The effect of calcium gluconate in the treatment of hyperkalemia

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Abstract:

OBJECTIVES: Intravenous (IV) calcium salts are routinely recommended as a cardio-protective therapy in the emergency treatment of severe hyperkalemia. However, this recommendation is supported by a low level of evidence and is anecdotal. The aim of this study is to determine the effectiveness of IV Calcium (Ca) gluconate in the treatment of hyperkalemia.

MATERIALS AND METHODS: Patients with hyperkalemia and with the electrocardiogram (ECG) changes due to hyperkalemia over a 1 year period were included in this prospective observational study. Patients’ ECGs were measured, before and after IV Ca‑gluconate treatment and after normalization of potassium levels. Wilcoxon test and McNemar’s test were used to compare the ECG parameters before and after Ca‑gluconate therapy.

RESULTS: The mean potassium value of 111 patients who met the inclusion criteria was 7.1 ± 0.6 mmol/l. In this study, a total of 243 ECG pathology related to hyperkalemia, 79 of which included main rhythm disorders, and the remaining 164 were nonrhythm disorders in ECG parameters, were analyzed. No statistically significant changes were determined in patients’ nonrhythm ECG disorders with IV Ca‑gluconate treatment (P = 0.125). However, nine of the 79 main rhythm disorders due to hyperkalemia improved with calcium gluconate treatment and this change was statistically significant (P < 0.004).

CONCLUSION: IV Ca‑gluconate therapy was found to be effective, albeit to a limited degree, in main rhythm ECG disorders due to hyperkalemia, but it was not found to be effective in nonrhythm ECG disorders due to hyperkalemia. Therefore, Ca‑gluconate may be effective only in the main rhythm disorders due to hyperkalemia.

Keywords: Acidosis, calcium gluconate, electrocardiography, hyperkalemia, renal failure

Introduction

Objectives

Hyperkalemia is a common electrolyte disorder with potential mortality due to its association with severe cardiac arrhythmia.[1] Hyperkalemia typically occurs as a result of a decrease in urinary potassium excretion due to acute or chronic renal failure (CRF) and/or certain medications, or less frequently as a result of an increased potassium (K+) release from cells, which is caused by metabolic acidosis or certain medications, such as beta-blockers.[2] Cases with severe hyperkalemia with clinical muscle weakness or paralysis, cardiac arrhythmia, or potassium >6.5 should be treated as a matter of urgency.[3]

The treatment of hyperkalemia often requires a combined treatment approach, including the treatment of the underlying clinical presentation along with potassium‑lowering and cardioprotective therapies. In addition to the treatment of the underlying clinical

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This was a single-center, prospective observational study of the efficacy of IV calcium salts in humans. Clinical level experiences in humans are at a case report level. Therefore, the level of recommendation is low, and it is anecdotally based on expert opinion.

What is the conflict on the issue? Has it important for readers?

Studies showing the effectiveness of calcium salts recommended in the treatment of hyperkalemia are at the level of case reports. Therefore, the level of recommendation is low, and it is anecdotally based on expert opinion.

How is this study structured?

This was a single-center, prospective observational study that includes data from approximately 111 patients.

What does this study tell us?

Intravenous Ca-gluconate therapy may be effective in rhythm disturbances due to hyperkalemia, but it has not been found to be effective in nonrhythm electrocardiogram disturbances.

Materials and Methods

Study design and setting

This prospective observational and single-center study was conducted in the Emergency Medicine Clinic of a tertiary 430-bed Training and Research Hospital between July 2015 and July 2017. Before the study, approval was granted by the Haseki Training and Research Hospital ethics committee on 8 July 2015 with an approval number of 230, and the study was registered as a Clinical Trial with the identifier number NCT02672930. The study was carried out over 1 year within daytime working hours. Prior written consent was obtained from each volunteer who participated in the study.

Participants

All patients with K+ ≥ 5.5 mmol/l in the laboratory results and with at least one electrocardiogram (ECG) changes due to hyperkalemia on ECG were included in the study. The study excluded patients with cardiopulmonary arrest; ECG changes or vital sign changes upon receiving antiarrhythmic drugs/cardioversion/defibrillation/positive inotropic therapy/atropine during emergency treatment before Ca-gluconate therapy; myocardial infarction and pericarditis/myocarditis; digoxin usage; trauma.

