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REVIEW

Arrhythmia/electrophysiology

Treating arrhythmias with adjunctive magnesium: identifying future research directions

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Magnesium is the fourth most abundant cation in the human body and is the second most prevalent cation in intracellular tissues. Myocardial cell action potentials are mediated by voltage-dependent Na^+, K^+, and Ca^{2+} channels which, when their function is altered, can lead to the genesis of cardiac dysrythmias. Magnesium regulates the movement of ions through these channels within myocardial tissues. The potential ability of magnesium supplementation to prevent and/or treat arrhythmias has been recognized in clinical medicine for years. This includes termination of torsade de pointes, prevention of post-operative atrial fibrillation, acute treatment of atrial fibrillation, and improving the efficacy and safety of antiarrhythmic drugs. Despite what is currently known about magnesium's therapeutic potential, a number of limitations and gaps to the literature exist. This includes an unclear link between correction of intracellular magnesium concentrations and both mechanistic and clinical outcomes, small sample sizes, varying routes of administration and doses, as well as short follow-up periods. This review highlights these gaps and recommends areas of need for future research.

Keywords Magnesium • Arrhythmia • Cardiovascular disease

Introduction

Magnesium is the fourth most abundant cation in the human body and is the second most prevalent cation in intracellular tissues.[1] Its primary physiologic roles involve enzyme activity and protein transport, including being an essential component of all adenosine triphosphate-utilizing systems.[2] As such, magnesium plays an integral role in a variety of functions related to cardiovascular disorders.[3] Reduced dietary intake of magnesium has been linked with a higher risk of hypertension,[4] atrial fibrillation (AF),[5] ischaemic heart disease,[6] and new-onset heart failure and heart failure-related hospitalization.[7,8] Similarly, a low serum magnesium level is associated with up to a 50% higher incidence of new AF,[9,10] left ventricular hypertrophy,[11] and is an important predictor of sudden cardiovascular death and overall mortality.[12–14]

The potential ability of magnesium supplementation to prevent and/or treat arrhythmias has been recognized in clinical medicine for years.[15–17] This includes prevention of AF following cardiac surgery,[18] acute treatment of rapid AF,[19,20] new-onset and treatment-refractory supraventricular tachycardia (SVT),[21,22] refractory ventricular fibrillation,[23] and a variety of drug-induced arrhythmias most notably torsade de pointes (TdP).[24–28] As a result, the American Association for Thoracic Surgery and European Society of Cardiology have incorporated magnesium into their recent guidelines for preventing and managing certain arrhythmias.[29,30]

Despite what is currently known about magnesium's therapeutic potential, a number of limitations and gaps to the literature exist. Examples include the true incidence and impact of intracellular magnesium deficiency, target serum and intracellular magnesium concentration targets, the most efficacious magnesium salt form (*Table 1*),[31] and the optimal dose and timing of magnesium administration. The purpose of this review is to critically evaluate the current literature base supporting the use of magnesium supplementation for preventing and/or treating clinical arrhythmias and to subsequently identify the key future research directions needed to better inform clinical decision making. Pertinent clinical investigations (randomized controlled trials, observational studies, and meta-analyses) as well as mechanistic studies were identified by searching MEDLINE from its inception through 31 August 2016. Medical Subject Heading and key words used included: Magnesium, Arrhythmias, Cardiac, Cardiac Surgical Procedures, and Cardiac Electrophysiology. Citation lists from identified studies and review articles were also examined for pertinent citations.

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Table 1 Comparison of oral magnesium supplements[31]

Magnesium salt	Elemental Mg^{++} dose, mg (mEq)	Bioavailability	Oral absorption, %	Dosage form	Recommended daily dose	Adverse effects
Carbonate	232 (19.0)	Very low	N/A	Tablet	70 mg elemental Mg (each tablet)	GI distress, diarrhoea
Chloride	64 (5.26)	Good	19.7	Enteric-coated tablets	640 mg/day (1–2 tablets TID)	GI distress, diarrhoea
Citrate	N/A	Good	29.6	Liquid, tablets	25 mEq Mg, 2–5 tablets	Laxative, evacuant
Gluconate	27 (tablets), 54 (liquid)	Good	19.3	Liquid, tablets	645 mg/day, 2–4 tablets t.i.d.	GI distress, diarrhoea
Hydroxide	10.3	Very low	N/A	Tablet	Two tablets	GERD, diarrhoea
L-Aspartate	5	Excellent	41.7	Tablet	One tablet	GI distress, diarrhoea
L-Lactate	84	Excellent	42.3	Sustained-release caplet	1–2 caplets b.i.d.	GI distress, diarrhoea
Oxide	241	Good	22.8	Tablets, capsules	2–4 tablets t.i.d.	Emesis, diarrhoea

b.i.d., twice/day; GERD, gastro-oesophageal reflux disease; GI, gastrointestinal; t.i.d., three times/day.

