WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care

Worksheet author(s)  
Deborah Diercks  
Date Submitted for review:  

Clinical question.
In adult cardiac arrest (out-of-hospital and in-hospital) (P), does the treatment of electrolyte disturbances (eg. hypo or hyper kalemia, hypo or hyper magnesiemia, hypo and hyper calcemia) (I) as opposed to standard care (according to treatment algorithm, but without treatment of electrolyte disturbances) (C), improve outcome (O) (eg. ROSC, survival)?

Is this question addressing an intervention/therapy, prognosis or diagnosis? Intervention/Therapy

State if this is a proposed new topic or revision of existing worksheet: Therapy

Conflict of interest specific to this question
Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? No

Search strategy (including electronic databases searched).

MeSH (all medical subject headings were searched as textwords)

<table>
<thead>
<tr>
<th>Heart Arrest</th>
<th>Hypercalcemia</th>
<th>Prognosis</th>
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<tbody>
<tr>
<td>Death, Sudden, Cardiac</td>
<td>Hyperkalemia</td>
<td>Disease-Free Survival</td>
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<td>Hypermanesemia</td>
<td>Medical Futility</td>
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<td>Hypocalcemia</td>
<td>Treatment Outcome</td>
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<td>Hypokalemia</td>
<td>Treatment Failure</td>
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<td>Hypomagnesemia</td>
<td>Mortality</td>
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<td>Potassium</td>
<td>Fatal Outcome</td>
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<td></td>
<td>Calcium</td>
<td>Survival Rate</td>
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<td></td>
<td>Magnesium</td>
<td>Survival</td>
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<td>Outcome Assessment (Health Care)</td>
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</table>

(potassium + cardiac arrest) AND (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract]) 112
(calcium + cardiac arrest) AND (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract]) 66
(magnesium+ cardiac arrest) AND (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract]) 292

Databases Searched: CINAHL, Ovid MEDLINE(R), EMBASE, Cochrane Database of Systematic Reviews, ACP Journal Club, DARE, Cochrane Clinical Trials Registry, Cochrane Methodology Register, Cochrane Health Technology Assessments, Cochrane Economic Evaluation Database from 1/80-9/09

References were reviewed and each article was reviewed for new citations. Primary studies were presented instead of subgroup analyses when available.

• State inclusion and exclusion criteria
Inclusion: All patients suffering a cardiac arrest
Exclusion criteria: No documentation of treatment for electrolyte disturbances.

• Number of articles/sources meeting criteria for further review:
A total of 160 trials met criteria for review. A total of 47 trials met final inclusion criteria. Last Search 1/14/2010
# Summary of evidence

## Evidence Supporting Clinical Question

**Magnesium**  Calcium  Potassium

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<tr>
<td>Fair</td>
<td>Stuevan 1985, 626 (A)</td>
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<td>Harrison 1983, 267 (A)</td>
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<td>Toby 1992, 92 (A,C)</td>
<td>Hulting 1981, 105 (E)</td>
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<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>1</th>
<th>2</th>
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<th>4</th>
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<tbody>
<tr>
<td>A = Return of spontaneous circulation</td>
<td>C = Survival to hospital discharge</td>
<td>E = Other endpoint</td>
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<tr>
<td>B = Survival of event</td>
<td>D = Intact neurological survival</td>
<td>Italics = Animal studies</td>
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* Both Magnesium and Potassium studied.
## Evidence Neutral to Clinical question

<table>
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<tr>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
<th>Evidence</th>
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## Evidence Opposing Clinical Question

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<th>Poor</th>
<th>Evidence</th>
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</thead>
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<tr>
<td>Stiell 1995, 264 (B)</td>
<td>Miller 1995, 3 (C)</td>
<td>Arad 1987, 405 (E)</td>
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The administration of magnesium and calcium has been incorporated into common practice in specific patient populations based on the initial cardiac rhythm or perceived risk of electrolyte abnormalities. In addition, correction of potassium abnormalities are managed in a similar way. This practice has been largely based on case reports that support the use of calcium salts or magnesium in specific patient populations.

