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Clinical paper

Effect of calcium in patients with pulseless electrical activity and electrocardiographic characteristics potentially associated with hyperkalemia and ischemia-sub-study of the Calcium for Out-of-hospital Cardiac Arrest (COCA) trial

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Abstract

Objective: The Calcium for Out-of-hospital Cardiac Arrest (COCA) trial was recently conducted and published. This pre-planned sub-study evaluated the effect of calcium in patients with pulseless electrical activity (PEA) including subgroup analyses based on electrocardiographic characteristics potentially associated with hyperkalemia and ischemia.

Methods: Patients aged ≥ 18 years were included if they had a non-traumatic out-of-hospital cardiac arrest and received adrenaline. The trial drug consisted of calcium chloride (5 mmol) or saline placebo given after the first, and again after the second, dose of adrenaline for a maximum of two doses. This sub-study analyzed patients with PEA as their last known rhythm prior to receiving the trial drug. Outcomes were return of spontaneous circulation and survival at 30 days.

Results: 104 patients were analyzed. In the calcium group, 9 patients (20 %) achieved return of spontaneous circulation vs 23 patients (39 %) in the placebo group (risk ratio 0.51; 95 %CI 0.26, 1.00). Subgroup analyses based on electrocardiographic characteristics potentially associated with hyperkalemia and ischemia showed similar results. At 30 days, 1 patient (2.2 %) was alive in the calcium group while 8 patients (13.6 %) were alive in the placebo group (risk ratio 0.16; 95 %CI 0.02, 1.26).

Conclusion: In adults with out-of-hospital cardiac arrest presenting with PEA, effect estimates suggested harm of calcium administration as compared to placebo but with wide confidence intervals. Results were consistent for patients with electrocardiographic characteristics potentially associated with hyperkalemia and ischemia. The results do not support calcium administration based strictly on electrocardiographic findings seen during out-of-hospital cardiac arrest.

Keywords: Cardiac arrest, Out-of-hospital, Calcium, Advanced Life Support, Electrocardiography

Introduction

To investigate whether calcium administration during adult out-of-hospital cardiac arrest is beneficial, the Calcium for Out-of-hospital Cardiac Arrest (COCA) trial was recently conducted and published.[1,2] The trial found that calcium, as compared to saline, did not improve patient outcomes, and the trial was stopped early because all point estimates suggested harm of the intervention.[1] These findings extended to 1-year follow-up.[2]

Current international guidelines recommend calcium administration during cardiac arrest when there is a strong suspicion of hyper-

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kalemia, hypocalcemia, hypermagnesemia, or calcium channel-blocker intoxication.[3,4] It is unknown whether the findings of the COCA trial extend to these special circumstances. While all these etiologies are thought to be rare in out-of-hospital cardiac arrest,[5] hyperkalemia is a potential cause in selected patient groups. Prehospital diagnosis of hyperkalemia relies upon patient medical history and electrocardiographic findings as blood tests are not readily available. A small randomized clinical trial from 1985 found that calcium increased return of spontaneous circulation in out-of-hospital cardiac arrest patients with pulseless electrical activity (PEA) displaying either widened QRS-complexes, peaked T-waves, or ST-elevation.[6] Such findings have been associated with both hyperkalemia[7–9] and acute myocardial ischemia.[10]

In patients included in the COCA trial, who presented with PEA, the current pre-planned study had three aims: 1) to describe electrocardiographic characteristics of patients presenting with PEA, 2) to determine the effect of calcium administration on return of spontaneous circulation in subgroups based on electrocardiographic characteristics potentially associated with hyperkalemia and ischemia, and 3) to describe rhythm transitions and changes in electrocardiographic characteristics after calcium administration.

