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Lessons from the trials

NIAMI: Towards the optimization of results in primary PCI

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ABSTRACT

The NAIMI trial has recently been published. It assessed one of the most contemporary and challenging issues in the management of acute myocardial infarction (AMI), namely prevention of reperfusion injury (RPI) after primary PCI for ST-elevation myocardial infarction (STEMI). It investigated the effect of the intravenous administration of Na nitrite given immediately prior to primary PCI for STEMI in 229 patients (118 in the treatment group, and 111 in placebo). The myocardial infarction (MI) size did not differ between the two groups as observed by cardiac MRI (CMR) with gadolinium enhancement at 6–8 days or plasma Troponin-I and creatine kinase (CK), or by left ventricular (LV) volume and ejection fraction (EF) as measured by echocardiography at 6–8 days and again at 6 months. They concluded that IV nitrites did not reduce the infarct size. There was, however, a trend towards benefit in diabetic patients in the post-hoc analysis. The small number of these subjects has probably lead to inconclusive outcome in this subset.

Keywords: ST-elevation myocardial infarction, primary PCI, reperfusion injury, nitrites

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PROLOGUE

STEMI is caused by an acute occlusion of one of the coronary arteries which leads to cessation of blood flow to the infarct zone and that in turn leads to a series of pathological processes. For decades huge efforts were directed towards perfection of therapeutic strategies that can open the occluded vessel, thus allowing restoration of coronary blood flow to the infarct zone. This goal was successfully achieved, first by thrombolytic therapy, and later by primary PCI.[1] Indeed, when delivered timely, both reperfusion strategies have lead to an improvement in survival and left ventricular (LV) function. However, it has gradually become clear from large studies that, even with successful and timely opening of the infarct related artery, variable and sometimes severe degree of LV dysfunction still occurs. This prompted massive research to better understand the complete sequence of the biochemical and pathological processes in AMI over the last decades. This revealed some amazing results. It may sound paradoxical but restoration of blood flow after a period of occlusion itself appear to cause further myocardial damage, often referred to as re-perfusion injury (RPI).[2] It became quickly clear that it was not enough just to restore blood flow to minimize the infarct size. The resulting heart failure is a major consequence of myocardial infarction with massive epidemiologic and economic impact.[3] The target for the ideal treatment for AMI has therefore moved from simply opening the infarct-related artery to include reduction and/or treatment of RPI with the aim to reduce as much LV dysfunction and prevent the untoward end of heart failure. Today any "comprehensive" strategy must not only include establishing reperfusion of the infarct related artery, but also prevent the deleterious effects re-perfusion injury. Unfortunately, while the achievement of the first goal is near its peak, the second goal of preventing reperfusion injury has not been as fortunate. This is despite much understanding of the mechanism of injury, which in theory should pave the way for an effective therapy or therapies.

Several agents have been proposed based on the mechanism of injury and indeed some of these agents have already been tried in experimental and clinical trials. Many have shown success in experimental models. The problem is that when applied to AMI in humans, the results are not as impressive. One of the most promising agents for the prevention of RPI in experimental models is sodium nitrite, which has it main mechanism of action on the mitochondrial permeability transport pores (MPTP) through conversion into nitric oxide (NO).[4] The investigators of the NIAMI study used Na-nitrite infusion, given intravenously, immediately prior to primary PCI for STEMI.

PATIENTS, METHODS AND RESULTS

This is the first large clinical study using Na-nitrites in primary PCI. It is a multi-center, double blind, placebo-controlled randomized trial.[5] The sample size was estimated assuming mean infarct size of 15–20% in STEMI patients, based on data from Bøtker et al.[6] They aimed to test at least a 4 point reduction in infarct size for relevance.

The primary outcome of the study was reduction in the infarct size which was assessed by echocardiography and cardiac MRI at 6–8 days (initial infarct size) and by echocardiography alone at 6 months (final infarct size). The median infarct size was 22% in the treatment group versus 20% in placebo group, which did not meet the hypothesis set at 4% reduction. It is of note that 22% and 16% of patients declined cardiac MRI in each group respectively. The left ventricular end systolic volume (LVESV) was 85 ml in both groups at 6–8 days, and 75 ml versus 78 ml at 6 months. Similarly LV ejection fraction was similar; 48% in treatment group versus 45% in placebo group at 6–8 days, and 53% in both groups at 6 months.

Interestingly there was no significant change in these echocardiographic parameters over the duration of follow up between 6–8 days and 6 months in both groups.

The secondary outcome was reduction in the rise of the plasma levels of biomarkers during the acute phase of STEMI. This was also similar between the two groups. Thus, the mean Troponin-1 was slightly lower in the treatment group compared to the placebo group (3734 vs 3807 arbitary units), while the creatine kinase levels were higher (67019 versus 59574 respectively).

Unlike the other negative findings, a very interesting upshot emerged in the pre-specified and post-hoc subgroup analysis. There was a treatment effect favoring nitrites in diabetic patients, which was not seen in non-diabetics. Thus there was 4.5% reduction in infarct size in diabetics, compared to only 0.2% in non-diabetics. However, the interaction was not statistically significant, perhaps because of the small number of diabetics in the study. Type II statistical error (only 12 diabetics in the treatment group and 11 in placebo). Given these post-randomization exclusions or missing data both in the treatment

and placebo groups, it is difficult to know how many of these have actually had incomplete biochemical records or CMR studies in the specific subgroups.