Physiologic and pharmacologic role of magnesium in the cardiovascular system

Magnesium is primarily an intracellular cation with 99% of total body concentrations found in bone, muscles, and non-muscular soft tissue.[32] The remaining 1% is located extracellularly within serum and red blood cells. Of this 1%, a small proportion (1–5%) is ionized with the remainder being protein bound. Magnesium is absorbed primarily within the small intestine through paracellular mechanisms with the remainder excreted in the feces.[33] Homeostasis is maintained by the kidneys where it is filtered in the glomerulus and ~95% is reabsorbed mostly within the proximal tubule and thick ascending limb of the loop of Henle.

The recommended daily allowance of magnesium is 4.5 mg/kg/day.[2] Foods known to be rich in magnesium include grains, nuts, and green vegetables, amongst others. Around 24–76% of dietary magnesium intake is absorbed.[34] Studies have suggested that the relationship between magnesium absorption and intake is curvilinear and may be a saturable process.[34] Known causes of low magnesium include inadequate dietary intake, malabsorption states, gastrointestinal losses (diarrhoea and vomiting), bowel resection surgery, and drugs (diuretics, laxatives, and insulin).[2] An additional challenge of diuretic-induced hypomagnesaemia is that potassium levels can also be lowered with these drugs; this means that simultaneous administration of magnesium and potassium supplements may be required to normalize serum levels of each.[35]

A major challenge when using oral magnesium preparations as a means of repletion is their generally poor bioavailability, as well as lack of consensus. Firoz and Graber[36] showed the fractional bioavailability of magnesium oxide to be ~4% with magnesium lactate, aspartate, and chloride averaging 9–11%. Other studies suggest magnesium acetate to have greater absorption than magnesium chloride, whereas others have reported higher bioavailability values.[31,34] This is an important consideration when evaluating the results of trials using oral magnesium supplements. The difference in total absorption between exogenous magnesium supplements and dietary sources could be due to either larger fractions of ingested magnesium being unabsorbed or slow-release mechanisms.[34] No evidence is currently available showing which of the commercially available products is most likely to correct either a serum or intracellular magnesium deficiency.

Given that a majority of magnesium is found within the cell, it is not surprising that disparities between intracellular and serum (reference range 0.65–1.05 mmol/L) magnesium concentrations have been seen in clinical studies.[37,38] Shah *et al.*[38] showed that 89% of patients undergoing radiofrequency catheter ablation of AF had intracellular magnesium deficiencies, despite serum values within the reference range for all participants. This suggests that routine screening and monitoring of serum magnesium concentrations are unlikely to represent a patient's true magnesium status. Accurate determination of intracellular magnesium concentrations is a recognized challenge in the field. Measurement of magnesium content within lymphocytes or erythrocytes has correlated to intramyocardial muscle magnesium and is likely the most accurate.[39,40] However, commercial labs do not currently run assays to determine these concentrations and are only available for research purposes. Other tests that measure intra-epithelial cell magnesium content (reference range 33.9–41.9 mEq/International Units) from buccal tissue samples are available, although only a single site within the USA performs the test.[37] This validated, non-invasive test can be performed in 60 s in any clinic situation and is available to both practitioners and researchers.[37]

Magnesium is a cofactor for a large number of adenosine triphosphate-mediated reactions.[41,42] This includes control of plasma and intracellular ion transport pumps responsible for movement of sodium (Na^{+}), calcium (Ca^{2+}), potassium (K^{+}), and intracellular pH.[43,44] Within the vasculature, magnesium is involved with the exchange of various smooth muscle vasodilators, such as nitric oxide and prostatyclin, as well as various thrombogenic and inflammatory mediators (*Figure 1*).[3,44,45] This promotes vasodilation, reduced