The use of calcium in the setting of cardiac arrest has been shown to be ineffective in ventricular fibrillation and asystole, but had some efficacy in those with the initial rhythm of pulseless electrical activity (PEA) (Stuevan 1984, 820 Harrison 1983, 267, Stuevan 1985, 630) In an observational study of patients receiving calcium IV in the prehospital setting eight of 48 who received calcium were resuscitated successfully in the field and two of 42 who received saline were resuscitated successfully (P=.07). (Stuevan 1985, 630) In another prospective observational study the use of calcium was inversely associated with unsuccessful resuscitation after cardiac arrest after adjusting for co-morbidities and initial cardiac rhythm (OR 0.32, 95%CI: 0.18-0.55), (van Walraven 1998, 544).

The use of magnesium in the setting of cardiac arrest has largely been supported by case reports (Allen 1989, 1202, Baraka 2000 196, Craddock 1991, 469). A systematic review by Reis et al. reported no data to support or refute the use if magnesium in the setting of cardiac arrest. (Reis 2008, 21). Fatovich et al performed a randomized trial of 5 gm of magnesium or placebo as the first line of treatment for patients in ventricular fibrillation arrest evaluated in the emergency department. The study enrolled a total of 67 patients and no difference in ROSC or survival between the group treated with placebo or magnesium (Fatovich 1997, 237). Similar results were reported in the study by Allegra et al. (Allegra 2001, 245) Both of these studies were underpowered to detect small difference in ROSC or survival.

Treatment of hyperkalemia or hypokalemia to improve ROSC and survival in patients in cardiac arrests is largely based on the extrapolation of data that suggests that patients in ventricular fibrillation who have an arrest hypokalemia associated with poor prognosis. (Clausen 1988, 531, Hingham 1993, 609 ,Nordrehaug 1985, 20D, Nordrehaug 1983, 525 ). Treatment with potassium to correct hypokalemia resulted in ROSC in a case report. (Curry 1976, 231)

In cardiac arrest setting the data regarding treatment of electrolyte disturbances is sparse and lacks rigorous randomized controlled trials. However these little data outside animal models that suggests harm associated with treatment.

Acknowledgements:

Citation List

Level of evidence 1, fair, neutral
Study was underpowered with at least 272 patients needed to show a 10% difference in ROSC. There was a lengthy delay to defibrillation and unclear protocols used. No difference after the administration in magnesium. Magnesium level not checked prior to treatment.

Level of evidence 4, poor, support
This is a case series of 11 patients with ventricular tachycardia were hemodynamically stable and give 2-5 gm of magnesium. Conversion to sinus occurred in 7/11 patients. Magnesium level was not checked prior to treatment.


Level of evidence 5, fair, against (animal)
Utilizing a ventricular fibrillation model 12 rats were exposed to 3 doses of calcium. Ventricular fibrillation threshold was lowered in those with higher level of infused calcium. There was a increased rate dependence on spontaneous defibrillation as the calcium concentration increased. The model used was for non-ischemic damage.


Level of evidence 5, fair, neutral (animal)
In a swine model the impact of magnesium infusion on vulnerability to fibrillation is assessed. At higher ventricular rates magnesium increased risk of fibrillation, this was not the case in setting of cardiac ischemia.


Level of evidence 4, poor, support
Case series of patients undergoing operative procedures who were in refractory ventricular fibrillation unresponsive to defibrillation and lidocaine. All responded to 2 gm of magnesium. Magnesium level was not checked prior to treatment.


Level of Evidence 5, fair, neutral
This is an animal study in which mogrels were randomized to standard CPR verse CPR with compression. In those animals in EMD after defibrillation they were given calcium chloride. None of the 3 had return of spontaneous circulation. No animals had hypocalcemia.


Level of Evidence 5, fair, oppose
In this swine model VF was induced. The administration of magnesium and epinephrine in swine with normal levels resulted in lower cardiac perfusion pressure. No analysis was done after administration of magnesium alone.

