The safety and efficiency of low-dose mineralocorticoid receptor antagonists in dialysis patients: a meta-analysis

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Abstract

Background: Our aim was to evaluate the safety and efficacy of low-dose mineralocorticoid receptor antagonists (MRAs) in dialysis patients.

Methods: We systematically searched PubMed, EMBASE, and Cochrane libraries for clinical trials on the use of MRAs in dialysis patients. Review Manager 5.3 software was used to analyze relevant data and evaluate the quality of evidence.

Results: We identified nine randomized controlled trials including 1128 chronic dialysis patients. In terms of safety, when hyperkalemia was defined as serum potassium level ≥ 5.5 mmol/L, low-dose MRAs were significantly associated with hyperkalemia (relative risk [RR] 1.76, 95% CI 1.07–2.89, $P = 0.02$); however, when hyperkalemia was defined as serum potassium level ≥ 6.0 mmol/L or serum potassium level ≥ 6.5 mmol/L, no significant association was observed between low-dose MRAs and hyperkalemia (RR 1.40, 95% CI 0.83–2.37, $P = 0.20$; RR 1.98, 95% CI 0.91–4.30, $P = 0.09$, respectively). Use of low-dose MRAs can reduce CV mortality by 57% compared with the control group (RR 0.43, 95% CI 0.25–0.75, $P = 0.003$). Similarly, the RR of all-cause mortality for the low-dose MRAs group was 0.44 (95% CI 0.28–0.68, $P = 0.0003$).

Conclusion: Low-dose MRAs may benefit dialysis patients without significantly increasing moderate to severe hyperkalemia.

Background

Cardiovascular disease (CVD) in chronic dialysis patients has long been a question of great interest worldwide. In some large-scale observational studies, the prevalence of CVD in patients with end-stage renal disease is approximately 80% [1, 2]. Meanwhile, CVD (such as heart failure, myocardial infarction, and sudden cardiac death) is the main cause of death in patients with end-stage renal disease (ESRD) [3], accounting for 45% of the total deaths [4].

The renin–angiotensin–aldosterone system (RAAS) is an important driver of the development and progression of hypertension, diabetes, CVD, and kidney disease. Currently, drugs that act on RAAS, such as ACEI/ARB, have been widely used in these diseases.

There is evidence that excessive activation of aldosterone, the final product of RAAS, plays a crucial role in regulating fluid retention, inflammation, oxidative stress, and fibrosis [5, 6]. Thus, the mineralocorticoid receptor antagonists (MRAs, such as spironolactone, eplerenone) have a significant effect on the treatment of hypertension, edema, and improvement of target organ fibrosis. In patients with left ventricular systolic dysfunction and heart failure (HF), MRAs can significantly reduce morbidity and mortality [7]. However, because of MRAs' serious side effects of hyperkalemia, there is very little published research about patients with ESRD. And in clinical settings, MRAs are usually prohibited in ESRD patients. Although some studies have shown that additional use of spironolactone in dialysis patients is beneficial both on LVMI [8] and CV morbidity [9, 10], its use in dialysis patients is still limited by hyperkalemia. Results from earlier RCTs [8, 10, 11] did not demonstrate a strong association between MRAs and hyperkalemia. Recently, a large US data analysis showed that MRAs are little used in ESRD patients with HF and were associated with a higher risk of death [12]. To date, there has been little agreement on whether it is safe for dialysis patients to use MRAs. It is worth mentioning that the risk of hyperkalemia caused by

MRAs is often related to its dose. Therefore, we performed an analysis on low-dose MRAs to assess their risk of hyperkalemia and the value of cardiovascular benefits.

Methods

1. Inclusion criteria

1) Type of study: randomized controlled trial (RCT); 2) study subjects: (a) more than 18 years old; (b) receiving maintenance dialysis, including hemodialysis and peritoneal dialysis; (c) receiving low-dose MRA, including spironolactone 25 mg/d or spironolactone 50 mg*3/week or eplerenone 50 mg/d.

