

Review

## Cardioprotection and effects of melatonin administration on cardiac ischemia reperfusion: Insight from clinical studies

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### ABSTRACT

Acute myocardial infarction (AMI) remains a leading cause of morbidity and mortality. Many treatments have been identified that confer robust cardioprotection in experimental animal models of acute ischemia and reperfusion injury. However, translation of these cardioprotective therapies into the clinical setting of AMI for patient benefit has been disappointing. Many cardioprotective strategies act through common end-effectors and may be suboptimal in patients with comorbidities. Melatonin is a pleiotropic molecule with several functions. Its potential to protect the heart against ischemia/reperfusion damage has attracted much attention, particularly in view of its possible clinical applications. In this brief overview, we discuss the possible clinical application of melatonin in human.

**Keywords:** melatonin, cardioprotection, ischemia/reperfusion, ST elevation, myocardial infarction, clinical trial.

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## 1. CARDIOPROTECTION: WHERE ARE WE HEADING

Despite success in animal studies, translation of cardioprotection to clinical practice has proven difficult (1). Several pharmacological treatments have failed or the results have been inconsistent (2). Differences between preclinical models of transient myocardial ischemia and the clinical scenario in patients, including age, comorbidities, and cotreatments (3), may help to explain the difficulties in translation in some case. In others, insufficient preclinical data or incorrect study design may be responsible (1-3).

### 1.1. Novel adjunctive treatment.

In view of the failure of several drugs to translate successfully from the bench to bedside, there has been an active interest in the development of novel adjunctive therapeutic strategies to limit myocardial ischaemia/reperfusion injury. The melatonin is a molecule present in many human cells. Its production in the pineal gland presents a circadian rhythmicity pattern along of day (4). Many extra pineal organs produce or store melatonin, such as, gastrointestinal, reproductive tracts and others organs (5). On the other hand, the principal subcellular source of

melatonin is the mitochondria (6). It has been shown to protect against ischaemia/reperfusion injury in the heart (7). The current interest in melatonin as cardioprotective agent is also reflected in the number of recent extensive reviews on this topic (8-10).

## 1.2. The literature search for melatonin and cardiac ischemia reperfusion.

The literature search for this investigation was made on April 30, 2019, using the database of the United States National Library of Medicine and the PubMed search engine. The search strategy consisted of the combination of the terms “melatonin” and “human” with “myocardial infarction” and “ischemic heart disease”. Among the articles initially identified, we selected only those that compared patients receiving and not receiving melatonin. Thus, studies not referring to treatment with melatonin, not providing their own data (mainly editorials and reviews), those presenting experience with the use of melatonin but not including its impact on patient outcome, and those limited to study designs were excluded.

## 2. EFFECTS OF MELATONIN ADMINISTRATION: CLINICAL REPORTS

The search identified five studies evaluating the use of melatonin in ischemic heart disease and its clinical outcomes. We summarize the data and the conclusions of these articles.

In 2015, Ghaeliet *al* (11) published a prospective, randomized study involving patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (pPCI). Their aim was to investigate the effects of short-term use of melatonin on cardiac biomarkers, troponin-T and creatine kinase-MB(CK-MB). Patients were divided into 2 groups of 20 each: those who received melatonin and those who do not received melatonin. The oral melatonin (3 mg) started on the night following pPCI and continued daily during the hospitalization, had mixed results on enzymatic myocardial infarct size following STEMI (CK-MB and troponin-T at 6 hours post-pPCI). Although, this study was underpowered (only 40 patients), revealed that melatonin can be considered as safe adjunctive medication to the standard regimen after pPCI in STEMI patients (11).

Another clinical study published in 2016, the melatonin (10 and 20 mg/day) was given orally in 45 patients with ischemic heart disease prior to undergoing elective coronary artery bypass graft (CABG) surgery (12). The study reported cardioprotective effects with 5 day's pre-treatment with melatonin in patients undergoing CABG surgery, as evidenced by less peri-operative myocardial injury when compared to placebo pre-treatment, suggesting that melatonin may be more effective as a cardioprotective agent when administered prior to index ischaemia (as in CABG surgery) rather than at the time of reperfusion (as in STEMI patients) (12).

