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Short paper

Effect of calcium vs. placebo on long-term outcomes in patients with out-of-hospital cardiac arrest

Mikael Fink Vallentin[a], *Asger Granfeldt*[b], *Carsten Meilandt*[a], *Amalie Ling Povlsen*[a], *Birthe Sindberg*[c], *Mathias J. Holmberg*[c,f], *Bo Nees Iversen*[a,b], *Rikke Mærkedahl*[a,d], *Lone Riis Mortensen*[a,e], *Rasmus Nyboe*[a,f], *Mads Partridge Vandborg*[a,g], *Maren Tarpgaard*[a,d], *Charlotte Runge*[a,h], *Christian Fynbo Christiansen*[i], *Thomas H. Dissing*[a,b], *Christian Juhl Terkelsen*[j], *Steffen Christensen*[b], *Hans Kirkegaard*[a,c], *Lars W. Andersen*[a,b,c,*]

Abstract

Objective: The Calcium for Out-of-hospital Cardiac Arrest (COCA) trial was a randomized, placebo-controlled, double-blind trial of calcium for out-of-hospital cardiac arrest. The primary and secondary outcomes have been reported previously. This article describes the long-term outcomes of the trial.

Methods: Patients aged ≥18 years were included if they had a non-traumatic out-of-hospital cardiac arrest during which they received adrenaline. The trial drug consisted of calcium chloride (5 mmol) or saline placebo given after the first dose of adrenaline and again after the second dose of adrenaline for a maximum of two doses. This article presents pre-specified analyses of 6-month and 1-year outcomes for survival, survival with a favorable neurological outcome (modified Rankin Scale of 3 or less), and health-related quality of life.

Results: A total of 391 patients were analyzed. At 1 year, 9 patients (4.7%) were alive in the calcium group while 18 (9.1%) were alive in the placebo group (risk ratio 0.51; 95% confidence interval 0.24, 1.09). At 1 year, 7 patients (3.6%) were alive with a favorable neurological outcome in the calcium group while 17 (8.6%) were alive with a favorable neurological outcome in the placebo group (risk ratio 0.42; 95% confidence interval 0.18, 0.97). Outcomes for health-related quality of life likewise suggested harm of calcium but results were imprecise with wide confidence intervals.

Conclusions: Effect estimates remained constant over time suggesting harm of calcium but with wide confidence intervals. The results do not support calcium administration during out-of-hospital cardiac arrest.

Trial registration: ClinicalTrials.gov-number, NCT04153435.

Introduction

Out-of-hospital cardiac arrest is a frequent and often fatal condition with a great need for interventions aimed at improving patient outcomes.[1] Calcium is commonly administered during cardiac arrest although there is limited evidence to support routine use.[2,3]

To test whether calcium is beneficial for adults with out-of-hospital cardiac arrest, the Calcium for Out-of-hospital Cardiac Arrest (COCA) trial was conducted. Recently published, the trial found that intravenous or intraosseous calcium, as compared to saline, did not improve return of spontaneous circulation, survival, or survival with a favorable neurological outcome at 30 or 90 days.[4] Point estimates consistently showed worse outcomes for patients

*. Corresponding author at: Prehospital Emergency Medical Services, Central Denmark Region, Olof Palmes Allé 34, 8200 Aarhus N, Denmark.
E-mail address: lwandersen@clin.au.dk (L.W. Andersen).

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who received calcium, and the trial was stopped early due to concerns of harm.

It remains unknown whether this suggestion of harm extends to more long-term outcomes. This article describes the patient outcomes at 6 months and 1 year.

Methods

Trial design and oversight

The trial protocol is available online.[4,5] The COCA trial was an investigator-initiated, randomized, placebo-controlled, parallel group, double-blind, superiority trial of calcium for out-of-hospital cardiac arrest. The trial was approved by relevant authorities including the regional ethics committee (reference number: 1-10-72-215-19). Procedures for consent followed Danish law for clinical trials conducted in emergency situations.[6,7]

Patients

Patients aged ≥18 years were included in the Central Denmark Region if they had an out-of-hospital cardiac arrest and received adrenaline during the cardiac arrest. Exclusion criteria were traumatic cardiac arrest, known or suspected pregnancy, prior enrollment in the trial, adrenaline prior to possible enrollment, and clinical indication for calcium at the time of randomization.

Intervention

The trial drug consisted of 10 mL 0.5 mmol/mL calcium chloride or 10 mL 0.9% saline given as soon as possible after the first dose of adrenaline and again after the second dose of adrenaline for a maximum of two doses. The trial drug could be given both intravenously and intraosseously. The trial was double-blind meaning that patients, investigators, clinicians, and outcome assessors were unaware of the allocation.