Level of evidence 5, poor, support
Retrospective analysis of patients to determine the association of magnesium levels with outcome. In this unadjusted analysis 42% had low magnesium levels. There is lack of data regarding treatment in this study.


Level of Evidence 5, fair, neutral (animal)
In this animal model of 9 dogs, VF was induced and multiple treatments were allowed. Levels of calcium were measured.


Level of evidence 5, poor, support
Retrospective analysis of patients to determine the association of magnesium levels with outcome. A positive correlation was shown with magnesium and outcome. No difference was noted with potassium levels or calcium levels.


Level of evidence 5, fair, support
In this observational study of 408 patients with myocardial infarction the authors attempted to correlate potassium levels with ventricular fibrillation. The investigators reported an 11% increase in ventricular fibrillation in patients noted to be hypokalemic (22% vs. 11%). There was also an increase in mortality in patients noted to be hypokalemic. No adjustment was made for treatment.


Level of evidence 5, fair, against
In this animal model of ischemia induced ventricular fibrillation, animals were infused with diltiazem and serum calcium levels lowered by infusion of sodium citrate. A reduced serum calcium level was associated with decreased ventricular fibrillation latency.


Level of Evidence 4, poor support
Single case report of patient with ROSC after magnesium. Magnesium level was not checked prior to treatment.

Level of evidence 4, poor, support
These 2 cases report ROSC in patients with ventricular arrhythmias as a result of low potassium levels. The rhythm improved with potassium supplementation. Potassium level was known to be low prior to treatment.


Level of evidence 5, fair, support (animal)
In this animal model of ischemic induction of ventricular fibrillation in mongrel dogs, animals were given dextrose, dextrose with potassium, or dextrose, potassium, and insulin. Potassium levels were within normal limits. Ventricular fibrillation threshold was increased in each group.


Level of Evidence 5, poor, support
This is a case series of 22 patients with hypocalcemia who received calcium supplementation. The study reports an improvement of QTc and no arrhythmias during the study period.


Level of Evidence, 1, fair, neutral
This is an underpowered prospective randomized trial. Study showed a 20% increase in repeat arrest in the magnesium group and no difference in ROSC. Only 30% were in ventricular fibrillation at the time of arrival. Almost 30% of the placebo group received treatment. Minimal documentation regarding concomitant ACLS therapy. Magnesium level was not checked prior to treatment.


Level of evidence 5, fair, against
In this animal model of cardiac arrest, animals which were kept hyperkalemic had a higher rate of survival.


Level of evidence 4, poor, support
This is a letter to the editor regarding a retrospective sample of 130 patients identified to have received calcium during their resuscitation. Calcium administration was inversely associated with time of resuscitation and survival. Calcium level was not checked prior to treatment.


Level of evidence 4, fair, support
This is a retrospective analysis of consecutive patients with cardiac arrest treated by EMS with a standing protocol to administer calcium IV or intracardiac in patients with EMD, ventricular fibrillation, and asystole after failed initial interventions. There were 480 patients evaluated and 200 received calcium. In this group of patients those with ventricular fibrillation or asystole had no response to calcium inject. However 13/119 (11%) responded in EMD.


Level of evidence 1, fair, neutral
Randomized trial of patients treated in the prehospital setting with refractory or recurrent VF. The study was underpowered to show a significant difference. Magnesium level was not known prior to treatment.


Level of evidence 5, fair, support
In this prospective cohort study magnesium and potassium levels were measured and association with VF determined. The sensitivity and specificity for VF in hypokalemia following acute infarction was 49% and 79% respectively. The sensitivity and specificity for VF in hypomagnesemia following acute infarction was 8% and 95% respectively.


Level of Evidence 5, poor, support
This study was observational study of 1315 patients admitted to a CCU and had a serum potassium level drawn. Early VF was associated with potassium levels <3.5 mmol.


Level of evidence 4, poor, support
Case series of patients with digoxin toxicity.


Level 4, poor, support
Case study of patient with refractory VF treated with magnesium. Magnesium level was not checked prior to treatment.