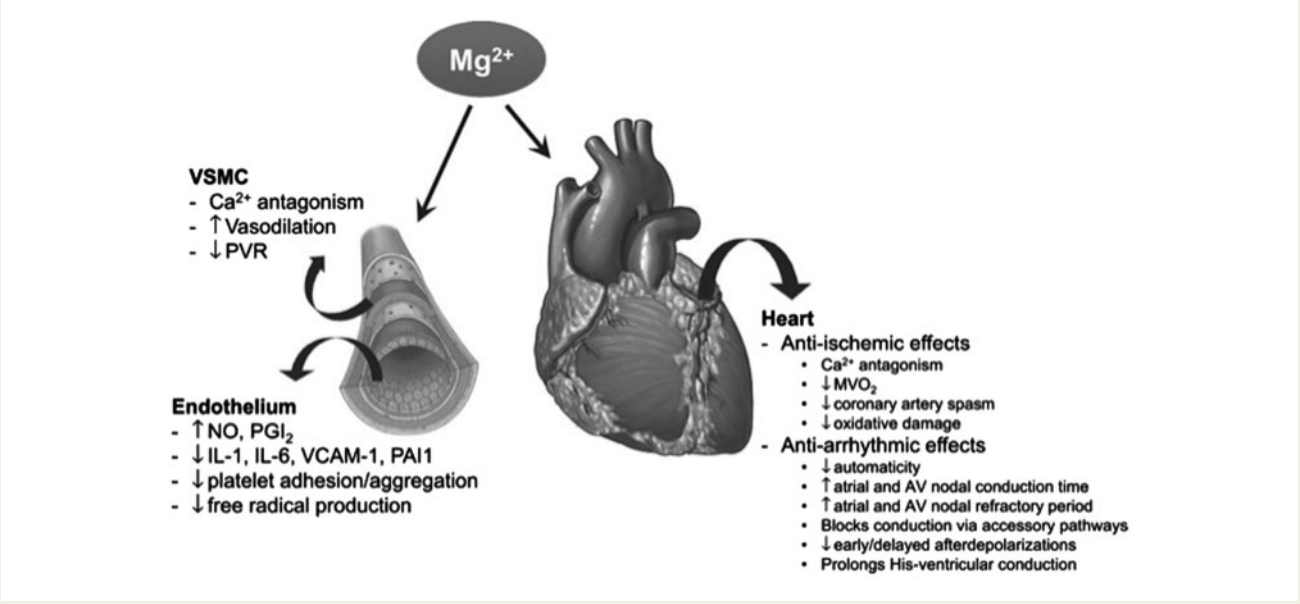

Figure 1 Effects of magnesium on the heart and vasculature. Reprinted with permission from reference 3. AV, atrioventricular; IL-1, interleukin-1; IL-6, interleukin-6; MVO_2, myocardial oxygen consumption; NO, nitric oxide; PAI1, plasminogen activator inhibitor-1; PGI_2, prostacyclin; PVR, peripheral vascular resistance; VCAM-1, vascular cell adhesion molecule-1.

vascular resistance, and lower systemic and coronary blood flow and pressure.[5,46] In myocardial tissues, the ability of magnesium to antagonize Ca^{2+} activity during ischaemia limits infarct size, reduces coronary artery spasm, and limits post-infarction oxidative damage.[47] However, evidence from clinical trials does not support the routine use of intravenous (i.v.) magnesium during an acute myocardial infarction.[48]

Electrophysiologic properties of magnesium

Myocardial cell action potentials are mediated by voltage-dependent Na^+, K^+, and Ca^{2+} channels which, when their function is altered, can lead to the genesis of cardiac dysrythmias. Magnesium regulates the movement of ions through these channels within myocardial tissues.[15,49] The cellular membrane sodium gradient is maintained by a magnesium-dependent Na^+-K^+-ADPase enzyme. The outward flow of Na^+ through these channels is highly dependent on intracellular magnesium and is blocked with increasing concentrations.[50] Intracellular magnesium also plays an integral role in the physiologic regulation of the voltage-gated Ca^{2+} current.[51] Increases in both intra- and extracellular magnesium concentrations have inhibitory effects on T- and L-type Ca^{2+} channels.[52,53] In addition to Na^+ and Ca^{2+} channel blockade, increasing magnesium concentrations decrease the activity of the rapid inward component of the delayed-rectifier K^+ channel (I_{Kr}).[54,55]

These channel-blocking properties result in a variety of electrocardiographic changes that play vital roles in the genesis of cardiac dysrythmias. In patients undergoing routine electrophysiologic assessment, infusion of i.v. magnesium resulted in prolonged atrioventricular (AV)-nodal conduction times as well as PR and QRS durations.[56] Similar findings of AV-nodal slowing have been seen in other studies,[57–59] although only one saw this effect in male participants.[56] Stiles *et al.*[59] observed that conduction was affected more prominently through the slow pathway in patients' dual AV-nodal physiology. Both atrial and ventricular refractory periods are also prolonged with magnesium use.[58,60]

One of the more common uses of i.v. magnesium is for the treatment of TdP.[28] In fact, low tissue magnesium concentrations is associated with increased QT dispersion, potentially representing a risk factor for the development of triggered arrhythmias such as TdP.[61] Torsade is thought to occur as a result of early after-depolarizations (EADs) resulting in triggered automaticity, unidirectional block, and intramural re-entry circuit development.[62] Magnesium suppresses the EADs and automaticity by decreasing I_{Kr} current and L-type Ca^{2+} activity (which is thought to be responsible for the triggered automaticity), thereby terminating the rhythm.[63–65] A canine model showed the ability of magnesium to homogenize the transmural dispersion of ventricular repolarization, which also aids in the termination of polymorphic ventricular tachycardias (VTs).[66]