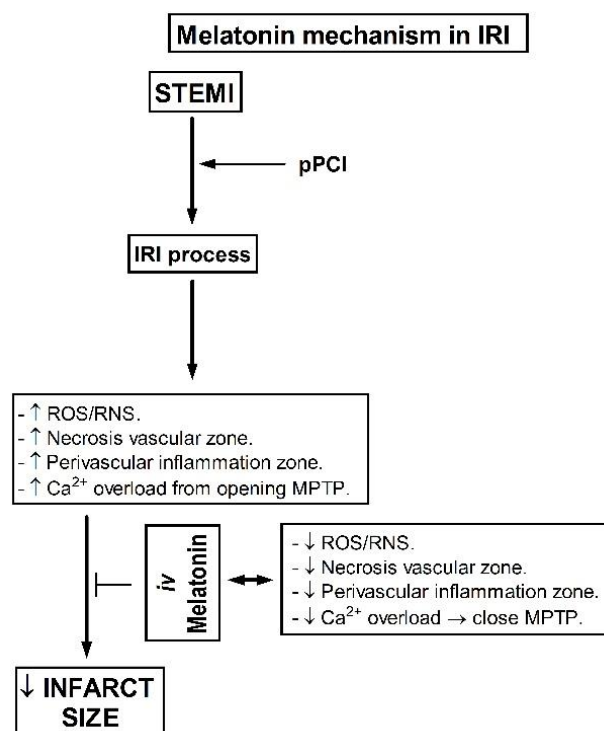
In 2017, three studies have provided additional data related to the effects of melatonin in STEMI patients. Dominguez-Rodriguez *et al* (13) prospectively analyzed 146 STEMI patients which were randomized to melatonin (intravenous and intracoronary) or placebo during pPCI. The authors found that melatonin administered at the time of reperfusion failed to reduce AMI size (assessed by cardiac magnetic resonance image). In fact, in that study, melatonin was found to actually worsen adverse post-myocardial infarction left ventricular remodeling when compared to placebo (with significantly higher left ventricular end diastolic and systolic volumes, and lower ejection fraction on cardiac magnetic resonance image at 4 months following pPCI) (13).

In a post-hoc analysis of the data of the MARIA trial (14), was done to determine whether the effect of melatonin was influenced by the time of administration. Randomized patients were divided into tertiles according to symptoms onset and balloon time: first tertile being 136±23min, second tertile 196±19 min, and third tertile 249±42 min. The data showed that the

effect of melatonin was determined by the timing of reperfusion: melatonin administered <2.5h after symptom onset could reduce infarct size by ~40%, while in the third tertile; the infarct size was smaller in the placebo treated subjects (14). Thus, it seems as if the timing of melatonin administration is critical for the achievement of cardioprotection.

Another study was published in 2017, and the results showed that intravenous administration of 0.1 mg/ml melatonin and intracoronary administration of 0.1 mg/ml at the onset of reperfusion did not improve left ventricular function, or reduce infarct size and improve clinical outcome in 48 STEMI patients (15).

These arguably inconclusive results might be due to the differences in time of melatonin administration, the severity of AMI, and the age of patients in each study. This highlights the fact that careful patient selection is crucial for optimizing the translation of promising cardioprotective therapies in the clinical setting (1-3). As far as our know, the role of melatonin in the ischemia/reperfusion injury process post STEMI is, as radical scavenger of radical oxygen species and radical nitrogen species (16) and to blocking the opening the mitochondrial permeability transition pore(17); both situations provoke the cardiomyocyte death. Recently in a posterior time, directly or indirectly, the melatonin also reduces as anti-inflammatory molecule, the local inflammation to peri-infarction zone (18). The Figure 1 shows the participation of melatonin in the ischemia/reperfusion injury process.



