Reply to letter

Melatonin as a cardioprotective therapy following STEMI – is it really promising?

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We thank Dominguez-Rodriguez & Abreu-Gonzalez[1] for their comment on our ESC Working Group (WG) Position Paper on cardioprotection[2], in which they propose melatonin to be a promising cardioprotective strategy. This was based, in part, on the recently published results of the MARIA trial, in which they investigated the cardioprotective effects of melatonin in ST-segment elevation myocardial infarction (STEMI) patients treated by primary percutaneous coronary intervention (PPCI)[3]. However, in the MARIA trial, the authors found that intravenous and intracoronary melatonin administered at the time of reperfusion failed to reduce acute myocardial infarct (MI) size (assessed by cardiac MRI)[3]. In fact, in that study, melatonin was found to actually worsen adverse post-MI left ventricular (LV) remodelling when compared to placebo (with significantly higher left LV end diastolic and systolic volumes, and lower ejection fraction on cardiac MRI at 4 months following PPCI)[3]. The cause of this detrimental effect of melatonin on post-MI LV remodelling is not clear, but may be related to its reported effects on increasing myocardial accumulation of collagen and glycosaminoglycans following infarction[4]. In another study, oral melatonin started on the night following PPCI and continued daily during the hospitalisation, had mixed results on enzymatic MI size following STEMI (CK-MB and hs-Troponin-T at 6 hours post-PPCI)[5], although the study was underpowered (only 40 patients), and the dosing regimen was suboptimal. Another clinical study reported cardioprotective effects with 5 days' pre-treatment with melatonin in patients undergoing coronary artery bypass graft (CABG) surgery, as evidenced by less peri-operative myocardial injury when compared to placebo pre-treatment[6], 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).

The neutral findings of the MARIA trial on a background of promising experimental data with melatonin, underscores the challenges in translating novel cardioprotective therapies from the bench to the bedside, as highlighted in our ESC WG Position paper[2]. It is important to note that the experimental animal data showing beneficial effects with melatonin on MI size were largely restricted to small animal MI models with no comorbidities and comedications[7], and most of these experimental studies had examined the long-terms effects

of melatonin on post-MI adverse remodelling. Of note, in a clinically relevant large animal closed-chest reperfused porcine MI model, it was reported that intravenous and intracoronary melatonin administered prior to reperfusion failed to reduce MI size[8], suggesting inconsistent cardioprotection with melatonin even in the experimental setting. These studies highlight the importance of thoroughly testing novel cardioprotective therapies in the laboratory setting, before proceeding with clinical cardioprotection studies[9].

In a post-hoc subgroup analysis of the MARIA trial, Dominguez-Rodriguez & Abreu-Gonzalez[1] found that melatonin reduced MI size in STEMI patients presenting within 2.5 hours of chest pain onset (although these results have been published so far only as an abstract)[10], a finding which is consistent with studies showing beneficial effects with cardioprotective therapies, such as adenosine and exenatide, administered to patients presenting with short ischaemic times (<3 hours)[11-13] - whether the detrimental effects of melatonin on post-MI LV remodelling observed in the MARIA study were also observed in this subgroup analysis was not reported. Moreover, in patients presenting with ischaemic times of >3.5 hours, melatonin actually increased MI size when compared to placebo, suggesting a detrimental effect of melatonin in these patients[10].

In summary, the aim of our ESC WG Position Paper on cardioprotection had been to review the current status of cardioprotection, highlight promising new cardioprotective targets and therapies, and unfortunately, the current clinical evidence does not appear to support melatonin as a promising therapy for reducing MI size in reperfused STEMI patients.

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