Methods

Trial design and patients

The trial protocol is available online. This sub-study was pre-defined in the protocol although details of the analyses were not.[1,11] The COCA trial was a randomized, placebo-controlled, double-blind trial of calcium for treatment of patients with out-of-hospital cardiac arrest. Patients aged $\geq$ 18 years were included in the Central Denmark Region if they had out-of-hospital cardiac arrest and received adrenaline. Exclusion criteria were traumatic cardiac arrest, known or suspected pregnancy, clinical indication for calcium, adrenaline administration prior to possible enrollment, and prior enrollment in the trial. Using a random-number generator, patients were randomized in a 1:1 ratio to either calcium or placebo in block sizes of 2, 4, or 6.

The current study included patients with PEA as the last known rhythm prior to the first trial drug administration (henceforth "baseline"). This was chosen over initial PEA (i.e., the first manually assessed rhythm during the cardiac arrest) to better reflect electrocardiographic characteristics in immediate relation to trial drug administration and to include patients who converted to PEA after the initial rhythm analysis. Patients with initial PEA who had rhythm transition prior to trial drug administration were not included in the primary analyses. Patients with missing electrocardiographic data were excluded.

Intervention and blinding

The trial drug was 10 mL of either 0.5 mmol/mL calcium chloride or 9 mg/mL sodium chloride (placebo) given as soon as possible after the first dose of adrenaline during the cardiac arrest. This was repeated after the second dose of adrenaline for a maximum of two doses. Patients, investigators, clinicians, and outcome assessors were unaware of the allocation.

Blood samples

For patients who survived to hospital admission, data were collected on in-hospital blood samples. None of the blood samples were part of the trial protocol. Data were entered from blood samples taken on clinical indication. The time point presented in this study is the first available sample after return of spontaneous circulation.

Electrocardiographic data and analyses

In the Central Denmark Region, it is standard clinical practice to record the electrocardiographic data in the prehospital environment. In the event of an out-of-hospital cardiac arrest, the electrocardiographic data are subsequently uploaded to a secure server. The data can then be accessed and analyzed. During the COCA trial, the monitor used for electrocardiogram acquisition was a LifePak® 15 (Physio-Control Inc., Washington, USA) and the software program was CODE-STAT v. 10.0 (Stryker, Michigan, USA).

Rhythm analyses were only made if the patient was in cardiac arrest, meaning that all analyses are based solely on the pad-lead, which approximates the V6-lead. All rhythm analyses were done manually for each patient by a trained and blinded member of the research team. In case of any doubt (e.g., in the presenting rhythm), an experienced cardiologist was consulted.

Subgroup definitions

Patients were divided into subgroups based on electrocardiographic characteristics that potentially reflect hyperkalemia: loss of P-waves, wide QRS-complexes, and large T-wave amplitude. PR-interval prolongation defined as a first degree atrioventricular block was also considered but was infeasible to analyze due to a limited number of patients with this characteristic. Loss of P-waves was defined as the absence of P-waves associated with sinoatrial activity. QRS-complexes were considered wide when > 110 ms.[12] For T-wave amplitude, patients with a positive amplitude were split by the median to create a binary variable. This was preferred over so-called "peaked T-waves" for two reasons: First, we could not find a consensus agreement on an objective definition of peaked T-waves, and most other studies used clinician judgment as their definition.[8,13–15] Second, since peaked T-waves are almost exclusively present in the precordial leads (V2-V4),[15,16] they are rarely visible during a cardiac arrest, where only the pad lead is available.

Patients were also divided into subgroups based on electrocardiographic characteristics that potentially reflect acute myocardial ischemia: ST-elevation, ST-depression, and T-wave inversion.[10] ST-elevation and ST-depression were measured at the J-point, and considered significant if at least 1 mm above or below the isoelectric line, respectively.[17] T-wave inversions were defined as a negative amplitude of at least 1 mm.[17] In order to reflect different risk categories of potential acute myocardial ischemia, the subgroups were 1) any of the three signs, 2) ST-elevation or T-wave inversion, and 3) ST-elevation only.