Prevention of post-operative atrial fibrillation

Approximately 25–40% of patients undergoing cardiac surgery develop post-operative AF, resulting in prolonged hospital length of stay, increased risk of stroke, and higher hospital costs.[67,68] Studies show a significant association between low pre-operative intracellular magnesium concentrations and an elevated risk of post-operative atrial fibrillation (POAF).[69,70] Low serum magnesium levels are also

Table 2 Published meta-analyses of magnesium for prevention of post-operative atrial fibrillation[18,73–81]

Study	Search period	Number of studies	POAF results of Mg^+ vs. control	Notes
Shiga *et al.* (2004)[73]	1966–2003	17	RR 0.77, 95% CI 0.63–0.93[a]	Included CABG +/or valve surgery & intraoperative only or cardioplegia Mg^+ supplementation
Miller *et al.* (2005)[74]	1966–2003	20	OR 0.54, 95% CI 0.38–0.75	Included CABG +/or valve surgery & intraoperative only or cardioplegia Mg^+ supplementation
Alghamdi *et al.* (2005)[75]	1966–2003	8	RR 0.64, 95% CI 0.47–0.87	Included CABG-only studies & excluded intraoperative only or cardioplegia Mg^+ supplementation
Henyan *et al.* (2005)[76]	1999–2004	8	OR 0.66, 95% CI 0.51–0.87	Excluded intraoperative only or cardioplegia Mg^+ supplementation
Burgess *et al.* (2006)[77]	1966–2005	22	OR 0.57, 95% CI 0.42–0.77	Included CABG +/or valve surgery & evaluated all prophylactic strategies & Mg^+ delivery including cardioplegia
Shepherd *et al.* (2008)[78]	2003–07	15	OR 0.65, 95% CI 0.53–0.79	Included CABG-only studies, providing update to Alghamdi *et al.*[75] & any Mg^+ delivery including cardioplegia
Gu *et al.* (2012)[18]	1966–2011	7	OR 0.64, 95% CI 0.50–0.83	Included CABG-only, double-blind RCTs
De Oliveira *et al.* (2012)[79]	1966–2012	20	OR 0.69, 95% CI 0.53–0.90	Included CABG-only & excluded studies of Mg^+ delivery in cardioplegia
Wu *et al.* (2013)[80]	1966–2012	5	OR 1.12, 95% CI 0.86–1.47	Included CABG-only studies with concomitant beta-blocker therapy & similar Mg^+ dose & AF definition
Cook *et al.* (2013)[81]	1966–2012	21	OR 0.58, 95% CI 0.43–0.79 (all) OR 0.94, 95% CI 0.61–1.44 (RCT only)	Included CABG +/or valve surgery & any Mg^+ administration. Sensitivity analysis of only RCT with ITT and AF as primary endpoint was performed

AF, atrial fibrillation; CI, confidence interval; CABG, coronary artery bypass graft; ITT, intention to treat; OR, odds ratio; POAF, post-operative atrial fibrillation; RCT, randomized controlled trial; RR, relative risk.
[a]Supraventricular arrhythmias.

common following cardiac surgical procedures that utilize cardiopulmonary bypass.[71,72] Thus, prophylactic use of magnesium has the potential to correct these deficiencies and reduce POAF risk.

A large number of clinical trials and meta-analyses have been published evaluating the impact of perioperative magnesium supplementation on rates of POAF with mixed results (*Table 2*).[18,73–81] The literature base is limited by studies with small sample sizes, varying magnesium doses and timing of administration, and differing study designs and quality. Not surprisingly, many meta-analyses found significant statistical and methodological heterogeneity in their analyses. Many of the clinical trials did not use a blinded design or intention-to-treat, did not adequately define AF, or reported POAF as a secondary outcome. When Cook *et al.*[81] performed a subgroup analysis of only those trials they deemed to be of high methodologic quality, no benefit or prophylactic magnesium on POAF risk was seen [odds ratio (OR) 0.94, 95% confidence interval (CI) 0.61–1.44].

The areas of uncertainly related to prophylactic magnesium supplementation in patients undergoing cardiothoracic surgery include the optimal timing and duration of treatment, most appropriate dose, and concomitant medication administration. The administration of i.v. magnesium sulfate during the operative procedure has not resulted in a reduction in POAF risk.[76,82] When studies of between 2 and 6 days duration of magnesium use were pooled, significant reductions in POAF risk were seen.[75] However, meta-regressions performed by duration of magnesium treatment have not showed a significant relationship with POAF risk ($P = 0.56$).[81] There is similar uncertainty surrounding the optimal dose of magnesium to provide, with no association between dose and POAF risk seen upon meta-regression.[81] Henyan *et al.*[76] suggested that lower doses of magnesium reduced POAF risk (OR 0.36, 95% CI 0.23–0.56) whereas moderate-high doses did not (OR 0.99, 95% CI 0.70–1.42). No trials have directly compared the impact of either timing or various magnesium dosing strategies on POAF risk and represent a significant gap in knowledge.

