Worksheet author(s)

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Date Submitted for review:

Nov 26, 2008 revised 2.10.09

Clinical question.

In adult cardiac arrest (asystole, pulseless electrical activity, pulseless VT and VF) (prehospital [OHCA], in-hospital [IHCA]) (P), does the use of calcium alone or combination with other drugs (I) compared with not using drugs (or a standard drug regimen) (C), improve outcomes (eg. ROSC, survival) (O)

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: New

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).

**PubMed**
(calcium AND ((Humans[Mesh])))) AND ((cardiac arrest) OR "Heart Arrest"[Mesh]) OR ("Cardiopulmonary Resuscitation"[Mesh]) OR ("Resuscitation"[Mesh]) OR (Heart arrest))
(Limits: Clinical Trial, Randomized Controlled Trial, Case Reports, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Controlled Clinical Trial, Multicenter Study)
-Cochrane Database
(Calcium) AND ("Heart Arrest"[Mesh]) OR (Heart arrest) OR (cardiac arrest) OR ("Cardiopulmonary Resuscitation"[Mesh]))

**End Note Library**

Search 1.Calcium and cardiopulmonary resuscitation
Search 2.Calcium and Heart arrest
Search 3.Calcium and Resuscitation
Search 4.Calcium and Cardiac arrest

**EMBASE (OVID)**

1. cardiopulmonary resuscitation.mp. or exp *Resuscitation/
2. Heart Arrest/
3. cardiac arrest.mp.
4. Calcium/
5. Calcium Chloride/
6. Gluconate Calcium/
7. 1 or 3 or 2
8. 6 or 4 or 5
9. 8 and 7
10. limit 9 to human
11. Clinical Trial/
12. controlled clinical trial/
13. Randomized Controlled Trial/
14. 11 or 13 or 12
15. 10 and 14
16. from 15 keep 37

• State inclusion and exclusion criteria

Inclusion criteria(all clinical trials and all age populations)
Exclusion criteria(no review articles, no animal studies)

• Number of articles/sources meeting criteria for further review:
12 studies met criteria for further review. 3 LOE-1, 5 LOE-2, 2 LOE-4
# Summary of evidence

## Evidence Supporting Clinical Question

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**Level of evidence**

A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = Other endpoint  
*Italics = Animal studies*
### Evidence Neutral to Clinical question

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<td>Stueven 1984 AC</td>
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<td>Gando 1988 A</td>
<td>Harrison 1983 C</td>
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**Level of evidence**

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### Evidence Opposing Clinical Question

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### REVIEWER’S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

**Discussion:** Early studies in animals and small case series in humans suggest that calcium may play a role in resuscitation of patients in cardiac arrest. However, subsequent better designed studies suggested that calcium does not only have minimal affect on survival but may actually decrease the chances of survival if used during cardiac arrest. *Kay* used calcium chloride in 4 children who were in “ventricular standstill” during cardiac surgery. There was no mention of what rhythm the patients were in before being administered the calcium. In all 4 cases calcium was considered successful in restoring a pulse.

*Harrison* conducted a larger case control study on calcium use in patients who presented in ventricular fibrillation, asystole and electromechanical dissociation(EMD) in the pre-hospital setting. Calcium was used once standard ACLS measures had failed to restore a pulse. Some patients that presented with EMD did show a positive response to calcium, how long term survival was still poor.

*Gando* conducted a retrospective cohort study of 30 patients presenting to the emergency department in cardiac arrest. This study found that calcium use did not make a difference in the success rate of resuscitation.

*Stueven et al conducted 3 randomized control trials* and one retrospective cohort study on calcium use in patients presenting with asystole or EMD in the pre-hospital setting. All the studies concluded that calcium had either no effect or reduced the chances of survival. However, calcium use did increase the chance of spontaneous return in circulation of patients presenting with EMD and QRS > 120ms.

