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Comparing the effect of sevelamer carbonate and sevelamer hydrochloride on plasma pH, bicarbonate and gastrointestinal complications in patients undergoing maintenance hemodialysis

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Abstract

Introduction: Regular dialysis, is not able to maintain phosphorus in the normal range. Therefore, using phosphate chelators to keep serum level of phosphorus in the normal range is essential. Sevelamer is a chelator for phosphate.

Objectives: The purpose of this investigation was to compare the therapeutic impact of sevelamer carbonate versus sevelamer hydrochloride on electrolytes and metabolic acidosis and gastrointestinal symptoms in a group of hemodialysis patients.

Patients and Methods: In this randomized clinical trial, patients were divided into two treatment groups; sevelamer carbonate and sevelamer hydrochloride. Sevelamer carbonate and sevelamer hydrochloride were prescribed as daily 800 mg tablets three times daily with their meals. Patients were evaluated for serum calcium, phosphorus, plasma bicarbonate and pH levels after one month.

Results: Around 44 patients were enrolled, of which 22 patients were treated with sevelamer hydrochloride and 22 patients in the intervention group with sevelamer carbonate. There was no significant difference between the effects of sevelamer carbonate and sevelamer hydrochloride on serum calcium and phosphorus levels at the end of the study ($P>0.05$). There was a significant difference between the effects of sevelamer carbonate versus sevelamer hydrochloride on plasma bicarbonate and pH levels ($P=0.036$ and $P=0.012$ respectively). In terms of gastrointestinal complications, two drugs did not differ significantly.

Conclusion: To prevent acidosis, along with increasing plasma bicarbonate and blood pH in patients undergoing hemodialysis, sevelamer carbonate is better than sevelamer hydrochloride. Therefore, the administration of sevelamer hydrochloride is preferable.

Trial Registration: The trial protocol was approved by the Iranian Registry of Clinical Trials (identifier: IRCT20141016019554N13, https://en.irct.ir/trial/28916, ethical code#IR.ZUMS.REC.1397.352).

Keywords: Sevelamer, ESRD, Metabolic acidosis, GFR, Hyperphosphatemia

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Introduction

According to the national institute of diabetes and digestive and kidney diseases, 1of 10 Americans has chronic kidney disease (CKD), in 2015. Kidney diseases are the 9th cause of death in the USA (1). End-stage renal disease (ESRD) is the terminal stage of CKD in which glomerular filtration rate declines to 15 ml/min. patients in ESRD stage almost need dialysis. ESRD has lots of complications but the most important are hypernatremia, hyperchloremia, hyperkalemia, hyperphosphatemia and hypocalcemia (2, 3).

Gastrointestinal disorders are one of the common complications in the general population that have a significant impact on quality of life (4). In patients undergoing dialysis, the occurrence of gastrointestinal symptoms due to several underlying conditions is more common and occurs in 32% to 85% of dialysis patients (5). Gastrointestinal symptoms in peritoneal dialysis patients usually include symptoms of gastroesophageal reflux, indigestion, and eating disorder (6), since gastrointestinal complications in hemodialysis patients mainly include constipation, abdominal pain, and diarrhea (7).

Metabolic disorders, especially metabolic acidosis, is a complication with major systemic effects in end-stage kidney diseases, which is associated with higher mortality (8). Hyperphosphatemia is another common complication in end stage kidney disease, which aggravates metabolic acidosis and affects the acid-base balance. Phosphate binders used to control hyperphosphatemia contribute to acid-base balance through their effects on serum phosphate too. Sevelamer hydrochloride is one of the agents in this category, which is associated with dose-dependent

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Implication for health policy/practice/research/ medical education

Controlling of electrolyte disturbances and gastrointestinal complications in patients with renal failure, especially in patients underlying dialysis is important for lowering the side effects and costs. Sevelamer is an agent that can prevent acidosis, along with increasing levels of bicarbonate and plasma pH in patients undergoing hemodialysis.

exacerbation of metabolic acidosis in patients with ESRD due to its hydrochloride content (9). This acidosis is improved by administration of sevelamer carbonate or other phosphate binders with alkaline content, such as calcium carbonate or lanthanum carbonate (10). However, the effect of phosphate binders on clinical outcomes, such as metabolic acidosis, has not been investigated (11). Sevelamer is a non-calcium chelator phosphate type and is free of aluminum composition. In comparison with lanthanum (which is a non-calcium chelator), sevelamer is cheaper, therefore in cases that phosphorus level is high (calcium × phosphorus > 55 mg^2/dL^2), it is the best phosphate binder to prevent the deposition of calcium in tissues, especially in the vessels.