The last area of uncertainty is whether magnesium, when used in combination with other proven pharmacologic agents, provides additional POAF risk reduction. Behmanesh *et al.*[83] showed that patients randomized to receive i.v. magnesium in combination with mandatory beta-blocker use with bisoprolol compared with control (continuation of pre-operative β-blocker only) significantly reduced the incidence of POAF ($P < 0.001$). However, when Cook *et al.*[82] randomized patients to receive either i.v. magnesium or placebo in addition to mandatory β-blocker use (atenolol), no difference in atrial arrhythmia incidence was seen. No trials have specifically studied the use of magnesium in addition to amiodarone, or in comparison with these other strategies. The guidelines published by the American Association for Thoracic Surgery in 2014 recommend i.v. magnesium supplementation to prevent POAF in patients with low serum magnesium levels, although only as a class IIb recommendation.[29] However, trials providing evidence of the optimal timing, dose, duration, and concomitant therapies are needed to better inform the clinical use of i.v. magnesium in patients undergoing cardiothoracic surgery to lower POAF risk.

Treatment of acute atrial and ventricular arrhythmias

Atrial fibrillation is the most common supraventricular arrhythmia and significantly increases stroke and mortality risk.[84] Patients with AF have been shown to have lower serum magnesium levels compared with healthy controls;[85] one in five patients with symptomatic AF is also hypomagnesaemic.[86] Management of AF includes either control of the ventricular response (rate-control) or conversion to normal sinus rhythm (rhythm-control) in addition to antithrombotic therapy.[87] Given the known effects of magnesium on voltage-dependent Na^+, K^+, and Ca^{2+} channels, it is plausible for it to have a beneficial impact as part of either a rate- or rhythm-control strategy.

Trial evidence shows i.v. magnesium to be effective for controlling the ventricular response in patients with AF. Early investigations showed significant reductions in pulse rates when i.v. magnesium was used in combination with digoxin for managing acute AF.[88,89] A trial of 190 patients with rapid AF presenting to the emergency department showed that i.v. magnesium sulfate use resulted in pulse rates of <100 b.p.m. more often than placebo ($P < 0.001$).[90] Similar reductions in pulse rates have also been shown when comparing i.v. magnesium sulfate with diltiazem.[91] Meta-analyses of clinical trial data show that magnesium is superior to placebo (when added to digoxin) for getting the pulse rate below 100 b.p.m., but is inferior to calcium channel blockers or amiodarone.[19,20]

In addition to ventricular rate control, studies have evaluated the role of magnesium for aiding in the successful conversion of AF to normal sinus rhythm. A small clinical trial by Moran *et al.*[92] showed that i.v. magnesium use (administered via continuous infusion) resulted in a greater number of conversions of atrial tachyarrhythmias (including AF) to normal sinus rhythm than amiodarone at 24 h ($P < 0.05$). Meta-analysis of clinical trial data shows that magnesium-treated patients are more likely to regain sinus rhythm than other agents, including placebo or calcium channel blockers (OR 1.60, 95% CI 1.07–2.39).[20] The findings related to magnesium use in patients undergoing direct current cardioversion of AF are mixed. Although one study showed that pre-treatment with a magnesium and potassium solution significantly improved cardioversion success rates vs. control (96.4% vs. 86.0%; $P = 0.005$),[93] 1-week pre-treatment with oral magnesium (either alone or in combination with sotalol) did not appreciably affect cardioversion success or AF recurrence rates.[94] The relation between serum and intracellular magnesium concentrations and efficacy remains unknown. In the study by Frick *et al.*,[94] relatively few patients (4 of 170) had a baseline serum magnesium deficiency with no differences seen in serum levels between patients in sinus rhythm or with AF recurrence. Intracellular magnesium determinations have not been performed in any of the AF studies to date. Thus, more mechanistic evaluations of the role that magnesium has with AF pathogenesis and outcomes are needed before it can be definitely recommended as a treatment strategy.