Study protocol and data collection

Potassium level; the normal blood level of potassium was defined as 3.5–5.5 mmol/l. Hyperkalemia was defined as K+ ≥ 5.5 mmol/l. ECG changes due to hyperkalemia; The ECG changes indicating hyperkalemia were defined as peaked T-wave, shortened QT interval, P-wave widening and flattening, PR segment lengthening, prolonged QRS interval, ST-segment alternations as nonrhythm ECG pathologies, and high-grade atrioventricular (AV) blocks, all conduction blocks (bundle branch blocks, fascicular blocks), sinus bradycardia or slow atrial fibrillation (AF), sine wave appearance, asystole, ventricular fibrillation, pulseless electrical activity (PEA), and all wide complex rhythms as a main rhythm ECG pathologies. All patients with a potassium level greater than K+ ≥ 5.5 mmol/l in the laboratory test and concurrently ECG changes or vital sign changes upon receiving antiarrhythmic drugs/cardioversion/defibrillation/positive inotropic therapy/atropine during emergency treatment before Ca-gluconate therapy were included in the study. A control examination and treatment of all study patients were performed and recorded by emergency medicine specialists in our study team with at least 5 years of experience. After the examination and vital signs measurements, all study patients underwent a 12-channel ECG using a GE Healthcare ECG MAC 200 brand ECG device within the first 5 min of presentation. The first ECG procedure was performed by placing the electrodes on standard described spots, which were marked. Repeated ECG measurements were obtained after placing the electrodes on the same spots using the same device. All ECGs were taken at a speed of 25 mm/sec and a height of 10 mm/mV. The ECGs were immediately evaluated by emergency medicine specialist in our study team with attending cardiologist and the ECG findings were recorded.
According to ECG and blood potassium value results, any emergency hyperkalemia treatment required by the patients was initiated as a matter of urgency. Patients were administered 10% 10 ml Ca-gluconate as an infusion without dilution over 3–5 min, as recommended for patients not using digoxin, via peripheral vascular access. Since calcium was expected to exert its effect in 5–10 min, the vital signs and ECG of the patient were repeated and recorded 10 min after the end of the calcium therapy. The 10% 10 ml Ca-gluconate dose was repeated up to three times, in accordance with recommendations for patients with persistent ECG changes related to hyperkalemia. ECG and vital signs measurements were repeated 10 min after each Ca-gluconate dose. The study data were based on the final ECG.

Simultaneously with the calcium therapy, 10–20 units of regular insulin in 500 ml 10% dextrose was infused in 60 min. Other anti-potassium therapies were adjusted on a patient-to-patient basis, based on the clinical picture, considering such factors as hypo-hypervolemia, pulse rate, and severe acidemia (pH <7.1). Patients with severe renal failure and treatment-resistant hyperkalemia underwent hemodialysis. An ECG was obtained and vital signs were measured and recorded again for all patients when the level of K+ decreased to the defined normal level.

All ECGs were evaluated by an emergency medicine specialist on our team and a cardiologist with at least 5 years of experience supporting our study. Main rhythm disturbances were first evaluated in ECGs. For this purpose, the presence of all conduction blocks (bundle branch blocks, fascicular blocks), sinus bradycardia or slow AF, sine wave appearance, asystole, ventricular fibrillation, PEA, and all wide complex rhythms, which are among the main rhythm disturbances attributed to hyperkalemia, were measured pre and post-Ca-gluconate treatment, and after the potassium level returns to the normal level. Second, the presence of amplitude and/or width anomalies of T wave, QT interval, P wave, PR interval, QRS wave, and ST-segment which are among the ECG parameters attributed to hyperkalemia, were measured pre and post-Ca-gluconate treatment and after the potassium level returns to the normal level.

Outcome measures

The primary outcome measure of the present study was the change in the hyperkalemic patient ECGs caused by IV Ca-gluconate. Whether the ECG changes were secondary to hyperkalemia or whether Ca-gluconate administration improved those changes were decided comparing the ECG findings after K levels returned to normal. In this way, if a pathology such as PR prolongation that was present in the first ECG persists in the basal ECG, this change was not attributed to hyperkalemia and changes that were also present in this basal ECG were excluded from the evaluation. In this way, ECG changes due to hyperkalemia and the effect of Ca-gluconate on this change were evaluated.