*Stiell* and van Walraven conducted 2 cohort studies on calcium use in out of hospital and in-hospital cardiac arrest patients. They concluded that calcium had either no effect or reduced the chances of survival from the event.
*Srinivasan*¹² conducted a large prospective cohort on calcium use in in-hospital cardiac arrest of pediatric patients using the National Registry on Cardiopulmonary Resuscitation. It was shown that calcium used was associated with a reduced chance of surviving the event.

*Samson*¹¹ conducted a prospective cohort on children who had in-hospital ventricular tachycardia or fibrillation cardiac arrest using the National Registry of Cardiopulmonary Resuscitation. Calcium had no effect on long term survival, return of spontaneous circulation, survival to 24 hours and survival with good neurologic outcome.

**Acknowledgements**: none

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**Citation List**


   Level 4, opposing, poor

   The study was conducted with the primarily goal of ascertaining the values of calcium before and after calcium administration in a series of cardiac arrest patients. There was no randomization. Two groups were identified, one (11 pts) who did receive calcium and group 2 (19 pts) who did not. However, the legend in tab 1 indicates that group 1 was treated with or without calcium whereas group 2 was treated without calcium. There is then no clear assignment of the groups.

   The statistical method appears weak: there is no clear specification when paired or unpaired t-test was used: Means are reported sometimes with SD and sometimes with SE. There is no indication of any of the treatment during cardiac arrest (down time, presenting rhythm, witness CPR, duration of CPR, pharmacological interventions). Accordingly, the comparison between the two groups is impossible.

   There are several spelling mistakes. Overall the manuscript is poorly written.


   Level 4 Neutral (Fair Quality)

   No patients presenting with asystole or ventricular fibrillation responded to Calcium administration. 27 out of 480 responded to calcium chloride all which had electromechanical dissociation. Patients received anywhere from 400mg to 1000mg of calcium chloride. Although 14 of the responders were admitted to the hospital with stable vital signs, only 3 long time survivors. No report on industry funding.


   Level 2(Good study, Neutral study)

   Observational cohort study that assessed the role of ACLS drugs with survival in out of hospital and in hospital cardiac arrest. 650 patients that were enrolled in a previous study that assessed high dose epinephrine to standard dose epinephrine were assessed for this study. 121 patients excluded since a reliable time from arrest to treatment could not be estimated. Outcome assessed were “successful resuscitation” (return of blood pressure and pulse for at least one hour) and hospital discharge. Only 29 patients in total received calcium. The odd ratio of receiving calcium and association with survival was 0.8(0.2-2.4) with a p-value of 0.64.


   Level 2 Opposing (Fair study)

   The prehospital resuscitation of patients presenting with asystole and electromechanical dissociation was significantly lower in patients that were given calcium chloride. Although the author does state that there was no differences between the calcium and no-calcium groups no p values were provided for each variable. Also the duration resuscitation for the no-calcium and calcium group was 23+/− 14 minutes and 29+/− 12 minutes(p>0.05), respectively.

Level 1 Neutral study (poor quality, underpowered)
They paper was mostly a review of studies to date on calcium chloride use in cardiac arrest. The methodology and results were not presented. Nothing further was mentioned besides that mentioned in the abstract.


Level 1 (Neutral study, good quality)
Ninety patients met the criteria for the study with 48 receiving calcium and 42 no calcium. Patients were administered either 500mg of calcium chloride or normal saline. Only 8 patients administered calcium were successfully resuscitated with a pulse to the emergency department, while only 2 in the no calcium group (p<0.07). In a post hoc analysis patients were divided according to their QRS morphology, which accounted for 39 patients in the calcium group and 31 in the no calcium group. Eight patients in the calcium wide QRS group survived to the ED, while only 1 in the normal saline wide QRS group (p<0.028). However, only one patient from the study survived to hospital discharge which was clinically nonsignificant.