Objectives

This study is aimed to compare the therapeutic effects of sevelamer carbonate versus sevelamer hydrochloride on some complications such as metabolic acidosis, hypocalcemia and hyperphosphatemia and its digestive side effects in patients undergoing hemodialysis.

Patients and Methods

Study design

In this randomized clinical trial, all participants have been informed by necessary information about the study and the methods. Patients were involved in the study with informed consent. We recruited two groups of ESRD patients which were undergone hemodialysis and allocated them equally between two groups of study.

Participants

Exclusion criteria were as follows:

1. Patients who have not taken phosphorus supplements.
2. Patients who lose their ability during the study.
3. Patients who are absent from dialysis session.
4. Patients who have crushed access.
5. Patients with a history of congestive heart failure (due to electrolyte imbalance).
6. Patients with chronic obstructive pulmonary disease (due to acid and base disorders).

Interventions

In the treatment group of sevelamer carbonate, 800 mg tablets of this drug were given triple daily with each meal and in the treatment group of sevelamer hydrochloride, 800 mg of tablets were administered triple daily with each meal. Patients received the drugs free of charge. Meanwhile, patients were assessed for complications during the study. If any complications in the intervention group were seen, the intervention terminated in the patient.

Randomization

Patients were divided into two groups of sevelamer carbonate and sevelamer hydrochloride by the random allocation based on randomization block, according to the variables such as age, gender, and duration of dialysis (Figure 1).

Statistical analysis

The data were analyzed using the *t* test, multivariate analysis of variance (MANOVA), Mann-Whitney U test, along with frequency distribution of tables and charts. Data were analyzed using SPSS software version 22. *P* value less than 0.05 was considered significant.

Results

The mean age in sevelamer carbonate and sevelamer hydrochloride groups was 58.29 ± 12.05 years and 58.5 ± 11.41 years, respectively. The mean duration of dialysis in the sevelamer carbonate and sevelamer hydrochloride groups was 3.93 ± 2.93 years and 3.82 ± 2.23 years, respectively. The number of men in both groups was 11 (50%) and women in both groups were 11 (50%).

Changes in calcium levels in the sevelamer carbonate versus sevelamer hydrochloride group were 0.85 ± 0.10 mg/dL ($P = 0.556$) and 1.49 ± 0.12 mg/dL ($P = 0.676$), which was not significant in both of the two groups. There was no significant difference between the effects of sevelamer carbonate versus sevelamer hydrochloride on serum calcium levels ($P = 0.147$). Changes in phosphorus levels in the sevelamer carbonate and sevelamer hydrochloride group were 1.72 ± 1.72 mg/dL ($P < 0.001$) and 1.88 ± 1.34 mg/dL ($P < 0.001$), respectively and these changes were significant in both groups. However, there was no significant difference between the effects of sevelamer carbonate and sevelamer hydrochloride groups on phosphorus concentration ($P = 0.935$).

The changes in the level of bicarbonate in the sevelamer carbonate and sevelamer hydrochloride group were 3.38 ± 14.55 mEq/L ($P = 0.267$) and 2.30 ± 1.85 mEq/L ($P = 0.001$), respectively, since the changes were significant in both groups. There was also a significant difference between the effects of sevelamer carbonate and evelamer hydrochloride on the plasma bicarbonate level ($P = 0.008$). Moreover, the changes in the plsma pH in the sevelamer carbonate and sevelamer hydrochloride group were 0.04 ± 0.04 ($P < 0.001$) and 0.03 ± 0.05 ($P < 0.001$) respectively, while these changes were significant in both groups. There was a significant difference between the effects of sevelamer carbonate and sevelamer hydrochloride groups on plasma pH value ($P = 0.012$).

