Giornale Italiano di Nefrologia

Comparison Among Potassium Binders on the Management of Hyperkalemia on Chronic Dialysis Patients: A Protocol for Systematic Review

Research in progress

Veronica Maressa [1], Alessandra Farina [1], Valeria Cernaro [1], Guido Gembillo [1], Elisa Longhitano [1], Giovanni Taverna[2], Domenica Santoro[1], Vincenzo Calabrese [3]*
The protocol review has been carried out by Prof. Gabriele Donati


Vincenzo Calabrese

1 Unit of Nephrology and Dialysis, Department of clinical and experimental medicine, University Hospital "G. Martino", Messina, 98100, Italy
2 Unit of Cardiology, Department of clinical and experimental medicine, University Hospital "G. Martino", Messina, 98100, Italy
3 Unit of Nephrology and Dialysis, Department of Medicine and Surgery, University of Enna "Kore", 94100, Enna, Italy

Corresponding author:
Vincenzo Calabrese,
e-mail: v.calabrese@outlook.it

ABSTRACT

Introduction. Treating hyperkalemia is one of the main goals of supportive care in patients on hemodialysis. In this context, therapy with new potassium binders is a promising resource.

Objective. The main aim is to evaluate the difference in serum potassium concentration after treatment with sodium zirconium cyclosilicate or patiromer compared to placebo/sodium polystyrene sulfonate/calcium polystyrene sulfonate.

Methods. We will perform systematic research in PubMed, EMBASE, CINAHLE, and grey literature will be screened. We will screen RCTs on patients treated with SZC or patiromer in chronic hemodialysis, without sex or age restriction, which include the differences in serum potassium concentration, adverse events (AEs), and mortality as outcomes.

Expected results. This systematic review is expected to provide a comprehensive evaluation of the efficacy and adverse effects of new potassium binders, compared to sodium polystyrene sulfonate or calcium polystyrene sulfonate or placebo, on serum potassium concentration, in a sample of hemodialysis patients. Furthermore, possible gaps in actual knowledge can be highlighted, suggesting new research.

Conclusions. The present protocol for a systematic review will consider all existing evidence from published RCTs about the efficacy of potassium binders on hemodialysis patients.

KEYWORDS: Potassium binders, sodium zirconium cyclosilicate, patiromer, hyperkalemia, CKD, Hemodialysis

Introduction

The incidence of Hyperkalemia is common in kidney diseases, and its incidence increases in patients who previously experienced hyperkalemia, similarly to patients with diabetes or assuming RAASIs, with successively shorter time between the episodes [1].

Patiromer and Sodium Zirconium Cyclosilicate (SZC), an ion-exchange polymer resin and an ion-exchange microporous resin, were developed in the second decades of the third millennium, reducing adverse events [2–4].

The increased risk of mortality and morbidity in hyperkalemia is well-known [5, 6], as well as their increased incidence in patients treated with RAASIs. It occurs because RAASIs reduce the aldosterone-related potassium excretion that physiologically occurs in the distal and collecting tubule. Despite this, RAASIs showed nephroprotective and cardioprotective action, and it makes RAASIs useful to use. For this, new potassium binders, also aimed to better manage hyperkalemia in patients treated with RAASIs, managing pre-dialysis serum potassium that is considered a risk factor of cardiovascular mortality [7].

Aims and scope

The main objective is to evaluate the difference in serum potassium levels at different time points after treatment with SZC and patiromer compared to placebo, sodium polystyrene sulfonate or calcium polystyrene sulfonate. The rationale for using potassium binders is to reduce pre-HD serum potassium, allowing a mitigation of interdialytic potassium changes and reducing the risk of arrhythmia.

Furthermore, the safety needs to be evaluated among these potassium binders in this population, due to the different pharmacokinetics that improve them.

Methods

Design and registration

This systematic review protocol follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA-P) guidelines [8]. This review protocol will also be registered in the PROSPERO database.

Search strategy

We will perform systematic research in MEDLINE, EMBASE, and CINAHLE, looking for published randomized controlled trials (RCTs). Grey literature will be screened through Google Scholar, Scopus and ClinicalTrials.gov. Only RCTs will be included in the study.

We will search for papers in the English language, and we will include only European and American countries, to avoid heterogeneity in the population. Reference lists from eligible trials and related reviews will also be reviewed, in order to find additional potential eligible studies. Ongoing, unpublished trials or further data from published trials will be researched on ClinicalTrials.gov. Finally, where needed, we will contact the experts in the field.