Statistical analysis

Descriptive statistics were expressed as frequency, percentage, mean, and standard deviation, median, minimum, and maximum levels. Categorical variables were expressed as numbers and percentages, while numerical variables were expressed as mean, standard deviation, minimum and maximum values, and interquartile ranges. Continuous variables were tested for normal distribution using histogram, kurtosis and skewness values, as well as a Shapiro–Wilks test. None ECG parameters of the patients had a normal distribution, and so the Wilcoxon test, which is a nonparametric test that is used when there are continuous variables in dependent groups, was used to compare the median value of the patient ECG parameters before and after Ca-gluconate therapy. The measurements of ECG rhythms and comparison of ECG parameters as improved and not improved, which is a categorical variable, were evaluated using McNemar’s test. A P < 0.05 was considered statistically significant. All statistical analyses were conducted using SPSS 24.0 software (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.), and all calculations were made at a 95% confidence interval.

Results

During the study period, a total of 512 patients with hyperkalemia were identified and 239 of these patients had at least one ECG change associated with hyperkalemia, and these patients were included in the study. 111 of these patients were followed until their K+ levels returned to the normal level and constituted the final study population. The detailed work flowchart is presented in Figure 1.

Of the patients, 56% were male and the mean age was 66 ± 18 years; the mean K+ value upon admission to the emergency department was 7.1 ± 0.6 mmol/l. Of these 111 patients, 108 received three doses of Ca-gluconate, 3 of them received two doses of Ca-gluconate and none of them received a single dose of Ca-gluconate. The patients’ demographic characteristics, laboratory parameters, and vital signs at admission are presented in Table 1.

In the present study population with hyperkalemia and ECG changes, there were 15 patients with a K+ level of 5.5–6.5 mmol/l, 76 patients with a K+ level between 6.5 and 8 mmol/l, and 20 patients
with a K+ level of 8 mmol/l and above. All 15 patients with a K+ level between 5.5 and 6.5 mmol/l had peaked T-wave, while 10 had a decreased P-wave amplitude and nine had a widened P-wave, none had main rhythm pathologies. 76 patients with potassium levels between 6.5 and 8 had 51 main rhythm disturbances (1st-degree AV-block in 25, 2nd-degree AV-block in one, sinus bradycardia in two, slow AF in one, escape beats in 16, right bundle branch block in one, left bundle branch block in three, left anterior fascicular branch block in two) due to hyperkalemia and 130 nonrhythm ECG changes. Of 20 patients with a K+ level above 8, two had 2nd-degree AV-block, four had 3rd-degree AV-block, two had sinus bradycardia and 1st-degree AV-block, three had slow AF, two of them escape beat, three had sine wave rhythm, two had VT, two had left bundle branch block and 1st-degree AV-block, and two had right bundle branch block and 1st-degree AV-block.

Changes occurring in the main rhythms on ECGs and changes nonrhythm ECG parameters upon IV Ca-gluconate therapy and potassium normalization are presented in Table 2. There were 382 pathologies totally that might be associated with hyperkalemia in the ECGs of 111 patients at the time of admission.

The number of these pathologies dropped to 369 after Ca-gluconate treatment. 139 ECG pathologies still persisted in the basal ECGs after K levels normalized and, those were considered not secondary to hyperkalemia and were excluded from statistical calculations. There were a total of 243 ECG pathologies associated with hyperkalemia in the study population, 79 of which included main rhythm disorders, and the remaining 164 were nonrhythm disorders in ECG parameters.

The main rhythm disorders associated with hyperkalemia and nonrhythm disorders were examined separately in the study. Table 3 shows the main rhythm disorders caused by hyperkalemia and the disorders in which Ca-gluconate improves. When major rhythm disorders caused by hyperkalemia were evaluated one by one, Ca-gluconate did not provide statistical improvement in any rhythm disorders. However, when the effect of IV Ca-gluconate on all main rhythm disorders was examined collectively, IV Ca-gluconate was found to improve nine of the...
79 rhythm disorders in total, which was statistically significant [Table 3].

The changes in nonrhythm ECG parameters due to hyperkalemia and changes with Ca-gluconate treatment are presented in Table 4. Four of the 164 nonrhythm ECG disorders associated with hyperkalemia were recovered with Ca-gluconate treatment. However, when each ECG pathology was evaluated separately or collectively, this change was not statistically significant.