A weak body of evidence also supports the ability of magnesium to terminate SVT. Case reports[21] and case series[22] show that i.v. magnesium can terminate SVT or, at a minimum, slows the pulse rate; the effect is most noticeable when the AV node is part of the reentrant circuit. Not all studies have supported these findings, however. Viskin *et al.*[95] did not show any difference in SVT conversion rate, despite repeated dosing of i.v. magnesium. They did, however, suggest potential efficacy of magnesium for terminating SVT via blocking retrograde conduction in accessory pathways. Conversely, a single-blind study by Gullestad *et al.*[96] showed that patients with recent-onset SVT receiving i.v. magnesium were more likely to convert to sinus rhythm within 4 h than those receiving verapamil. However, verapamil was more efficacious from 4 to 24 h, and no difference was found between groups beyond 24 h. Taken together, the current data (most of which is more than 20 years old) do not support the routine use of i.v. magnesium for the rapid termination of SVT. No studies to date have evaluated oral magnesium preparations for managing SVT.

Studies have shown that up to 38% of patients with sustained ventricular arrhythmias have a serum magnesium deficiency and 72% have an excessive magnesium loss.[97] Correction of this deficiency with i.v. magnesium resulted in a decrease in ventricular ectopic beats ($P < 0.0001$), couplets ($P < 0.003$), and episodes of non-sustained VT ($P < 0.01$) vs. placebo.[97] Oral supplementation with magnesium and potassium also reduced ventricular premature beats ($P = 0.001$) vs. placebo over a 3-week period.[98] A number of case reports have also showed magnesium to be effective for terminating various drug-induced ventricular arrhythmias.[24–27]

The primary use of magnesium is for the termination of polymorphic VT/TdP.[24,30] In fact, hypomagnesaemia has been associated with polymorphic VT and TdP following an acute myocardial infarction.[99,100] As mentioned earlier, magnesium suppresses the EADs and automaticity by decreasing I_{Kr} current and L-type Ca^{2+} activity (which is thought to be responsible for the triggered automaticity), thereby terminating TdP (*Figure 2*).[3,63–65,101] Guidelines recommend immediate administration of i.v. magnesium as first-line management of TdP.[102] The initial data supporting this recommendation came from a case series of 12 patients who developed TdP, mostly (75%) due to antiarrhythmic drug use with QTc intervals ranging from 540 to 720 ms.[28] The TdP resolved following a single 2 g dose of i.v. magnesium sulfate in 9 of the 12 patients (75%). An additional dose was required in the other three patients and for three others who had a recurrence of TdP. Additional evidence comes from investigations of paediatric populations with TdP resulting from congenital or acquired long QT syndrome.[103,104]

Use of adjunctive magnesium with antiarrhythmic drugs

The adjunctive use of magnesium supplementation added to antiarrhythmic drugs has received the most research focus in recent years. The theory behind this usage stems from the ability of magnesium to not only treat drug-induced TdP (as was discussed in the previous section) but also prevent it as well. Animal models show that addition of magnesium to antiarrhythmic drugs prevents EADs and lessens TdP risk without appreciable affecting QTc.[65] A clinical trial of 20 patients undergoing chemical cardioversion of AF or atrial flutter showed that the QTc interval increased by 29% from baseline when patients received the ibutilide ($P = 0.007$) but did not change when 2 g of i.v. magnesium sulfate was given immediately before ibutilide administration ($P > 0.05$).[105] A number of subsequently published observational studies supported and extended these findings.[106–109]

A multicentre cohort study of three large, tertiary care centres by Kalus *et al.*[106] showed that AF or flutter patients who received