Search details are summarized in Table 1.

MEDLINE 127
((Potassium binders) OR (lokelma) OR (sodium zirconium cyclosilicate) OR (Veltassa) OR (patiromer)) AND ((Placebo) OR (Kayexalate) OR (sodium polystyrene sulfonate) OR (sorbisterit) OR (calcium polystyrene sulfonate)) AND ((dialysis) OR (Hemodialysis) OR (peritoneal dialysis) OR (CKD) OR (Chronic Kidney Disease)) AND ((Potassium) OR (hyperkalemia)) 'Filters: Clinical Trial, Randomized Controlled Trial'
CINAHL 8
#1 Potassium Binders #2 Lokelma #3 Sodium zirconium cyclosilicate #4 Veltassa #5 Patiromer #6 Placebo #7 Kayexalate #8 Sodium polystyrene sulfonate #9 Sorbisterit #10 Calcium polystyrene sulfonate #11 Dialysis #12 hemodialysis #13 Peritoneal dialysis #14 CKD #15 Chronic Kidney Disease #16 Potassium #17 Hyperkalemia #18 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 #19 #11 OR #12 OR #13 OR # 14 OR #15 #20 # 16 OR #17 #21 #18 AND #19 AND #20 in Trials
EMBASE 87
(('Potassium binders/exp' OR 'lokelma' OR 'sodium zirconium cyclosilicate' OR 'Veltassa' OR 'patiromer') AND ('Placebo' OR 'Kayexalate' OR 'sodium polystyrene sulfonate' OR 'sorbisterit' OR 'calcium polystyrene sulfonate') AND ('dialysis'/exp OR 'hemodialysis'/exp OR 'peritoneal dialysis'/exp OR 'chronic kidney disease' OR 'CKD'/exp) AND ('potassium' OR 'hyperkalemia'/exp)) AND ('Clinical Trial' OR 'Randomized Controlled Trial')

Table 1. Search strategy PubMed and EMBASE.

Eligibility criteria

PICO strategy will be applied as follows:

– Population: we will compare the efficacy and the adverse effects in patients treated with SZC or patiromer. Eligible RCTs will consider subjects with chronic hemodialysis, without sex or age restriction. Exclusion criteria correspond to CKD in conservative treatment, acute hemodialysis, and oncological disorders.

– Intervention: SZC or Patiromer

– Comparator: placebo, sodium polystyrene sulfonate or calcium polystyrene sulfonate.

– Outcome: differences in serum potassium concentration, Adverse events (AEs), and mortality.

– Study design: Randomized clinical trials (RCTs)

Literature screening and study selection

The summary will be shown using the PRISMA flow diagram [9]. Duplicate will be removed.

Studies will be screened first by title and abstracts by two independent authors and any disagreement will be discussed with a third author. All abstracts will be screened using Rayyan software, whereas all full-text articles will be screened using the Mendeley software desktop.

Data extraction

Studies will be screened first by title and abstracts by two independent authors and any disagreement will be discussed with a third author with Rayyan software. Subsequently, the full texts of the selected studies will be read and assessed by two independent authors and any disagreement will be discussed with a third author. Reasons for the exclusion will be reported for each study. The selection process will be described through the PRISMA flow diagram.

The following data will be extracted through a standardized extraction Excel sheet by two independent authors:

1. General characteristics of the study (design, settings, sample size)
2. Participant characteristics: inclusion and exclusion criteria; number of participants screened and included; average age; comorbidities; sex; area of recruitment
3. Intervention characteristics: type and duration of the treatment and the follow-up
4. Adverse events: number of participants affected by adverse events, description of the adverse events and number of dropouts.

Missing data will be obtained by contacting the included studies' authors. We will send emails three times in three months.

We will include RCTs to allow a high-grade validity of this systematic review. If needed for insufficient data, we will include non-RCTs and observational studies.

Data items

Identification of the study: this will include the name of the journal, article DOI, article title, authors, publication year, short citation, and country.

Methods: study objectives, study design, inclusion and exclusion criteria, intervention, comparator characteristics, population details and results will be included.

For intervention and comparator will be specified type, dose, duration, frequency, and mode of administration.

For population, detail will be detailed mean age, sex, and number of participants. Results will describe summary statistics, effect estimates, confidence intervals, p-values, subgroup analyses, sensitivity analyses, risk of bias, and GRADE.

We plan to perform subgroup analyses based on age (< or > 18 years), hemodialysis or peritoneal dialysis, and a network analysis for different potassium binders will be performed.