Time points for rhythm analyses

To describe rhythm transitions and changes in electrocardiographic characteristics of PEA after trial drug administration, the first available rhythm analysis after each trial drug administration was chosen. As a sensitivity analysis, analyses were repeated for the second rhythm analysis after each trial drug administration.

Rhythm analyses were only made during the cardiac arrest. Patients who achieved return of spontaneous circulation after trial drug administration were therefore excluded from subsequent time points. Return of spontaneous circulation ("sustained") was defined as palpable pulse or other signs of circulation with no further need for chest compressions for at least 20 minutes. If a patient had

non-sustained return of spontaneous circulation, that patient's subsequent data were included until sustained return of spontaneous circulation or termination of resuscitation.

Patient outcomes

To test the effect of calcium in patients with electrocardiographic characteristics potentially associated with hyperkalemia and ischemia, subgroup analyses were made for return of spontaneous circulation. It was the original intent to repeat these analyses for 30-day survival. However, this was infeasible since only one patient with baseline PEA survived in the calcium group. 30-day survival are provided for all patients with baseline PEA.

As a sensitivity analyses, the analyses were repeated for patients with initial PEA.

Statistical analyses

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 for the current sub-study.

Binary data are presented as counts with percentages. Continuous data are presented as means with standard deviations (SD) if normally distributed, alternatively as medians with 1st and 3rd quartiles. Baseline characteristics, rhythm transitions, and changes in electrocardiographic characteristics are presented descriptively. For the subgroup analyses, differences between groups are presented as risk ratios with 95 % confidence intervals (95 %CI), which were estimated using generalized linear models with a binomial distribution and a log link function.

Table 1 – Baseline characteristics of patients with baseline pulseless electrical activity.

	All PEA patients (n = 104)	Calcium (n = 45)	Placebo (n = 59)
Patient characteristics			
Age – mean (SD), years	70 (13)	68 (13)	71 (12)
Sex – no. (%)			
Male	76 (73)	30 (67)	46 (78)
Female	28 (27)	15 (33)	13 (22)
Cardiac arrest characteristics			
Location – no. (%)			
Non-public area	83 (80)	34 (76)	49 (83)
Public area	21 (20)	11 (24)	10 (17)
Witnessed – no. (%)			
Bystander	59 (57)	27 (60)	32 (54)
EMS	17 (16)	9 (20)	8 (14)
Not witnessed	28 (27)	9 (20)	19 (32)
Bystander CPR – no. (%*)	74 (85)	30 (83)	44 (86)
Bystander AED shock – no. (%*)	8 (9)	3 (8)	5 (10)
Time to trial drug – median (1st, 3rd quartile), minutes	17 (12, 23.5)	16 (11, 24)	18 (14, 22)
Electrocardiographic characteristics			
Heart rate – median (1st, 3rd quartile), per minute	42 (33, 72)	42 (36, 60)	48 (30, 96)
Rhythm – no. (%)#			
Sinus rhythm	21 (20)	11 (24)	10 (17)
Atrial flutter or fibrillation	8 (8)	0 (0)	8 (14)
Atrioventricular node re-entry tachycardia	6 (6)	2 (4)	4 (7)
Junctional rhythm	17 (16)	8 (18)	9 (15)
Idioventricular rhythm	39 (38)	17 (38)	22 (37)
Pace rhythm	13 (13)	7 (16)	6 (10)
Loss of P-wave – no. (%)	55 (53)	24 (53)	31 (53)
1st degree atrioventricular block – no. (%)	4 (4)	3 (7)	1 (2)
QRS width - median (1st, 3rd quartile), milliseconds	130 (110, 170)	130 (115, 160)	130 (100, 180)
> 110 ms (no. (%))	72 (70)	34 (76)	38 (64)
≤ 110 ms (no. (%))	32 (30)	11 (24)	21 (36)
ST-segment (no. (%))			
Depression	29 (28)	10 (22)	19 (32)
Isoelectric	21 (20)	7 (16)	14 (24)
≥ 1 mm elevation	54 (52)	28 (62)	26 (44)
T-wave (no. (%))§			
Positive amplitude	58 (56)	25 (56)	33 (56)
> Median (2 mm)	26 (25)	14 (31)	12 (20)
≤ Median (2 mm)	32 (31)	11 (24)	21 (36)
Negative amplitude ("inverted")	40 (38)	18 (40)	22 (37)
QT-interval – mean (SD), milliseconds	430 (125)	435 (135)	420 (115)