DISCUSSION AND CRITIQUE

The NAIMI study[5] tackles and important problem that arises from both occlusion and reperfusion injury of the myocardium after AMI, which eventually lead to LV dysfunction and heart failure. It is a serious attempt to move the bar forward to a more global strategy in the management of AMI, a strategy that offers not only effective and timely reperfusion, but also prevents the subsequent reperfusion injury. The investigators used Na-nitrites, which showed much promise to prevent reperfusion injury in experimental studies.[2]

Despite much studied science and understanding of the mechanisms of reperfusion injury, this is yet another negative trial to prevent reperfusion in clinical trials. The investigators carefully worked out the sample size assuming 4 points reduction in infarct size. They also evaluated the dose required to achieve optimal plasma level of Na-nitrites. However, this remains a blood level that is based on animal models and then translated to the human clinical situation. At these plasma levels, the results were promising in animal models, but disappointing in man. Could higher plasma levels give different outcomes?. Was it a matter of dose?. Was the duration of infusion short?

The authors were rightly cautious of the potential side effects of higher doses. In a study by Gonzalez et al.[7] longer infusion (1 hour) resulted in higher plasma levels, but with significant haemodynamic changes, sometimes needing saline infusion to maintain blood pressure. The matter is also complicated further by the fact that nitrites, and indeed organic nitrates, appear to have a biphasic effect with more favorable outcomes at smaller doses, and may be none at higher doses. However, given that the drug has shown great promise in animal models, further research into all these questions may be worthwhile.

Another question is: could direct infusion of the nitrites into the coronary arteries during primary PCI result in a better outcome based on better delivery of the agent? This question is being addressed by Jones et al. for which the methodology has already been published.[8]

The selection of both treatment and placebo group was obviously rigorous and this is reflected by the high exclusion rates in both the pre- and post-randomization periods. Thus out of 652 patients screened, only 280 patients were eventually included. Another 51 were excluded because of incomplete results. Therefore, after all the exclusions, only 229 made it to the final analysis (118 in the treatment group and 111 in placebo).

Several studies have shown that all aspects of AMI are worse in diabetics than non-diabetics, including the left ventricular dysfunction and remodeling, and subsequently heart failure.[9] Therefore, this is group is of special importance, not only in terms of perfusion strategies and antiplatelet therapy, but also for strategies that can limit the reperfusion injury.

In the current study, while the results were unimpressive in the whole group, there is evidence in their sub-analysis that diabetic patients may obtain greater benefit than non-diabetics. Unfortunately the number of diabetic patients in the study was small, thus may be misleading (type II statistical error).

With the relatively high number of diabetics in the Gulf, a modified study is underway in our center to address some of the above questions, especially in diabetic patients, which make nearly half of the STEMI patients that we see in the primary PCI program.

The investigators used a single dose of 70 μmoles of Na-nitrites in 5 ml of water, which is reasonable since multiple doses could dilute the conclusions with the limited number of patients. This dose was calculated based on a previous study to achieve adequate plasma levels in an average 70 kg normal subjects. This, in turn, was suggested by a previous animal model which showed that 5 μmol per liter gave an impressive level of prevention of reperfusion injury. Another study in healthy individuals showed that this plasma concentration can be achieved by giving an intravenous infusion of 50 μmol of Na-nitrites over 5 minutes. They used 70 μg over the same period of time in the study, thus assuring an adequate dose for the study.

WHAT HAVE WE LEARNT?

The NAIMI study has tackled one of the most challenging contemporary issues in the management of acute myocardial infarction and used one of the most promising agents currently available to prevent reperfusion injury. Nonetheless, it failed to show a significant difference, despite much evidence to support its use from both the science and the experimental models.

The first lesson is inevitably is how complex and illusive the issue of prevention of reperfusion injury is today. The second lesson is that there may be vital differences between experimental models and clinical AMI in humans that need to be explored further. Third, we have learnt how carefully the investigators went about estimating the appropriate dose of Na-nitrites in the clinical setting, projecting from data in both experimental models and healthy volunteers. Fourth, there is a call to carefully examine the possibility of different doses and/or different routes for the administration of nitrites in STEMI patients. Fifth, the study highlights how difficult it is to avoid exclusions and missed data which make the task of analysis and conclusions tricky. Sixth, and perhaps the most important lesson from the NIAMI study, is that it gives a glimpse of hope to one of the highest risk groups in AMI, namely diabetics. It is our intention to set up a research protocol to concentrate on this group that we see frequently in the Gulf region.

The quest for the optimal strategy to prevent reperfusion injury is intense and is as varied as the mechanisms of injury. It went as far using immunosuppressant agents[10] and catheter cooling as in the CHILL-MI study,[11] a reminder of the previous experience during cardiac surgery.[12]

In conclusion, the NIAMI study tackled an important issue in the management of reperfusion injury after STEMI and used one of the most promising agents in experimental models, namely Na-nitrites. Although the overall result is negative, the study highlighted important issues, especially the promise in diabetic patients.

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