Level of evidence 4, poor, support
Case study of a patient with hypokalemia presents with shortness of breath and known hypokalemia. Patient on hospital day 2 developed VF that responded to 14 gram of calcium gluconate.


Level of evidence 4, poor, support
This is a case series of 5 patients with asystole following ventricular fibrillation. Patients were undergoing surgery for congenital heart disease. All regained spontaneous circulation after calcium administration.


Level of Evidence 1, fair, neutral
Magnesium placebo group had higher rate of witnessed events. Magnesium plus placebo group had up to a 16% increase in percent awake over the other groups. This study is unique in that patients were randomized to receive therapy after ROSC and had a blood pressure of at least 90mmHg. Electrolyte levels were not known prior to treatment.


Level of Evidence 5, fair, support (animal)
Investigators used a rabbit model that they created to determine the impact of calcium on the initiation and maintenance of VF. The investigators used 3 different techniques to reach this goal. The investigators report that the use of calcium channel blockers limits the development of VF, and alterations in calcium levels may result in an increase in VF rates.


Level of evidence 3, fair, neutral
This is a single center study comparing magnesium sulfate with standard to standard therapy alone in subjects with refractory cardiac arrest. The study is underpowered to show a difference, however the results suggest an improvement in neurologic function. Magnesium level was not checked prior to treatment.

**Level of Evidence 5, fair, neutral (animal)**
In this animal model administration of CaCl had no effect on aortic pressures.


**Level of Evidence 5, fair, support**
In those patients with a MI, hypokalemia was associated with increased incidence of VF. There was no adjustment made for comorbidities in this study.


**Level of Evidence 5, fair, support**
Observational study of patients post MI who had potassium levels assessed. In those who developed VF, patients with hypokalemia 78% developed VF within 2 hours of admission compared to 39% of those with normal potassium levels.


**Level 5, fair, support (animal)**
This is dog model in which glucose, insulin, and potassium was infused in 11 dogs to determine the impact on VF thresholds in non-ischemic myocardium. Dogs also underwent hemodialysis to determine the effect of potassium levels on VF. VF threshold was noted to decrease as potassium levels were reduced from 40 to 27 mA during the first hr. The investigators propose that this action was mediated by administration of insulin.


**Level of evidence 1, fair, neutral**
This is a systematic review of the use of magnesium in treatment of cardiac arrest and is the summary of the last ILCOR review.


**Level of Evidence 2, fair, neutral**
This is an observational study to look at factors associated with survival in patients under cardiac arrest. The use of calcium was not independently associated with improved outcome. There was not a standard protocol and it is difficult to determine when calcium was given and levels were not checked.

Level of Evidence 1, fair, support
This is one analysis from a randomized trial that evaluated patients with asystole and EMD who were given 500 mg calcium. The study is underpowered. Interesting subgroup identified that had increase benefit noted in those with prolonged QRS.


Level of Evidence 1, fair, neutral
This is one analysis from a randomized trial that evaluated patients with asystole and EMD who were given 500 mg calcium. The study is underpowered. No benefit or harm noted in those receiving calcium.


Level of evidence 1, fair, neutral
Patients received 5. There is lack of documentation regarding the rhythm at the time of calcium administration. The study is underpowered.


Level of evidence 1, fair, neutral
This is an underpowered study of patients with in-hospital cardiac arrest. Patients were randomized at the time of arrest to received a bolus of magnesium followed by 24 hours infusion. There was no difference in ROSC or survival. Magnesium levels were not known prior to enrollment.


Level of Evidence 5, poor, support
Case report of magnesium administration in a young man. Magnesium level was not checked prior to treatment.
Limited discussion of other treatments.


Level of Evidence 4, poor, support
Case report of the administration of calcium.

Level of Evidence 3, good, support
In this observational study the administration of calcium in conjunction with other medications was inversely associated with unsuccessful resuscitation. No knowledge of calcium levels at time of treatment.


Level of Evidence 5, poor, support
Although this review reports evaluation in a pericardiac arrest setting there is little no information regarding search strategies. In addition the 3 studies regarding magnersium are in models of cerebral ischemia and show support for neurologic outcome