* EMS-witnessed cardiac arrests excluded from the denominator.

§ 6 patients did not have identifiable T-waves at the time point (2 in the calcium group, 4 in the placebo group). AED: automated external defibrillator, CPR: cardiopulmonary resuscitation, EMS: emergency medical services, PEA: pulseless electrical activity, SD: standard deviation.

All analyses were performed in STATA version 17.0 (StataCorp LLC, Texas, USA).

Results

The COCA trial included 391 patients with 193 patients in the calcium group and 198 patients in the placebo group. Only one patient was not included due to a clinical indication for calcium prior to the time of randomization (strong suspicion of ketoacidosis and hyperkalemia). A CONSORT-diagram for selection of patients into the current study is presented in eFigure 1. 138 included patients had PEA as either their first ("initial") or last known manually assessed rhythm before trial drug administration ("baseline"). 19 patients with initial PEA were excluded due to rhythm transition at the baseline assessment – 17 of these were transitions to asystole. Another 15 patients were excluded due to missing electrocardiographic data at baseline. The analyses ultimately included 104 patients with baseline PEA (45 in the calcium group and 59 in the placebo group).

Plasma potassium and pH for the first available blood sample after return of spontaneous circulation are presented in eTable 1. At this time point, severe hyperkalemia (>6.5 mmol/L) was very rare in the COCA-population with no events among patients with baseline PEA. Treatment with bicarbonate during the cardiac arrest as well as coronary angiography and percutaneous coronary intervention are also presented in eTable 1.

Patient, cardiac arrest, and electrocardiographic characteristics

Patient, cardiac arrest, and baseline electrocardiographic characteristics were generally balanced between groups (Table 1). The mean age was 70 years and 27 % were female. 80 % of cardiac arrests were in a non-public area while 73 % were witnessed. Baseline PEA tended to present as bradycardia with a median heart rate of 42 (1st quartile = 33, 3rd quartile = 72). Common characteristics were loss of P-waves (53 %), ST-elevation (52 %), and inverted T-waves (38 %). Patients with initial PEA (n = 81) had similar characteristics to patients with baseline PEA (eTable 2).

Rhythm transition and electrocardiographic changes

Rhythm transitions after trial drug administration are presented in Table 2. At the first analysis after the first trial drug administration, 1 patient (2 %) in the calcium group vs 11 patients (19 %) in the placebo group had achieved return of spontaneous circulation. In the patients who remained in cardiac arrest after trial drug administration, the proportions of PEA and asystole remained similar between groups. Similar results were seen for patients with initial PEA (eTable 3).

Changes in electrocardiographic characteristics after trial drug administration are presented in Table 3. The proportion of patients with loss of P-waves, QRS-widening, and positive T-wave amplitude above the median were similar between groups at both time points after trial drug administration. For variables potentially associated with ischemia, there was no consistent pattern in how the calcium group differed from the placebo group.

Sensitivity analyses using the second rhythm analysis after each trial drug administration showed similar results (eTable 4 and eTable 5).

Return of spontaneous circulation

In all patients with baseline PEA, 9 patients (20 %) in the calcium group as compared with 23 patients (39 %) in the placebo group achieved return of spontaneous circulation (risk ratio 0.51; 95 %CI 0.26, 1.00). Subgroup analyses related to electrocardiographic characteristics potentially associated with hyperkalemia and ischemia are presented in Fig. 1 and Fig. 2, respectively. None of the subgroup analyses showed signs of effect modification. Repeating the analyses for patients with initial PEA showed similar results (eFigure 2 and eFigure 3).