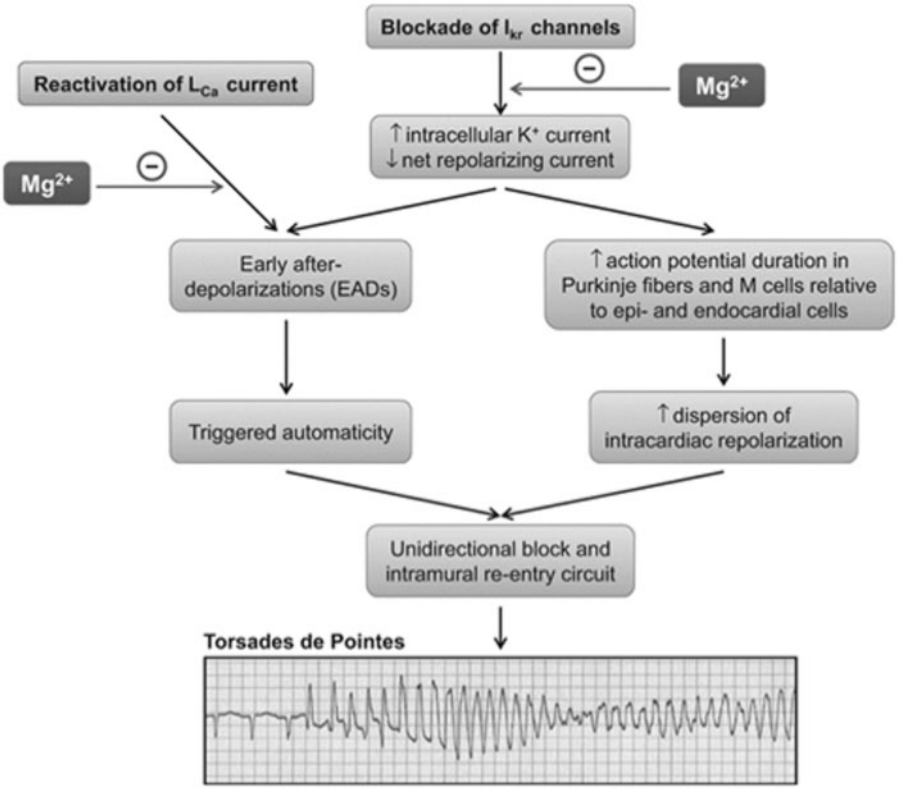

Figure 2 Mechanism of benefit of magnesium in treating torsade de pointes. Reprinted with permission from references 3 and 101.

magnesium within 2 h of ibutilide administration had a 19% higher rate of successful cardioversion to normal sinus rhythm vs. those who did not receive magnesium ($P = 0.040$). The need for subsequent direct current cardioversion was also reduced by 34% in the magnesium group. Interestingly, the cardioversion success rates with concomitant magnesium appeared to increase in a dose-related fashion (*Figure 3*). A significantly lower rate of TdP has also been seen when magnesium was used along with ibutilide (0%) vs. ibutilide alone (3.5%; $P = 0.009$).[109] The strategy of administering i.v. magnesium within 2 h of ibutilide in AF or flutter patients is also a cost-effective strategy, from a US hospital-payer prospective.[110] Similar results were seen in a retrospective cohort evaluation of patients receiving dofetilide for chemical cardioversion of AF or flutter where concomitant magnesium increased the rate of successful conversion two-fold.[108]

Clinical trial data supporting these findings are limited. Steinwender *et al.*[111] randomized 117 patients with persistent atrial flutter to receive either 4 g of i.v. magnesium or placebo immediately preceding ibutilide administration for chemical cardioversion. The primary endpoint or successful conversion to sinus rhythm within 4 h of the procedure occurred in 85% of the magnesium patients vs. 59% of the placebo patients ($P = 0.017$). This difference was most notable in patients with typical ($P = 0.017$) vs. atypical atrial flutter ($P = 0.189$). Interestingly, although the QTc interval significantly increased from baseline following ibutilide administration, no post-dose differences were seen between the magnesium and placebo groups ($P = 0.139$). These findings are inconsistent with the pilot and observational data previously discussed. A number of questions remain regarding the role of adjunctive magnesium in AF/flutter patients undergoing chemical cardioversion. The optimal dosage of magnesium, route of administration (i.v. or oral), and duration of therapy all remain unanswered in this population. Given the promise of the current body of evidence, there is a critical need for both mechanistic as well as clinical outcome-based trials to help inform this practice.

Studies have also evaluated whether chronic oral magnesium improves the efficacy and safety of antiarrhythmic agents. McBride *et al.*[112] randomized 34 patients with either atrial or ventricular tachyarrhythmias receiving sotalol or dofetilide to receive twice-daily magnesium L-lactate (504 mg elemental magnesium daily) or placebo for 48 h. The intracellular magnesium concentration, which was low in 63% of participants regardless of the experimental group, significantly increased in the magnesium group ($P = 0.002$) and was unchanged with placebo ($P = 0.32$). Magnesium significantly reduced the QTc interval from baseline at both 3 and 51 h vs. placebo ($P = 0.015$ and $P = 0.001$, respectively). The investigators also calculated the Tpeak–Tend interval which is a marker of transmural dispersion of repolarization.[113] Decreases in dispersion within the myocardium have been suggested to reduce TdP risk.[114] A non-significant reduction in Tpeak–Tend was seen in the magnesium