Outcomes

The primary outcome of the COCA trial was sustained return of spontaneous circulation and has been presented elsewhere along with 30- and 90-day outcomes.[4] This manuscript focuses on the 6-month and 1-year outcomes survival, survival with favorable neurological outcome defined as a modified Rankin Scale (mRS) score of 3 or less,[8] and health-related quality of life assessed using the EuroQol 5-Dimension 5-Level (EQ-5D-5L)-questionnarie.[9–11] Patients who died prior to a follow-up time point were given an mRS-score of 6, while only survivors were included in analyses of health-related quality of life. Health-related quality of life outcomes are reported both as the numeric value directly assessed by the patient and as the indexed value.[9,10] The numeric value is reported on a scale from 0 to 100 with higher scores indicating a better health-related quality of life, while the indexed value can also be negative. Outcomes were assessed primarily by telephone interview. If the patient was not able to participate, a relative or clinical personnel provided the assessment.

Statistical analysis

Patients were analyzed according to their randomized assignment. The analyses only included patients who had the first trial drug dose administered and who met all inclusion criteria and no exclusion criteria.

Binary data are presented as counts with percentages and continuous data are presented as means with standard deviations (SD). Differences between groups are presented as both risk differences and risk ratios with 95% confidence intervals. Differences between groups in continuous outcomes are presented as mean differences with 95% confidence intervals obtained from generalized linear models with robust errors.

Results

Patient characteristics

391 patients were analyzed (193 in the calcium group, 198 in the placebo group). There was no loss to follow-up. As presented elsewhere, baseline patient and cardiac arrest characteristics were generally balanced between groups.[4] The mean age was 68 years and 29% were female. 82% of cardiac arrests occurred at home, and 75% had an initial nonshockable rhythm. 60% received the trial drug through an intraosseous vascular access of which 90% were tibial.

Outcomes

Survival over time is presented in Fig. 1, while outcomes at 6 months and 1 year are presented in Table 1. All effect estimates were consistent over time suggesting harm of calcium but with wide confidence intervals. At 1 year, 9 patients (4.7%) were alive in the calcium group while 18 (9.1%) were alive in the placebo group (risk ratio 0.51; 95% confidence interval 0.24, 1.09). At 1 year, 7 patients (3.6%) were alive with a favorable neurological outcome in the calcium group while 17 (8.6%) were alive with a favorable neurological outcome in the placebo group (risk ratio 0.42; 95% confidence interval 0.18, 0.97). At 1 year, the patient-assessed value of the ED-5Q-5L numeric rating scale score was 71 in the calcium group and 83 in the placebo group (mean difference −12; 95% confidence interval −31, 8).

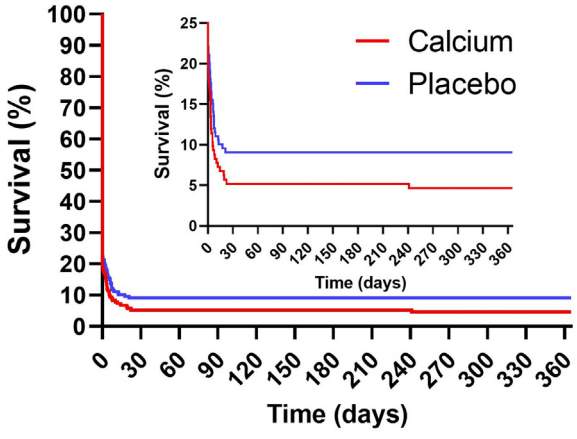

Fig. 1. – Survival over time.

Large figure: Plot of survival over time with survival on the y-axis and time in days on the x-axis.

Small figure: Y-axis stopping at 25% as a large number of patients never achieved return of spontaneous circulation and died at day 0.

Table 1. – Long-term outcomes according to treatment assignment.

	Calcium (n = 193)	Placebo (n = 198)	Risk ratio (95 %CI)	Difference[a] (95 %CI)
6-month outcomes				
Survival – No. (%)	10 (5.2)	18 (9.1)	0.57 (0.27, 1.18)	−3.9% (−9.4, 1.3)
Favorable neurologic outcome (mRS 0–3) – No. (%)	8 (4.2)	17 (8.6)	0.48 (0.22, 1.07)	−4.4% (−9.7, 0.4)
EQ-5D-5L	72 (29)	79 (17)	–	−8 (−26, 11)
EQ-5D-5L – Index	67 (35)	82 (22)	–	−15 (−38, 8)
1-year outcomes				
Survival – No. (%)	9 (4.7)	18 (9.1)	0.51 (0.24, 1.09)	−4.4% (−9.8, 0.6)
Favorable neurologic outcome (mRS 0–3) – No. (%)	7 (3.6)	17 (8.6)	0.42 (0.18, 0.97)	−5.0% (−10, −0.2)
EQ-5D-5L	71 (31)	83 (11)	–	−12 (−31, 8)
EQ-5D-5L – Index	76 (21)	84 (24)	–	− 8 (−25, 9)

Continuous variables are presented as means with standard deviations and categorical variables as numbers and percentages. mRS refers to modified Rankin Scale, which is a 7-point scale with higher scores indicating worse outcomes. A score of 0 to 3 is considered a favorable outcome. The results from the EQ-5D-5L are reported both as the numeric value directly assessed by the patient and as the indexed value. The numeric value is reported on a scale from 0 to 100 with higher scores indicating a better health-related quality of life, while the indexed value can also be negative.