Survival at 30 days

There was no loss to follow-up. In all patients with baseline PEA, 1 patient (2.2 %) in the calcium group as compared with 8 patients (13.6 %) in the placebo group survived to 30 days (risk ratio 0.16; 95 %CI 0.02, 1.26). Subgroup analyses were not feasible due to the low event rate. For patients with initial PEA, 1 patient (2.6 %) in the calcium group as compared with 2 patients (4.7 %) in the placebo group survived to 30 days (risk ratio 0.57; 95 %CI 0.05, 5.99).

Table 2 – Rhythm transitions after trial drug administration in patients with baseline pulseless electrical activity.

	After 1st trial drug dose		After 2nd trial drug dose	
	Calcium (n = 43)	Placebo (n = 57)	Calcium (n = 45)	Placebo (n = 58)
PEA – no. (%)	30 (70)	38 (67)	19 (42)	27 (47)
Asystole – no. (%)	4 (9)	3 (5)	4 (9)	3 (5)
VF – no. (%)	1 (2)	3 (5)	7 (16)	2 (3)
pVT – no. (%)	5 (12)	2 (4)	3 (7)	2 (3)
ROSC (sustained or non-sustained) at the time of analysis – no. (%)	1 (2)	11 (19)	6* (13)	15* (26)
Termination of resuscitation prior to analysis – no. (%)	2 (5)	0 (0)	6# (13)	9# (16)

The baseline time point was the last available electrocardiographic analysis prior to administration of the first trial drug dose. For the time points after the trial drug doses the first available rhythm analysis after each trial drug administration was chosen. Each time point only included those still in cardiac arrest. Percentages are given with *n* as the denominator which excluded patients with missing data at the time point.

* These include patients with sustained ROSC prior to administration of a second trial drug dose (2 in the calcium group and 8 in the placebo group).

All these patients had termination of resuscitation prior to administration of a second trial drug dose. PEA: pulseless electrical activity, ROSC: Return of spontaneous circulation, VF: ventricular fibrillation, pVT: pulseless ventricular tachycardia.

Table 3 – Change in electrocardiographic characteristics of baseline pulseless electrical activity after trial drug administration.

	Baseline		After 1st trial drug dose		After 2nd trial drug dose	
	Calcium (n = 45)	Placebo (n = 59)	Calcium (n = 30)	Placebo (n = 38)	Calcium (n = 19)	Placebo (n = 27)
Heart rate – median (1st, 3rd quartile), per minute	42 (36, 60)	48 (30, 96)	57 (36, 102)	48 (36, 66)	60 (36, 100)	54 (36, 72)
Loss of P-wave – no. (%)	24 (51)	31 (51)	15 (50)	19 (50)	11 (58)	14 (52)
1st degree atrioventricular block – no. (%)	3 (7)	1 (2)	1 (3)	1 (3)	0 (0)	1 (4)
QRS width - median (1st, 3rd quartile), milliseconds	130 (115, 160)	130 (100, 180)	120 (110, 180)	120 (100, 160)	140 (110, 150)	120 (100, 160)
> 110 ms (no. (%))	34 (76)	38 (64)	21 (70)	24 (63)	14 (74)	18 (67)
≤ 110 ms (no. (%))	11 (24)	21 (36)	9 (30)	14 (37)	5 (26)	9 (33)
ST-segment, depression (no. (%))	10 (22)	19 (32)	11 (37)	7 (18)	5 (26)	11 (41)
ST-segment, isoelectric (no. (%))	7 (16)	14 (24)	2 (7)	11 (29)	1 (5)	7 (26)
ST-segment, ≥ 1 mm elevation (no. (%))	28 (62)	26 (44)	17 (57)	20 (53)	13 (68)	9 (33)
T-wave, positive amplitude – no. (%)[§]	25 (56)	33 (56)	17 (57)	17 (45)	15 (79)	15 (56)
> Median (2 mm)	14 (31)	12 (20)	8 (27)	6 (16)	7 (37)	4 (15)
≤ Median (2 mm)	11 (24)	21 (36)	9 (30)	11 (29)	8 (42)	11 (41)
T-wave, negative amplitude – no. (%)[§]	18 (40)	22 (37)	12 (40)	19 (50)	4 (21)	10 (37)
QT-interval – mean (SD), milliseconds	435 (135)	420 (120)	415 (140)	430 (120)	410 (125)	415 (145)

