of six weeks while all other studies were conducted for 12 weeks or more.[20-23] However absolute relief was only in (16% vs 5.6%). There were no significant side effects in both groups except complaint of dizziness in two patients taking Ranolazine. Better results of our study may be attributed to the use of long acting nitrate in both groups and almost 50% of the patients in both groups were diabetics with suboptimal glycemic control as the TERISA study reveals that Ranolazine reduced frequency of anginal episodes in patients with higher Hb A1C value. TERISA study also revealed that Ranolazine slowed the progression to overt diabetes. Optimization of anti-anginal treatment with the help of Ranolazine and Trimetazidine may provide the result beyond what is documented in COURAGE trial and wide availability of both drugs need further studies to evaluate their full therapeutic benefits.[24-25]

CONCLUSION

The Ranolazine is more effective in controlling the angina symptoms as compared to Trimetazidine as early as six weeks.

Author's Contribution:

Concept & Design of Study: Khalil-ur-Rehman
Drafting: Khalil-ur-Rehman
Data Analysis: Muhammad Jahanzeb Khalil
Revisiting Critically: Tayyaba Gull, Muhammad Amer Saeed
Final Approval of version: Khalil-ur-Rehman

Conflict of Interest: The study has no conflict of interest to declare by any author.

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