2. Exclusion criteria

1) Follow-up time was less than 3 months; (2) seriously lost to follow-up and without clear explanation; (3) study did not provide sufficient data; (4) full text could not be obtained.

3. Search strategy

We first searched the electronic databases PubMed, EMBASE, and The Cochrane Library for studies published up to May 2019. No restrictions were imposed on the publication language for articles.

4. Study selection

The selection of the study was done independently by two reviewers. Irrelevant researches were removed by browsing the titles, abstracts, and full texts based on inclusion criteria and exclusion criteria. If there were disagreement between two reviewers, we reached consensus through discussion or consultation with experts.

5. Data extraction

Data from the included studies was independently extracted by two reviewers according to a predesigned form. Disagreements were resolved by discussion or consensus. We extracted the first author's name, publication year, design type, follow-up time, enrolled subject characteristics, and safety outcomes: the incidence of serious hyperkalemia (≥ 5.5 mmol/L, ≥ 6.0 mmol/L, or ≥ 6.5 mmol/L), cardio- and cerebrovascular mortality (CCV), all-cause mortality, and incidence of breast enlargement or tenderness.

6. Quality assessment

The quality of each RCT was assessed by two reviewers via the Cochrane risk-of-bias tool.

7. Statistical analysis

Analysis was performed on Review Manager software (RevMan 5.3) provided by the Cochrane website. As dichotomous variables, the incidence of hyperkalemia, severe hypertension, breast enlargement or tenderness, CCV mortality, all-cause mortality, were all assessed by relative risk (RR) with 95% CI. The I^2 statistic was used to evaluate the statistical heterogeneity [13]. According to the Cochrane Handbook, 0% to 40% might not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity, and 75% to 100% may represent considerable heterogeneity. When $I^2 < 50\%$, fixed-effect models were used, and when $I^2 \geq 50\%$, random-effects models were used.

Results

1. Study selection

We searched 1667 articles in total, and the flowchart of the selection is shown in Figure 1.

2. Characteristics and quality assessment

According to the inclusion and exclusion criteria, nine studies were eventually included, a total of 1128 subjects (554 were included in the low-dose MRAs group and 574 were included in the control group). The characteristics of each study are shown in Table 1.

Cochrane's risk-of-bias tool was used to evaluate the risk of bias in each article. The evaluation result of the risk of bias is shown in Figure 2. Overall, the included articles have a relatively low risk of bias. However, two of these articles used an open-label design and had a high rate of loss of follow-up [9, 14].

3. Hyperkalemia

The baseline potassium level of each study is shown in Table 1. The definition of hyperkalemia varies in different studies. The study by Vukusich et al. was excluded because no hyperkalemia was reported [15]. As described above, in order to unify the criteria, we defined hyperkalemia a priori as serum potassium level ≥ 5.5 mmol/L, ≥ 6.0 mmol/L, or ≥ 6.5 mmol/L. When hyperkalemia was defined as serum potassium level ≥ 5.5 mmol/L, low-dose MRAs were significantly associated with hyperkalemia (RR 1.54, 95% CI 1.05–2.26, $P = 0.03$; Fig. 3); when hyperkalemia was defined as serum potassium level ≥ 6.0 mmol/L or serum potassium level ≥ 6.5 mmol/L, no significant association was observed between low-dose MRAs and hyperkalemia (RR 1.29, 95% CI 0.87–1.91, $P = 0.21$, Fig. 4; RR 1.85, 95% CI 0.90–3.80, $P = 0.09$, Fig. 5, respectively). No significant heterogeneity was observed in any of these models ($I^2 = 32\%$, $P = 0.18$; $I^2 = 0\%$, $P = 0.46$; $I^2 = 23\%$, $P = 0.26$, respectively).

4. CV mortality and all-cause mortality

A total of 986 subjects from seven studies were included in the analysis; 19 of the 481 subjects in the experimental groups and 44 of the 505 subjects in the control groups died of a cardiovascular-related cause. Use of low-dose MRAs can reduce CV mortality by 54% compared with control (RR 0.46, 95% CI 0.28–0.76, $P = 0.003$; Fig. 6). No significant heterogeneity was observed ($I^2 = 0\%$, $P = 0.51$). The RR of all-cause mortality for low-dose MRAs was 0.48 (95% CI 0.33–0.72, $P = 0.0003$; Fig. 7). There was no significant heterogeneity for all-cause mortality ($I^2 = 0\%$, $P = 0.43$).