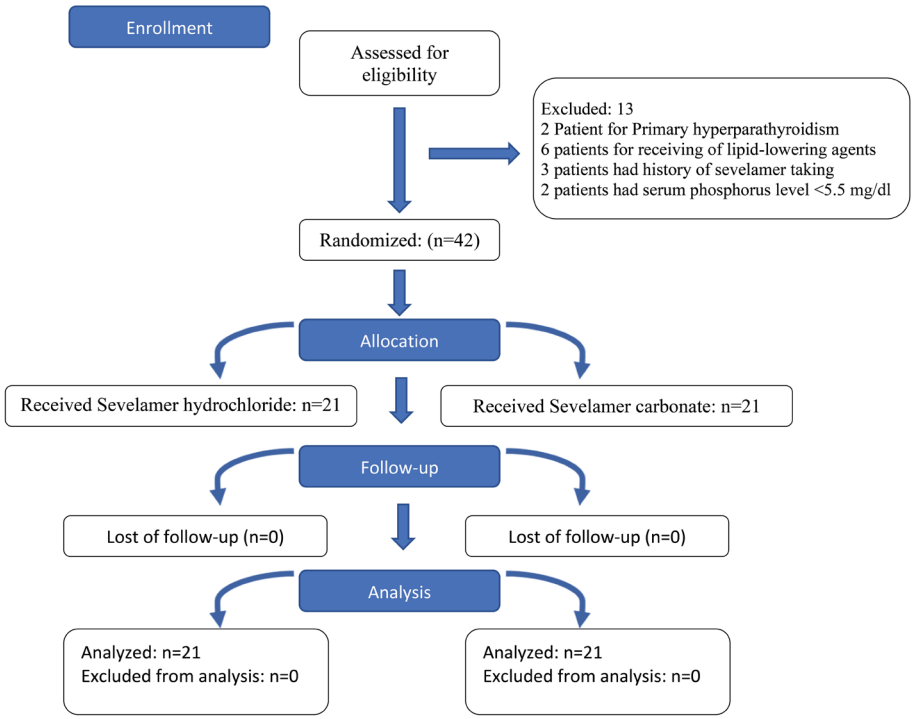

Figure 1. Consort diagram of the study.

Discussion

In a previous study, Phan et al concluded that hyperphosphatemia and the increment of serum intact parathyroid hormone was similar in sucroferric oxyhydroxide, lanthanum carbonate and sevelamer carbonate treated groups. Only sucroferric oxyhydroxide was associated with a significant reduction in fibroblast growth factor-23. In all three treatment groups, total serum calcium significantly increased after the intervention (12).

Previously, Zayed et al showed that administration of sevelamer hydrochloride in hemodialytic patients is beneficial for reducing the phosphorus level (13). In this study, we also showed that both sevelamer carbonate and sevelamer hydrochloride are equally efficient to significantly decrease the plasma phosphorus level.

Meanwhile, Yang et al indicated that, in comparison with sevelamer carbonate, sevelamer hydrochloride can significantly reduce blood bicarbonate levels (14). Moreover, Jokihaara et al, following of nine weeks of treatment with various drugs, including sevelamer hydrochloride, showed that sevelamer hydrochloride significantly reduced blood pH and lowered the bicarbonate level (15). In a review article by Pham et al showed that sevelamer hydrochloride can significantly reduce the level of blood bicarbonate too (16).

We also assessed the gastrointestinal side effects of both drugs, there were no significant differences between them. The power of our study is that there is not any similar study to ours regarding these two drugs, even these drugs have been studied seperately in hand finger count numbers.

Conclusion

Our study showed, sevelamer carbonate would be the better choice for modulating bicarbonate level and blood pH in hemodialytic patients. However, there is no privilege for none of them in tunning the serum calcium and phosphorus blood level.

Limitations of the study

We suggest to conduct larger and multi-centric clinical trials with a longer follow-up period to obtain more accurate results. The low sample size was the mail limitation of our study which lowered the power of the analysis of results based on age, gender and other underlying factors.

Authors' contribution

BH, were the principal investigators of the study including conceptualization, validation, investigation, resources, supervision, project administration and funding acquisition. BF was included in data curation and writing (original draft preparation). BH was included in methodology and formal analysis. All authors participated in preparing the final draft of the manuscript, review and editing.

Conflicts of interest

The authors declare that they have no competing interests. This study is a part of a large investigation on sevelamer, which a part of it was published as the M.D., thesis of Milad Almasi previously (17). The data presented here has not overlap data with previous publication, since this paper addressed other features of sevelamer therapy in hemodialysis. Additionally, patients received the drugs free of charge. The authors had not any relation with the company which distributing the drugs and the drugs were purchased directly from the market.

Ethical issues

The research followed the tents of the Declaration of Helsinki. This study was conducted by approval of the Research Council of Zanjan University of Medical Sciences with the design code A-11-969-7 and the approval of the ethics committee of Zanjan University of Medical Sciences (Ethical code#IR.ZUMS.REC.1397.352). The study protocol was also registered in the Iranian Registry of Clinical Trials (identifier# IRCT20141016019554N13, https://en.irct.ir/trial/28916). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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