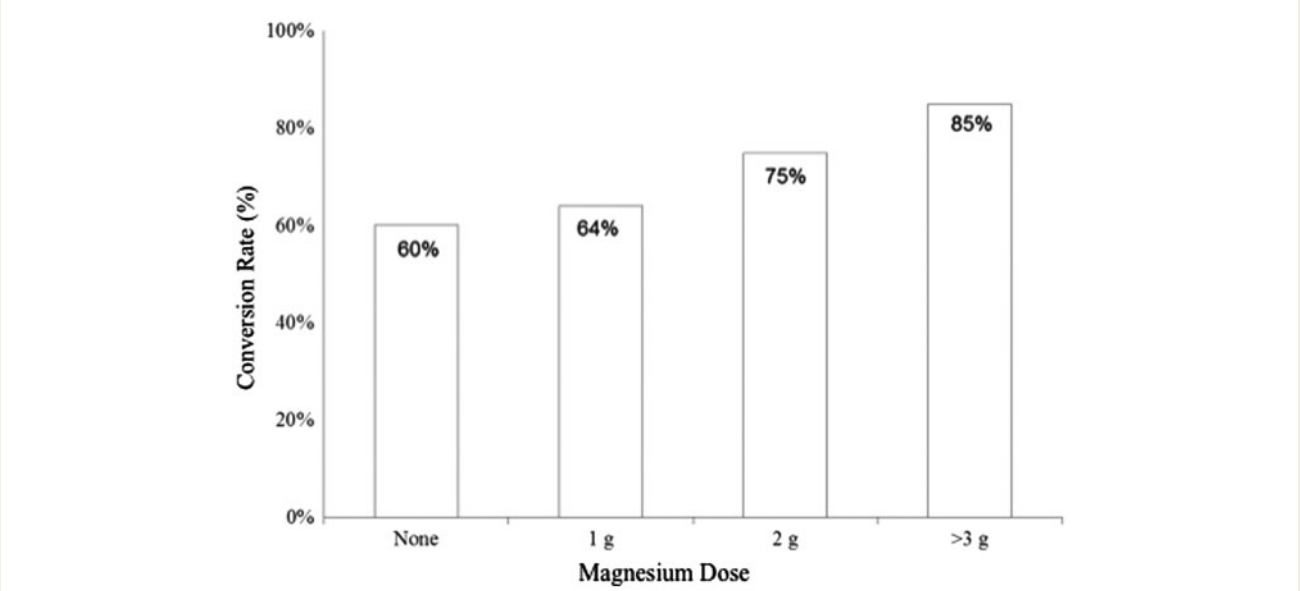

Figure 3 Dose–response relation of magnesium for cardioversion of atrial fibrillation/flutter in combination with ibutilide. Originally published in 2003, American Society of Health-System Pharmacists, Inc. All rights reserved. Reprinted with permission from reference 106 (R1609).

group ($P = 0.293$). Taken together, this pilot study showed that giving three tablets twice daily of magnesium L-lactate (providing 504 mg elemental magnesium daily) to arrhythmia patients receiving sotalol or dofetilide corrected the intracellular magnesium concentration and shortened their QTc interval.

Despite the positive findings, not all trials have revealed beneficial effects. Baker *et al.*[46,115] randomized 70 patients with an implantable cardioverter defibrillator (as either primary or secondary prevention) to receive either magnesium L-lactate (six tablets daily, providing 504 mg of elemental magnesium) or placebo for 12 months. Similarly to previous investigations, 86% of individuals in this trial (regardless of randomization) had a baseline intracellular magnesium deficiency. Twenty (28.6%) dropped out before the 12-week follow-up time-point, mostly due to excessive pill burden (six tablets per day) or diarrhoea. No difference in either intracellular or serum magnesium concentrations was seen between the magnesium and placebo groups. Not surprisingly, the primary endpoint of the cumulative incidence of implantable cardioverter defibrillator therapy did not differ between the groups (HR 0.84, 95% CI 0.33–2.12; $P = 0.706$).[115] Quality-of-life measures were also similar between the magnesium and placebo groups. Magnesium did, however, significantly lower systolic blood pressure at 12 weeks vs. placebo (117.7 ± 11.8 vs. 126.3 ± 16.7 mmHg, respectively; $P = 0.04$).[46]

Conclusions

Magnesium has a number of potential beneficial effects on the cardiovascular system, most notably antiarrhythmic properties. This includes control of intracellular ion transport pumps responsible for movement of sodium (Na^+), calcium (Ca^{2+}), and potassium (K^+) as well as reductions in EADs and slowed AV nodal conduction times. These physiologic properties provide promise of the therapeutic benefits that magnesium may have in managing various tachyarrhythmias. These benefits may stem from correcting the intracellular magnesium deficiency that has been found in many patient populations.

Taken together, a number of important clinical questions remain unanswered by this evidence base. The relationship between normalization of intracellular magnesium concentrations and improvements in clinical outcomes remains unknown. This includes pharmacologic investigations such as thorough QTc studies, correlations between magnesium levels and both surrogate and clinical outcomes, and dose-ranging studies. The most appropriate route (i.v. vs. oral), salt (oxide vs. lactate, etc.), dose, and duration of therapy for magnesium supplementation are also not available to clinicians. These gaps in evidence make incorporating the potentially important research findings into practice a challenge for clinicians caring for high-risk patients. They also represent critical need of study to allow the large body of evidence with magnesium to be translated to clinical practice.

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