5. Breast enlargement or tenderness

During the follow-up, 37 people in the experimental groups experienced breast enlargement or tenderness compared with four people in the control group. The RR of breast enlargement or tenderness for low-dose MRAs was 6.74 (95% CI 2.86–15.90, $P < 0.0001$; Fig. 8).

Discussion

MRAs play an important role in chronic HF, especially in patients with left ventricular function changes and HF after myocardial infarction. In terms of kidney disease, MRAs also play a critical role, such as preventing the transition from acute kidney injury to chronic kidney disease [16, 17], protecting against diabetic nephropathy [18], and

delaying the progression of glomerulonephritis [19]. The underlying mechanism by which MRAs work may be by reduction of oxidative stress [20], reduction of inflammation [21], regulation of vascular tone [22], or antifibrosis [23].

Although MRAs thus have their cardiovascular and renal benefits, their adoption in ESRD is still stalled, mainly because of severe hyperkalemia. Prior studies have noted the problem of hyperkalemia in ESRD patients treated with MRA. A meta-analysis by Quach et al. of nine trials published up to 2015, which enrolled a total of 829 patients, found the RR for hyperkalemia among patients in dialysis for MRA treatment was 3.05 (95% CI, 1.21–7.70) [24]. More recently, the randomized, placebo-controlled, multiple-dosage trial by Raj et al. found that low doses of spironolactone did not increase the risk of hyperkalemia, but when the dose of spironolactone reached 50 mg, the risk of hyperkalemia was significantly higher during the 36-week follow-up [25]. Another important finding, from the placebo-controlled, parallel-group trial by Hammer et al., was that 50 mg spironolactone increased the frequency of moderate hyperkalemia (155 vs. 80 events, $P = 0.034$), but not that of severe hyperkalemia [26]. On the question of hyperkalemia, we define serum potassium level ≥ 5.5 mmol/L as mild hyperkalemia, serum potassium level ≥ 6.0 mmol/L as moderate hyperkalemia, serum potassium level ≥ 6.5 mmol/L as severe hyperkalemia respectively; Surprisingly, we found that low-dose MRAs increased the risk of mild hyperkalemia (RR 1.54, 95% CI 1.05–2.26, $P = 0.03$); however, it did not increase the risk of moderate to severe hyperkalemia. This observation supports the hypothesis that low-dose MRAs use may be safe because they did not increase the risk of moderate to severe hyperkalemia. However, close monitoring of serum potassium levels is required.

A prior meta-analysis [24] has noted the importance of improvements in CV mortality and all-cause mortality. The RR for CV mortality among patients in dialysis for MRA treatment was 0.34 (95% CI, 0.15–0.75), and for all-cause mortality was 0.40 (95% CI, 0.23–0.69). Consistent with the literature, our research found that participants who reported using low-dose MRAs also had similar results. Our findings suggest that low-dose MRAs may bring survival benefits.

In addition, we also found that the incidence of breast enlargement or tenderness in patients taking spironolactone was 12%. This finding supports evidence from clinical observations of the Randomized Aldactone Evaluation Study (RALES) [27] that gynecomastia or breast tenderness was found in 10% of men who were treated with spironolactone.

The ongoing ACHIEVE RCT (NCT03020303) is planning to recruit 2750 participants and have a mean follow-up of 5 years. The primary outcome is death or hospitalization for HF. Meanwhile, the ALCHEMIST RCT (NCT01848639) is planning to recruit 825 high-risk chronic hemodialysis patients and have a mean follow-up of 2 years to determine if spironolactone (25 mg) reduces death or hospitalization for HF and is well tolerated in patients that require dialysis. These two large, well-designed trials may change medical behavior and improve patient outcomes upon completion.

