

Magnesium in the acute management of atrial fibrillation: noise or music?

Stosowanie magnezu w doraźnym leczeniu migotania przedsionków – dźwięki czy muzyka?

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The acute management of atrial fibrillation (AF) is a clinical challenge particularly in patients presenting with AF either at the emergency room or in intensive care units. In spite of the relevance of AF little consensus is available on the best management and the evidence available on this topic is rather sparse. In the last 2 decades very few new antiarrhythmic drugs have been developed for the acute management of AF. Other than Ibutilide and Dofetilide, both class III antiarrhythmics with moderate efficacy, not much is available in the therapeutic horizon [1]. This deficiency motivated some investigators to go back to basics and explore other alternatives.

The cardiac effects and potential therapeutic uses of ions such as magnesium have been previously explored; but the clinical efficacy of magnesium replacement therapy remains unclear [2,3]. Magnesium prolongs the atrial and atrioventricular nodal refractory periods potentially facilitating rate control in AF [4,5]. Onalan et al. [6] recently published a meta-analysis that addressed the effect of magnesium therapy in the acute management of AF. The purpose of this editorial is to review this meta-analysis and determine whether these findings should indeed trigger a change in our daily clinical practice.

Let us first address whether this meta-analysis is methodologically sound. The authors have done a very thorough literature search and have used appropriate inclusion and exclusion criteria to select trials for the systematic review. Appropriate techniques were used for literature search, data abstraction and quality assessment of the trials. After a detailed literature search only nine trials were found eligible for inclusion. Significant heterogeneity was noted in the trials with respect to clinical characteristics of trial patients, quality of trial methodology (most of the trials scored poorly), type and dose of control medications, dose of magnesium used, and methods used to assess outcomes. The authors have indicated that there

is a high likelihood of publication bias. A formal adjustment for publication bias was not performed. A fixed-effects model was used to perform the meta-analysis. However, given the significant inter-trial heterogeneity a random-effects model would have been more appropriate. Even though both models have their limitations, in the presence of significant heterogeneity, a random-effects model tends to be more conservative and is less likely to indicate a beneficial effect when there is none [7]. It would have been interesting to find out whether the results would have been different if a random-effects model had been used in this meta-analysis.

The point estimates for the primary outcomes of rate control, rhythm control and overall response to therapy in this meta-analysis seem to indicate that magnesium is more effective than control (placebo, calcium blockers and antiarrhythmic agents) in the acute management of AF. However, upon careful analysis it is apparent that the placebo control trials are the main drivers of this finding. For instance – in the rate control analysis the trials comparing magnesium to placebo show a benefit for magnesium. On the other hand trials using calcium-channel blocking agents as control do not show such a benefit for magnesium therapy. It is well known that calcium-channel blockers and β -blockers are very effective atrioventricular (AV) nodal blocking agents and if more trials comparing magnesium with these agents had been available we might have had a less positive outcome for the effect of magnesium therapy for rate control of AF in the acute setting [8].

Similarly, in the rhythm control analysis magnesium seems to be superior to placebo, particularly calcium blockers and ajmaline. However, in the trial comparing magnesium with amiodarone magnesium was inferior to Amiodarone in maintaining sinus rhythm. The overall point estimate in this analysis is once again in favor of magnesium (albeit by not much) because of trials using placebo or calcium channel blockers as control. As we know calcium channel blockers are not very effective in achieving rhythm control of AF. If more trials using antiarrhythmic medications (amiodarone, class I antiarrhythmic agents etc.) as controls had been available for analysis we might have had different results. The same logic applies to the analysis looking at the primary outcome of overall response to therapy [8].

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The secondary outcomes analyses indicate that patients on magnesium therapy achieve adequate rate control in a shorter period of time compared to those treated with placebo or calcium channel blockers. The onset of the effect is on an average about four to nine minutes quicker than control medications. Even though this is statistically significant it is not of much practical significance in the acute management of AF. The side effect profile and adverse event rates for magnesium are comparable to placebo and control medications used in these trials. The optimal dose and duration of therapy with magnesium in this setting is not clear from the systematic review and this needs to be clarified.

Ho et al. [9] recently published another meta-analysis using mostly the same studies as Onalan et al. addressing the same question. Interestingly enough this study suggested that adding magnesium to digoxin reduced ventricular rate response more effectively than placebo but there was no difference when this outcome was compared to patients receiving calcium-channel blockers or Amiodarone. This finding supports our prediction that the main benefit of magnesium is seen when compared to placebo. Both studies conclude that magnesium may be a safe adjunct to achieve faster control of ventricular response in the acute setting of atrial fibrillation. Additionally the study by Ho et al did perform a funnel plot showing that indeed there is publication bias albeit small.

What is the goal when a patient presents to the ER or the intensive care setting with acute onset AF? This of course varies largely on the clinical presentation. The patient in the intensive care usually has a poor response to rapid AF and cardioversion is a must. On the other hand the patient with no structural heart disease and well-tolerated acute onset AF rate control may be sufficient. Does this meta-analysis provide enough support to change our daily practice and start an intravenous infusion of magnesium on all patients presenting with acute onset AF? A meta-analysis is as good as the data that is available for analysis. Unfortunately, the data available for this particular meta-analysis is not of optimal quality. There are multiple sources of bias that could have influenced the outcomes. Based on this meta-analysis and the one performed by Ho et al. we conclude that magnesium is not superior to conventional AV nodal blocking agents (calcium

blockers, β -blockers) and antiarrhythmic agents (amiodarone, class I agents) in the acute management of AF. However, it is reasonable to conclude that magnesium is better than placebo particularly when combined with digoxin in the acute management of AF as assessed by achieving a ventricular rate <100 beats per minute. Of note magnesium does not improve the rate of reversion to sinus rhythm, which should remain the main therapeutic goal in the presence of acute onset AF. Magnesium may have a role in the acute management of AF in patients who are not able to tolerate conventionally used pharmacological agents. Are these findings noise or music? Undoubtedly a few chords have been stricken but these are far from being music! Well-designed clinical trials are required to assess the efficacy of magnesium in the acute management of AF. In the meantime magnesium should not be considered as a first line agent for the acute management of AF.

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From the Editor

Synopsis: Onalan O, Crystal E, Daoulah A, et al. Meta-analysis of magnesium therapy for the acute management of rapid atrial fibrillation. *Am J Cardiol*. 2007; 99: 1726-1732.

In this metaanalysis of 8 randomized controlled trials, in which participated 476 patients with atrial fibrillation with rapid ventricular rate, it has been shown that magnesium in the initial dosage 1.2–5 g compared to placebo is more effective in achieving rate control but not rhythm control. Magnesium caused the restoration of sinus rhythm more often than calcium channel blockers and amiodarone and less frequently than ajmaline, but majority of comparisons was based on one trial only. There was no significant difference in the adverse event rate between magnesium and placebo or antiarrhythmic drugs.

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