Main findings: this will include patient characteristics and other relevant clinical outcome measures.

Methodological quality assessment

For the systematic review, the method of assessing the risk of bias or study quality, and for the data extraction will be structured as follows: studies will be screened first by title and abstracts by two independent authors and any disagreement will be discussed with a third author with Rayyan software.

Blinding: the study selection, data extraction, and risk of bias assessment will be performed without blinding the assessors to the study authors or the journal of publication.

Strategy for data synthesis: qualitative synthesis of the results based on risk of bias will be performed. If applicable, quantitative synthesis through a meta-analysis will follow. The risk of bias will be assessed independently by two authors, using the ROB 2.0 Tool for each outcome of interest.

Any disagreement will be discussed with a third reviewer. RobVis visualization tool will be used to create the RoB graph.

Meta-analysis

Primary analysis will compute serum potassium differences between SZC/Patiromer and placebo/sodium polystyrene sulfonate or calcium polystyrene sulfonate. Secondary analysis will consist on a network metanalysis comparing each potassium binder/placebo. All data will be analyzed with fixed-effect model or random-effect model based on the heterogeneity of the studies. Mean differences, and 95% confidence interval (CI), will be calculated for continuous outcomes. For dummy outcomes, the Odds Ratio (OR), computing 95% confidence interval (CI), will be computed. Data were pooled using the fixed-effects model and also analyzed with the random-effects method to guarantee the strength of the model. We plan to test for heterogeneity using the χ^2 statistic related to freedom degrees, with a P value of 0.05 used as the cut-off value to determine statistical significance. In addition, the degree of heterogeneity will be investigated by calculating the I^2 statistics. We will consider I^2 low if <25%, moderate if 25-50%, moderate-high if 50-75% and very high if >75%. In case of high heterogeneity, we will perform sensitivity analyses to explore sources of heterogeneity, such as study quality, year of publication, intervention or control variables, participants characteristics, and risk of bias. In addition, sub-group analyses will be conducted. We will use RevMan 5.4 software to perform the meta-analysis of all outcomes, and R4.4.0 software to perform the Network meta-analysis of all outcomes.

We will assess funnel plot asymmetry and the contour-enhanced funnel plot to explore publication bias. GRADE System will be used to evaluate the certainty of the evidence and to summarize the study conclusions.

Ethics

This is a systematic review that will use published data and does not require ethical approval, but each included study have to enrol patients after written consent and approval ethical code.

Status of the study and dissemination plan

We are starting the literature search, but the selection has not already started. We expect to complete the project and report it in 12 months. We will follow the updated PRISMA guideline to report the final paper and we will upload the progress on the PROSPERO website. Furthermore, we hope to publish a systematic review in a Nephrological journal.

Discussion

Serum potassium levels deviation from the normal range increases morbidity and mortality, both in conservative CKD [10, 11] and dialysis patients [12].

Considering that levels both lower or upper normal range are related to increased mortality and morbidity, hyperkalemia seems to significantly increase mortality and morbidity [5, 6]. This can be explained by the higher risk of arrhythmia in patients with rapid potassium intradialytic oscillations. About this, guaranteeing normal serum potassium on interdialytic days is needed to avoid rapid intradialytic oscillation [13].

The hyperkalemic effect of RAASIs can be physiologically explained, by a reduced urinary potassium excretion in the distal and collecting tubule, as well as by an increased potassium movement through the extracellular space [14].

It is well known that RAASIs are able to reduce fibrosis [15] and that they can reduce mortality and hospitalization [16], for this is needed to find a solution to manage hyperkalemia RAASIs-related.

Indeed, new potassium binders allow for better management of RAASI treatment in CKD patients, as well as reduced hypokalemia as an adverse effect compared to old potassium binders. For these reasons, an inclusive systematic review is needed to evaluate the efficacy and safety of each potassium binder.

Conclusion

This protocol deeply describes the methods and criteria used to perform a systematic review of the literature, including selection, extraction, biases evaluation, and synthesis of data from published RCTs evaluating the efficacy and safety of various potassium binders. We hope that this systematic review will increase the current knowledge and will hypothesize possible future research to overpass current gaps.