**Fig. 1. Melatonin mechanism in IRI.**

*IRI: Ischemia/reperfusion injury. STEMI: ST-segment elevation myocardial infarction. pPCI: primary Percutaneous Coronary Intervention. ROS: Radical Oxygen Species. RNS: Radical Nitrogen Species. MPTP: Mitochondrial permeability transition pore. IV: intravenous.*

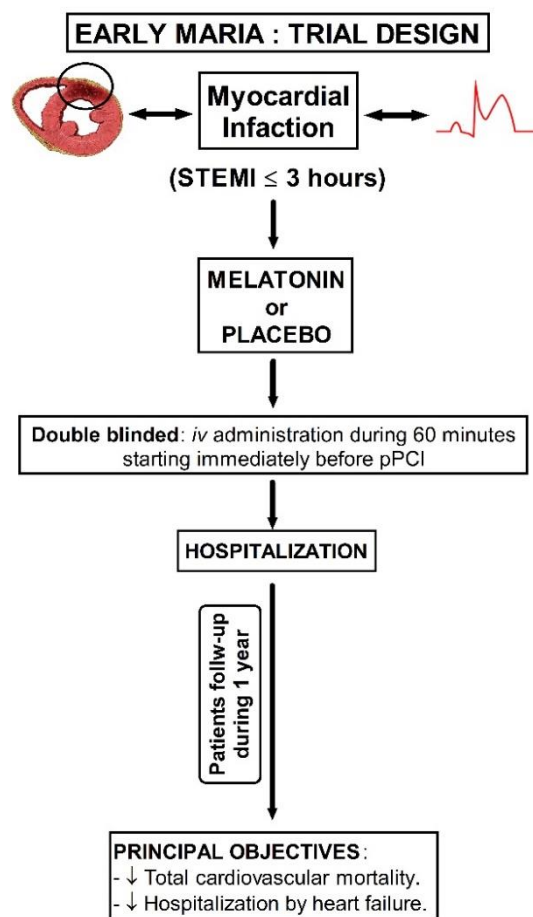
### 3. MELATONIN AS A PROMISING CARDIOPROTECTIVE AGENT

The possibility of using melatonin as therapy in the setting of STEMI has been the major interest to our group. In fact, a recent editorial by Dominguez-Rodriguez *et al* addressed the

question as follows: “melatonin for cardioprotection in ST elevation myocardial infarction: are we ready for the challenge” (19).

The timing of cardioprotective strategies is vital in patients with STEMI. The data of post-hoc analysis suggest that the earlier melatonin is given, the better the result (14). As such, timing is a key determinant of effect. (3) Therefore, the group of Dominguez-Rodriguez et al wishes to execute a phase III clinical trial to determine whether administering melatonin in patients with STEMI within 3 hours of symptom onset reduces the incidence of adverse cardiovascular events.

The EARLY MARIA (Melatonin as Adjunct patients with acute myocaRdial Infarction undergoing primary Angioplasty) trial is designed to test the hypothesis that an intravenous administration of melatonin given by a time period of 60 minutes starting immediately before pPCI in STEMI patients presenting < 3 hours from symptom onset, reduces the composite of 1-year all cause mortality, rehospitalization for heart failure or left ventricular remodeling in STEMI-patients referred for pPCI (Figure 2). The EARLY MARIA study is a prospective, randomized, international, multicenter, placebo-controlled trial in STEMI patients referred for pPCI. This is an academic project with participation of tertiary cardiology centres in Spain and China with capability to perform pPCI.



**Fig. 2. EARLY MARIA (Melatonin as Adjunct patients with acute myocaRdial Infarction undergoing primary Angioplasty) trial design.**

#### 4. CONCLUSIONS

It is only the results of phase III randomized clinical trials that we will be able to obtain an answer to the question as to whether the use of melatonin is necessary in STEMI. Meanwhile,

we have a lot of enthusiasm to champion melatonin as a promising cardioprotective agent against ischemia-reperfusion injury in the setting of STEMI.

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## AUTHORSHIP

A-DR and P-AG contributed in conception, design, and drafting of the manuscript. YC revised the manuscript critically and approved it. All authors approved the final version for submission.

## CONFLICT OF INTEREST

Authors declare no conflict of interest.

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