The table only includes patients with baseline PEA who did not have rhythm transition or return of spontaneous circulation for the given time points.

[§] At baseline, 6 patients did not have identifiable T-waves at the time point (2 in the calcium group, 4 in the placebo group). After the first trial drug dose, 3 patients did not have identifiable T-waves at the time point (1 in the calcium group, 2 in the placebo group). After the second trial drug dose, 2 patients did not have identifiable T-waves at the time point (all in the placebo group).

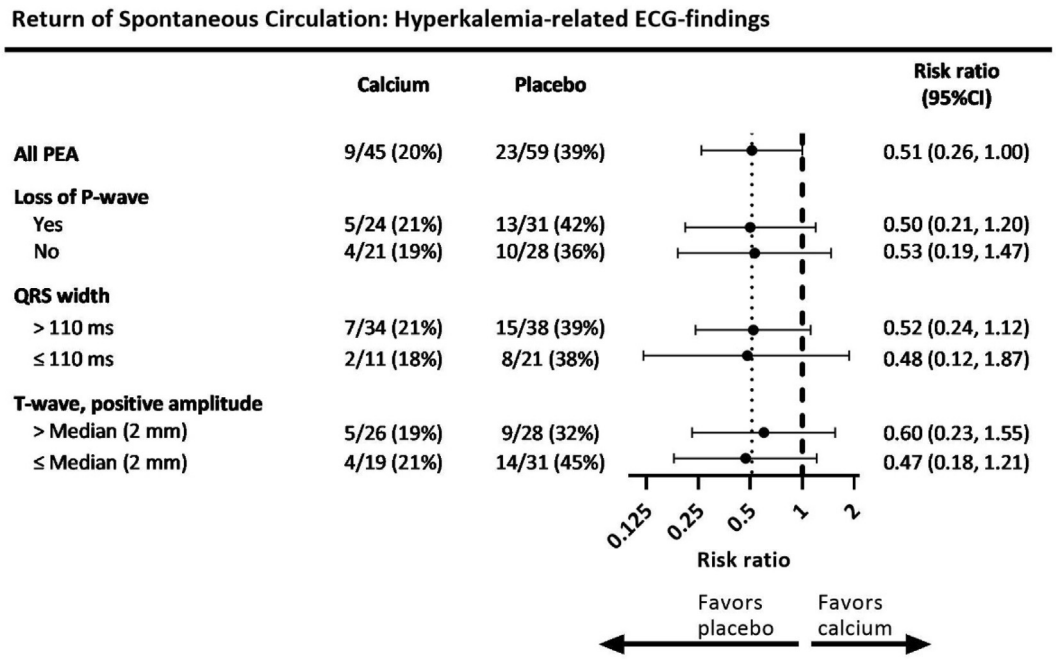

Fig. 1 – Effect of calcium administration on return of spontaneous circulation in subgroups based on electrocardiographic characteristics of baseline pulseless electrical activity: findings potentially associated with hyperkalemia 95%CI: 95% confidence intervals, ECG: Electrocardiography, PEA: Pulseless electrical activity.