**Discussion**

Animal studies at a cellular level suggest that IV calcium...
The efficacy of IV calcium salts in the treatment of hyperkalemia in humans has yet to be demonstrated in clinical trials, as all experience is at a case report level. IV calcium salts are routinely recommended for hyperkalemia treatment, however, this recommendation is supported by a low level of evidence and is anecdotal. The present study is the first clinical trial to investigate the efficacy of IV Ca-gluconate in the emergency treatment of hyperkalemia in a large case series. In this study, patients were monitored until their potassium levels had returned to the normal level, after which the basal ECGs of all patients were obtained. It was thus clarified whether ECG findings such as changes in the ST-T waves that may occur as acute or chronic for several reasons other than hyperkalemia, were actually related to hyperkalemia. Based on such a design, the effects of Ca-gluconate on ECG were examined through a two-stage data analysis. The first stage included an examination of the effect of Ca-gluconate on main rhythm disorders on ECG, such as AV blocks, bundle branch blocks, and ventricular arrhythmias, caused by hyperkalemia, while the effect of Ca-gluconate on nonrhythm ECG changes, such as ST changes, QRS width, and T wave changes due to hyperkalemia, was examined in the 2nd stage. Ca-gluconate was found to cause no statistically significant change in any of the main rhythm disorders (when examined one by one) on ECG or nonrhythm ECG parameters in our study population. Furthermore, the collective assessment of main rhythm disorders revealed that Ca-gluconate caused a statistically significant improvement by improving nine of 79 pathological rhythms. This suggests that IV Ca-gluconate is likely to be effective only in main rhythm disorders in humans, and may have no effect on the nonrhythm ECG changes caused by hyperkalemia.

In the present study, patients with hyperkalemia-related ECG changes were mostly in the elderly group (mean age: 66 ± 18 years) and the most common comorbidity was hypertension (60%), followed by CRF (41%). When the medications that may be facilitating factors for hyperkalemia were examined, ACEI ranked first (46%), followed by potassium-sparing diuretics (16%). Acker et al. reported the most common cause of hyperkalemia to be renal failure (77%), followed by medications (63%) among hospitalized patients. In our study population, 46% of the patients had renal failure when acute and CRFs were evaluated together. The study population of Christopher et al. comprised only hospitalized patients, while our study population included all patients with hyperkalemia and with ECG changes due to hyperkalemia. We believe that such a difference in our study population was the most important factor behind the difference in findings. The study by Montague et al. reported acute renal failure and CRF to be 55% and 47%, respectively among the pathologies accompanied by hyperkalemia. Although the authors did not mention the category under which they presented acute exacerbations of CRF, it can be understood from the numbers that they were included on both lists. The study population of Montague et al. included patients with K+ >6 mmol/l and hyperkalemia-related ECG changes, partly resembling our study population. Despite the differences in data presentation, our findings are similar to those reported by Montague et al.

The animal experimental study by Bisogno et al. suggested that atrial and ventricular rate changes,
P-wave changes, PR interval, QRS complex, and T-wave changes caused by hyperkalemia could be restored with calcium salts.\[12\] However, IV Ca-glucuronate produced no statistically significant change in any of these ECG parameters that changed due to hyperkalemia in our study population. Our study failed to identify any statistically significant change in these parameters, even when the main rhythm-rate changes were examined individually. When the rhythm disorders were evaluated collectively, however, a statistically significant change was found in main ECG rhythms, similar to the findings reported by Bisogno \textit{et al.}

The efficacy of IV calcium salts in the treatment of hyperkalemia in humans has been assessed only at a case report level to date. There are case reports suggesting that IV calcium salts are beneficial in ventricular tachycardia (VT) and ventricular fibrillation,\[13\] sine-wave appearance,\[18\] severe bradycardia,\[21\] and AV blocks\[22\] caused by hyperkalemia in humans. In the present study, IV Ca-glucuronate led to improved rhythm in two of the 31 first-degree AV blocks, one of the four third-degree AV blocks, one of three sine-wave appearances, one of two VTs, three of the 18 escape beats (not completely improved, caused a decreased frequency of escape beats in all three), and one of 3 right bundle blocks. None of these changes alone were statistically significant. However, as can be seen in Table 3, when the rhythm disorders in our population are examined individually, patients with each rhythm disorder are too low in number to achieve a statistically reliable finding. When all rhythm disorders were grouped, a relatively adequate number was reached; Ca-glucuronate can thus be said to cause a statistically significantly improvement in hyperkalemia-related rhythm pathologies and Ca-glucuronate was not effective in nonrhythm ECG disorders.