[a] Risk difference for binary outcomes and mean difference for continuous outcomes.

Discussion

The current manuscript is the first to report on long-term outcomes following administration of calcium during out-of-hospital cardiac arrest. As with the 30- and 90-day outcomes,[4] all point estimates suggested substantial harm with calcium administration as compared to placebo, but confidence intervals were wide. Except for survival with a favorable neurologic outcome at 1-year, 95% confidence intervals included no difference between the two groups.

The consistent effect estimates for survival and neurological outcome over time are in line with former cardiac arrest trials where the primary purpose of the intervention was to increase the rate of return of spontaneous circulation. Both the Vasopressin and Methylprednisolone for In-hospital Cardiac Arrest (VAM-IHCA)-trial and the Prehospital Assessment of the Role of Adrenaline: Measuring the Effectiveness of Drug Administration in Cardiac Arrest (PARAMEDIC2)-trial found largely unchanged effect estimates for survival and neurological outcome at long-term follow-up.[12,13] This may indicate that any effects of such interventions emerge early, and outcome assessment beyond 90 days may add only little incremental value when estimating treatment effects.

Limitations

The number of patients with long-term survival was low resulting in wide confidence intervals. The trial was stopped early based on suggestions of harm in a pre-planned interim analysis, and this increases the risk of overestimating effect sizes.[14] It is unknown how the results extend to the special circumstances of cardiac arrest under which international guidelines currently recommend calcium administration, e.g., if hyperkalemia is strongly suspected.[15,16]

Conclusions

Calcium administration during adult out-of-hospital cardiac arrest did not improve survival, neurological outcome, or health-related quality-of-life at 1-year follow-up. Effect estimates consistently suggested harm of the intervention. These results do not support the use of calcium in out-of-hospital cardiac arrest.

Funding sources and their role

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Data Access, responsibility, and analysis

Dr. Andersen had full access to all of the data in the trial and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of interest

Dr. Granfeldt reported being a member of a data and safety monitoring board and receiving personal fees from Noorik Biopharmaceuticals. No other disclosures were reported.

CRediT authorship contribution statement

Mikael Fink Vallentin: Funding acquisition, Project administration, Writing – review & editing, Writing – original draft, Data curation, Investigation, Resources, Conceptualization, Methodology. **Asger Granfeldt:** Project administration, Writing – review & editing, Writing – original draft, Investigation, Resources, Conceptualization, Methodology. **Carsten Meilandt:** Writing – review & editing, Conceptualization, Methodology. **Amalie Ling Povlsen:** Writing – review & editing, Data curation, Investigation, Resources. **Birthe Sindberg:** Writing – review & editing, Investigation, Resources. **Mathias J. Holmberg:** Writing – review & editing, Investigation, Resources. **Bo Nees Iversen:** Writing – review & editing, Investigation, Resources. **Rikke Mærkedahl:** Writing – review & editing, Investigation, Resources. **Lone Riis Mortensen:** Writing – review & editing,

Investigation, Resources. **Rasmus Nyboe:** Writing – review & editing, Investigation, Resources. **Mads Partridge Vandborg:** Writing – review & editing, Investigation, Resources. **Maren Tarpgaard:** Writing – review & editing, Investigation, Resources. **Charlotte Runge:** Writing – review & editing, Investigation, Resources. **Christian Fynbo Christiansen:** Writing – review & editing, Investigation, Resources, Conceptualization, Methodology. **Thomas H. Dissing:** Writing – review & editing, Investigation, Resources, Conceptualization, Methodology. **Christian Juhl Terkelsen:** Writing – review & editing, Investigation, Resources, Conceptualization, Methodology. **Steffen Christensen:** Writing – review & editing, Investigation, Resources, Conceptualization, Methodology. **Hans Kirkegaard:** Writing – review & editing, Investigation, Resources. **Lars W. Andersen:** Funding acquisition, Project administration, Supervision, Formal analysis, Visualization, Writing – review & editing, Writing – original draft, Data curation, Investigation, Resources, Conceptualization, Methodology.

Author details

[a.] *Prehospital Emergency Medical Services, Central Denmark Region, Aarhus, Denmark* [b.] *Department of Anesthesiology and Intensive Care, Aarhus University Hospital, Aarhus, Denmark* [c.] *Research Center for Emergency Medicine, Department of Clinical Medicine and Emergency Department, Aarhus University and Aarhus University Hospital, Aarhus, Denmark* [d.] *Department of Anesthesiology and Intensive Care, Gødstrup Regional Hospital, Denmark* [e.] *Department of Anesthesiology and Intensive Care, Randers Regional Hospital, Denmark*[f.] *Department of Anesthesiology and Intensive Care, Horsens Regional Hospital, Denmark*[g.] *Department of Anesthesiology and Intensive Care, Viborg Regional Hospital, Denmark* [h.] *Elective Surgery Centre, Silkeborg Regional Hospital, Denmark* [i.] *Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark* [j.] *Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark*

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