BIBLIOGRAFIA

1. Thomsen RW, Nicolaisen SK, Hasvold P, Sanchez RG, Pedersen L, Adelborg K, Egstrup K, Egfjord M, Sørensen HT. Elevated potassium levels in patients with chronic kidney disease: occurrence, risk factors and clinical outcomes-a Danish population-based cohort study. Nephrol Dial Transplant. 2018 Sep 1;33(9):1610-1620. https://doi.org/10.1093/ndt/gfx312. PMID: 29177463.
2. Vifor Pharma. Patiromer US Prescribing Information 2016.
3. PubChem. Sodium zirconium cyclosilicate. Available at: https://pubchem.ncbi.nlm.nih.gov/compound/91799284#section=Top (Accessed October 2019);
4. Stavros F, Yang A, Leon A, Nuttall M, Rasmussen HS. Characterization of structure and function of ZS-9, a K+ selective ion trap. PLoS One. 2014 Dec 22;9(12):e114686. https://doi.org/10.1371/journal.pone.0114686. PMID: 25531770; PMCID: PMC4273971.
5. Luo J, Brunelli SM, Jensen DE, Yang A. Association between Serum Potassium and Outcomes in Patients with Reduced Kidney Function. Clin J Am Soc Nephrol. 2016 Jan 7;11(1):90-100. doi: https://doi.org/10.2215/CJN.01730215. Epub 2015 Oct 23. PMID: 26500246; PMCID: PMC4702219.
6. Collins AJ, Pitt B, Reaven N, et al. Association of serum potassium with all-cause mortality in patients with and without heart failure, chronic kidney disease, and/or diabetes. Am J Nephrol. 2017;46:213–221. https://doi.org/10.1159/000479802.
7. Palmer BF, Carrero JJ, Clegg DJ, Colbert GB, et al. Clinical Management of Hyperkalemia. Mayo Clin Proc. 2021 Mar;96(3):744-762. https://doi.org/10.1016/j.mayocp.2020.06.014. Epub 2020 Nov 5. PMID: 33160639.
8. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4: 1. https://doi.org/10.1186/2046-4053-4-1.
9. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. The BMJ. 2021. https://doi.org/10.1136/bmj.n71.
10. Borrelli S, De Nicola L, Minutolo R, Conte G, Chiodini P, Cupisti A, Santoro D, Calabrese V, Giannese D, Garofalo C, Provenzano M, Bellizzi V, Apicella L, Piccoli GB, Torreggiani M, Di Iorio BR. Current Management of Hyperkalemia in Non-Dialysis CKD: Longitudinal Study of Patients Receiving Stable Nephrology Care. Nutrients. 2021 Mar 15;13(3):942. https://doi.org/10.3390/nu13030942. PMID: 33804015; PMCID: PMC8000881.
11. Calabrese V, Cernaro V, Battaglia V, Gembillo G, Longhitano E, Siligato R, Sposito G, Ferlazzo G, Santoro D. Correlation between Hyperkalemia and the Duration of Several Hospitalizations in Patients with Chronic Kidney Disease. J Clin Med. 2022 Jan 4;11(1):244. https://doi.org/10.3390/jcm11010244. PMID: 35011985; PMCID: PMC8746076.
12. Calabrese V, Tripepi GL, Santoro D. Impact of hyperkalemia in length of hospital stay in dialysis-dependent patients. Ther Apher Dial. 2022 Oct;26(5):1050-1051. https://doi.org/10.1111/1744-9987.13847. Epub 2022 Apr 11. PMID: 35366057.
13. Ferraro PM, Bolignano D, Aucella F, et al. Hyperkalemia excursions and risk of mortality and hospitalizations in hemodialysis patients: results from DOPPS-Italy. J Nephrol. 2022;35(2):707-709. https://doi.org/10.1007/s40620-021-01209-5.
14. Palmer BF, Clegg DJ. Physiology and Pathophysiology of Potassium Homeostasis: Core Curriculum 2019. Am J Kidney Dis. 2019 Nov;74(5):682-695. https://doi.org/10.1053/j.ajkd.2019.03.427. Epub 2019 Jun 19. Erratum in: Am J Kidney Dis. 2022 Nov;80(5):690. PMID: 31227226.
15. Koszegi S, Molnar A, Lenart L, et al. RAAS inhibitors directly reduce diabetes-induced renal fibrosis via growth factor inhibition. J Physiol. 2019;597(1):193-209. https://doi.org/10.1113/JP277002.
16. Beusekamp JC, Tromp J, Cleland JGF, et al. Hyperkalemia and Treatment With RAAS Inhibitors During Acute Heart Failure Hospitalizations and Their Association With Mortality. JACC Heart Fail. 2019;7(11):970-979. https://doi.org/10.1016/j.jchf.2019.07.010.