**Limitations**

The present study tested whether IV Ca-glucuronate caused a significant improvement in ECG parameters in 111 cases; however, the number of patients was very low, especially for some rhythm disorders when considering the patients with each rhythm disorder individually in an analysis of rhythm disorders. The most important limitation of the present study is, therefore, the relatively low number of patients, preventing an individual assessment of rhythm disorders. Furthermore, this study is not a randomized controlled trial. The studies that can most strongly determine the effectiveness of calcium on hyperkalemia are randomized studies in two randomized groups by giving calcium to one of them and not to the other. Therefore, randomized controlled studies are needed to more strongly evaluate the effectiveness of calcium in the treatment of hyperkalemia.

Calcium salts are expected to be beneficial in two ways in the treatment of hyperkalemia. The first is to correct the already formed ECG pathologies due to hyperkalemia, and the second is that the existing pathology does not progress to more fatal rhythms. This study evaluates only the ability of ca-glucuronate to correct already formed ECG pathologies due to hyperkalemia. It is not possible to comment on the protective effect of calcium salts from this study, it is necessary for randomized studies.

In this study, insulin therapy was started together with calcium gluconate therapy. In the treatment of hyperkalemia, the effect of Calcium salts begins in 5–10 min,\[17\] but the effect of insulin starts in 20–30 min and reaches a maximum in 30–60 min,\[23-26\] For this reason, it seems very unlikely that the efficacy of calcium gluconate therapy applied in our patient population is theoretically superimposed with the efficacy of insulin. However, this possibility remains to be tested in practice. Furthermore, in this study, the ECGs taken during the period when the patients were hyperkalemic and the ECGs obtained after the K level returned to normal were compared. The measured change was attributed to hyperkalemia. However, other conditions such as acidosis other than hyperkalemia may also affect the ECG in these patients. However, as it is known, Calcium gluconate is fast-acting and this study was completed within a maximum of 45 min of ECG measurements. Since it takes more time to correct other factors that will affect the ECG, such as acidosis, the study is expected to be largely unaffected by such effects.

**Conclusion**

IV Ca-glucuronate caused no statistically significant improvement in the nonrhythm ECG disorders of hyperkalemic patients. IV Ca-glucuronate was found to make a limited contribution to treatment in the presence of rhythm disorders on ECG. The efficacy of calcium salts should be tested on a larger case series.

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**Author contributions statement**

Conceptualization; Nalan Gökçe Çelebi Yamanoglu (equal), Adnan Yamanoglu (equal), Data curation; Nalan Gökçe Çelebi Yamanoglu (equal), Adnan Yamanoglu (equal), Formal analysis; Adnan Yamanoglu (equal), Nalan Gökçe Çelebi Yamanoglu (equal), Funding acquisition; Nalan Gökçe Çelebi Yamanoglu (equal), Adnan Yamanoglu (equal), Investigation; Nalan Gökçe Çelebi Yamanoglu (equal), Adnan Yamanoglu (equal), Methodology; Nalan Gökçe Çelebi Yamanoglu (equal), Adnan Yamanoglu (equal), Project administration; Nalan Gökçe Çelebi Yamanoglu (equal), Adnan Yamanoglu (equal), Resources; Adnan Yamanoglu (equal), Nalan Gökçe Çelebi Yamanoglu (equal), Software; Nalan Gökçe Çelebi Yamanoglu (equal), Adnan Yamanoglu (equal), Supervision; Nalan Gökçe Çelebi Yamanoglu (equal), Yamanoglu and Yamanoglu: Cardioprotective effect of calcium salts
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Gökçe Çelebi Yamanoğlu (equal), Adnan Yamanoğlu (equal), Validation; Nalan Gökçe Çelebi Yamanoğlu (equal), Adnan Yamanoğlu (equal), Visualization; Nalan Gökçe Çelebi Yamanoğlu (equal), Adnan Yamanoğlu (equal), Writing – review & editing; Nalan Gökçe Çelebi Yamanoğlu (equal), Adnan Yamanoğlu (equal).

Conflicts of interest
None Declared.

Ethical approval
Prior to the study, approval was granted by the local hospital ethics committee of Haseki Training and Research Hospital with approval number of 230 (approval date 8th July 2015) and the study was registered as a Clinical Trial with the identifier NCT02672930.

Consent to participate
A signed consent form was obtained from the patient and/or his/her relatives.

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References