Discussion

The current study investigated calcium's effect on return of spontaneous circulation and survival in out-of-hospital cardiac arrest with baseline PEA. The findings of the main publication for the COCA trial[1] extended to patients with baseline PEA as point estimates suggested harm of the intervention but with wide confidence intervals. The effect on return of spontaneous circulation was evident already

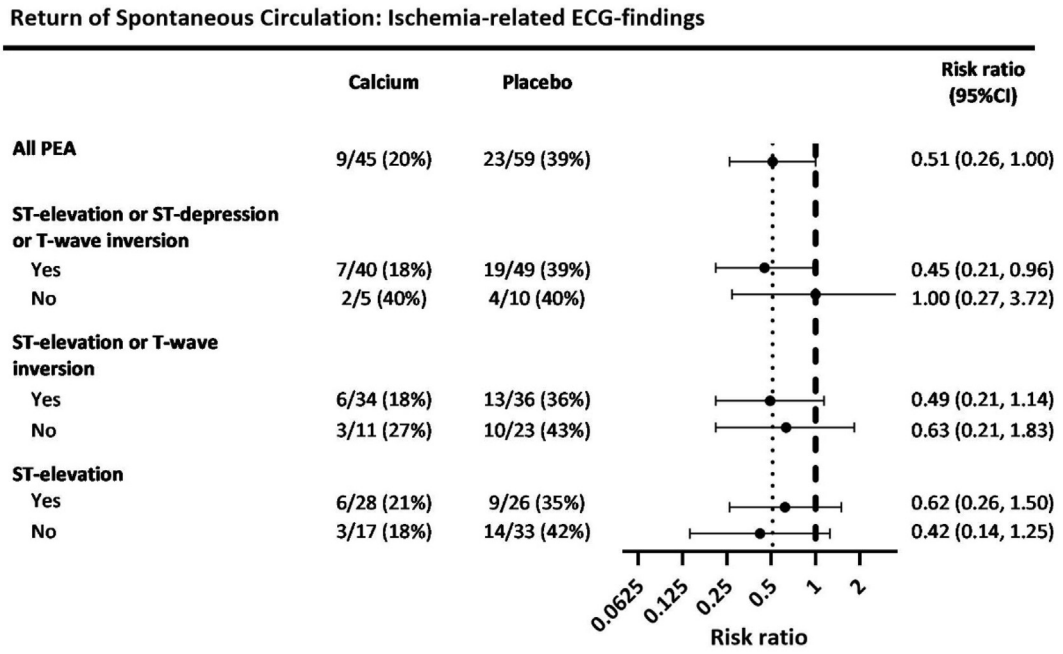

Fig. 2 – Effect of calcium administration on return of spontaneous circulation in subgroups based on baseline electrocardiographic characteristics of pulseless electrical activity: findings potentially associated with ischemia 95%CI: 95% confidence intervals, ECG: Electrocardiography, PEA: Pulseless electrical activity.

at the first rhythm analysis after trial drug administration. For patients with baseline electrocardiographic characteristics potentially associated with hyperkalemia or ischemia, there were no signs of effect modification. In patients who continued to have PEA after trial drug administration, the findings suggested that calcium did not clearly affect the electrocardiographic characteristics. These results do not support calcium administration for out-of-hospital cardiac arrest on the basis of electrocardiographic findings potentially associated with hyperkalemia or ischemia.

The current results are in contrast to those of a 1985 randomized clinical trial that, in a post hoc subgroup analysis, found calcium to increase return of spontaneous circulation in out-of-hospital cardiac arrest presenting with either widened QRS-complexes, peaked T-waves, or ST-elevation.[6] It is unknown how ST-elevation alone contributed to this finding. Calcium administration for cardiac arrest with signs of ischemia has never been a part of international guidelines, mostly because the finding was never validated and lacks a known physiologic rationale. The current results do not support calcium administration to cardiac arrest patients with electrocardiographic characteristics potentially associated with acute myocardial ischemia.