Level 1 (Neutral study, fair quality, underpowered)
73 patients qualified for the study, with 39 receiving calcium and 34 no calcium. Patients had 500mg calcium administered in the calcium group. Down time prior to the initiation for CPR was estimated for 79% of patients and no significant difference was found between the calcium and no calcium groups. Only 3 patients were successfully resuscitated in the calcium group and only 1 for the no calcium group (p<0.37). No patients survived to hospital discharge.


Level 2 (Opposing, Fair study)
Prospective cohort study of drug therapy including calcium in in-hospital cardiac arrest patients. Outcome was measure as survival to one hour past when CPR was discontinued. Data was analyzed for association of each ACLS medication with survival to one hour by determining whether the drug was given or not and at time point. 773 patients were analyzed in total, of whom 269 survived to one hour and only 84 survived to discharge. Calcium was the only drug for which earlier administration was significantly associated with survival (survivors 8.47 minutes versus non-survivors 15.00 minutes; p<.001). It was suggested that this may be related to a subset of patients whose cardiac arrest was caused by hyperkalemia or calcium channel blockers. However, the odds ratio of survival after calcium chloride administration to patients presenting with ventricular tachycardia or fibrillation, pulseless electrical activity and asystole was 0.32(.13, .79), 0.24(.08, .76) and 0.41(.16,1.05), respectively.

**Supplementary Bibliography**


Level 4 Supportive, Poor study
Case control study with 4 children who had undergone cardiac arrest during open heart surgery (3 patients were less than 18 months in age). Unclear whether other drugs were concurrently used and their time line. 3 of the children had cardiac standstill while the 4th child had diminished contractions. No note was made of the actual rhythm the children before being given the calcium. However, it was reported that all 4 of the patients responded immediately to calcium with regaining myocardial contractility and blood pressure, and were all long term survivors.

Level 2 study (good study, Neutral)

Prospective cohort on data obtained from National Registry of Cardiopulmonary Resuscitation on in-hospital pediatric cardiac arrests. Primary outcome was survival to hospital discharge with secondary outcome measured was return of spontaneous circulation > 20 minutes, 24 hours survival and neurologic outcome. Out of 1005 patients with in-hospital cardiac arrest, 272 patients had documented ventricular tachycardia or fibrillation during the event. 404 patients received calcium sometime during the event. The odds ratio of a patient receiving calcium and surviving the event was 0.6(0.4-1.0). The odds ratio between calcium use and spontaneous return of circulation > 20 minutes, 24 hour survival and survival with good neurologic outcome was 0.8(0.6-1.2), 0.8(0.5-1.1) and 0.6(0.4-0.9), respectively.


Level 2 study (good study, opposing results)

This study use the National Registry of Cardiopulmonary Resuscitation to assess the characteristics of calcium use during in-hospital pediatric cardiac arrest. The primary outcome measured was survival to hospital discharge, while secondary outcomes measured were survival of event (return of circulation for > 20 minutes) and neurologic outcome. Out of 1477 pediatric cardiac arrest patients 659 received calcium during CPR. Calcium was more often used in pediatric facilities and ICUs than mixed adult facilities, adult facilities and Emergency Rooms. Medium duration of CPR in the group that received calcium was 30 minutes vs 15 minutes for the no calcium group. Similarly, more doses of epinephrine were given and loss of pulse during the event in the calcium group. Presence of pulse during the event was less likely to be associated with calcium use (p<0.001). Standard ACLS medications were more often used in the calcium group than the no calcium. After controlling for confounding factors, calcium administration during CPR was independently associated with poor survival to discharge and poor neurologic outcome. In the setting of metabolic/electrolyte abnormalities and toxicologic abnormalities, calcium use was not associated with worse event survival or survival to discharge. Even examining patients who received CPR for <15 minutes, calcium use was still associated with worse survival to discharge (aOR:0.7; 95% CI:0.4-0.9) and with worse neurological outcome (aOR:0.6; 95% CI:0.3-0.9).