Current international guidelines recommend calcium administration if there is known, or a strong suspicion of, hyperkalemia during the cardiac arrest.[3,4] European guidelines add that there should be a strong suspicion that hyperkalemia has caused the cardiac arrest.[3,18] With the current results, prehospital calcium administration during cardiac arrest should not be based on electrocardiographic findings potentially associated with hyperkalemia. During an out-of-hospital cardiac arrest, this leaves clinical judgment based on co-morbidity, medications, and case history for the decision to administrate calcium for potential hyperkalemia. If hyperkalemia truly is a pathogenic factor of the cardiac arrest, calcium is thought to treat as well as protect against arrhythmia.[18] Clinical evidence for these effects of calcium are sparse both within and outside of cardiac arrest, and no randomized clinical trial has ever been conducted in any setting.[18,19]

While the proportion of patients receiving calcium is unknown for out-of-hospital cardiac arrest, nearly a third of all in-hospital cardiac arrest patients in the United States receive calcium.[20] The indications by which calcium is given at such a high rate are unknown but there are potential explanations: First, the most recent numbers are from 2016 (before the COCA trial),[1,20] and clinicians may have thought calcium to be beneficial for the general cardiac arrest patient. Second, clinicians may give calcium based on a perceived etiology for which calcium is currently recommended by international guidelines.[3,4] For hyperkalemia, international guidelines currently do not provide a threshold above which calcium administration is recommended.[3,4] Severe hyperkalemia ($\geq$6.5 mmol/L) was a very rare finding in the COCA trial patients who survived to hospital admission, and even then it may be secondary to ischemia and severe metabolic acidosis rather than being a pathogenic factor of the cardiac arrest.

Limitations

The COCA trial did not reach its pre-planned sample size, and event rates for the subgroup analyses were consequently low resulting in wide confidence intervals. The trial only tested one dosing regime in out-of-hospital cardiac arrest. The findings may not extend to patients with in-hospital cardiac arrest.

The results do not exclude a beneficial effect of calcium in out-of-hospital cardiac arrest truly caused or affected by hyperkalemia. While the electrocardiographic findings associated with hyperkalemia were quite frequent in our trial, severe hyperkalemia following return of spontaneous circulation was very rare.[1] This indicates a lack of specificity for the electrocardiographic findings during cardiac

arrest where only the pad lead is available. Generally, out-of-hospital cardiac arrest due to hyperkalemia is thought to be rare.[5]

The results are not valid outside of cardiac arrest where a 12-lead electrocardiogram is readily available. Some electrocardiographic characteristics associated with hyperkalemia, e.g. peaked T-waves, are much more frequent in leads not associated with the pad lead.[15,16] The consensus definitions of ST-elevation and ST-depression require that the finding is present in two neighboring leads, which is most often not available during cardiac arrest.[10] Lastly, the pad lead does not cover the entire myocardial tissue which could lead to an underestimation of the prevalence of acute myocardial ischemia.

Conclusion

In adult out-of-hospital cardiac arrest patients presenting with baseline PEA, calcium administration, as compared with saline, did not improve return of spontaneous circulation or survival at 30 days, and point estimates consistently suggested harm of the intervention although with wide confidence intervals. Subgroup analyses based strictly on electrocardiographic findings potentially associated with hyperkalemia or ischemia showed similar results. The results do not support calcium administration based on electrocardiographic findings seen during out-of-hospital cardiac arrest.

Conflicts of interest

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

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Data access, responsibility, and analysis

Mikael Fink Vallentin had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

CRediT authorship contribution statement

Mikael Fink Vallentin: Methodology, Software, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Project administration. **Amalie Ling Povlsen:** Methodology, Software, Validation, Data curation, Writing – review & editing. **Asger Granfeldt:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration. **Christian Juhl Terkelsen:** Methodology, Validation, Data curation, Writing – review & editing, Supervision. **Lars W. Andersen:** Conceptualization, Methodology, Validation, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2022.11.006.

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