Several limitations to this meta-analysis need to be acknowledged. First, there were differences in baseline potassium levels of the included studies. Barrera suggests in the latest review that when we analyze blood potassium, it is best to set the threshold of baseline serum potassium levels, clarify the definition of hyperkalemia, and explain the predefined procedures to be used in case of hyperkalemia [28]. Second, the follow-up time is not long enough for survival research. Of the nine studies included, two trials were followed up for 3 months [11, 29], two trials for 6 months [8, 30], one trial for 9 months [25], three trials for 24 months [10, 14, 15], and one trial for 36

months [9]. Third, an excessive number of people lost to follow-up may have an impact on results. In the trials of Matsumoto [9] and Ito [14], the rates of loss to follow-up were 32% and 22%, respectively.

Conclusion

This study has shown that low-dose MRA did not cause moderate to severe hyperkalemia but may bring survival benefits. In general, therefore, it seems that low-dose MRA with strict serum potassium testing may benefit patients. Large RCTs could provide more definitive evidence. In addition, side effects such as breast enlargement or tenderness caused by low-dose spironolactone require more attention.

Abbreviations

ESRD: end-stage renal disease; MRAs: mineralocorticoid receptor antagonists; CVD: Cardiovascular diseases; CV: Cardiovascular; HD: hemodialysis; PD: peritoneal dialysis; RR: relative risk; CI: confidence intervals; HF: heart failure.

Declarations

Competing Interests

The author(s) declared that there were no potential conflicts of interest in this article.

Consent to publish

Not applicable.

Ethical approval and consent to participate

Not applicable.

Authors' contributions

Yifan Zhu, Yueming Liu and Qiang He collaborated on research idea, study design, and study selection. All authors had access to the data and a role in writing the manuscript.

Availability of data and materials

All datasets analyzed in this systematic review are referenced in the manuscript and its Additional files.

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Table 1

Table 1. Characteristics of included trials

Study	Type	Follow-up (months)	Intervention	Control	Sample size (I/C)	Age (year)	Sex (male, %)	Potassium ^a
Feniman2015[31]	HD	6	25 mg/d spironolactone	placebo	I:10 9	I:52±19.2 56±10.9	I:50 55.6	I: 4.5 ± 0.9 5.0 ± 0.9
Ito2014[14]	PD	24	25 mg/d spironolactone	None	I:78 80	I:57.4±12.3 55.6±14.4	I:70.5 72.5	I: 4.3±0.66 4.3±0.65
Lin2016[10]	HD/PD	24	25 mg/d spironolactone	placebo	I:125 128	I:70.3±10.9 70.6±8.4	I:58.4 62.5	I: 4.12±0.42 3.96±0.51
Matsumoto2014[9]	HD	36	25 mg/d spironolactone	None	I:157 152	I:67.4±12.3 67.7±11.2	I:72 59.2	I:5.16 -
Ni2014[11]	HD/PD	3	25 mg/d spironolactone	placebo	I:40 36	I:55.7±12.3 54.9±14.2	I:60 50.8	I: 4.1±1.5 3.9±0.9
Raj2018[25]	HD	9	12.5/25/50 mg/d spironolactone	placebo	I:26 51	I:53.3±13.5 56.8±11.5	I:73.1 62.7	I: 4.8 ±0.6 4.8 ±0.6
Taheri2009[30]	HD	6	Spironolactone 25mg*3/w	placebo	I:8 8	I: 59.5±6.5 56.8±9.3	I:63 75	I:3.86±0.33 4.66 ±0.41
Vukusich2010[15]	HD	24	Spironolactone 50mg*3/w	placebo	I:33 33	I: 60.1±5.2 55.6±3.6	I:61 66.7	I: 4.7 ±0.87 4.71±0.74
Walsh2015[29]	HD	3	Eplerenone 50mg/d	placebo	I:77 77	I:62.1±14.6 63.1±13.7	I:61 63.6	I: 4.7±0.6 4.9±0.6

Abbreviations: *HD*, hemodialysis; *PD*, p peritoneal dialysis; -: missing data

^a Baseline serum potassium level

Figures

Figure 1

Study selection process

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Feniman2015	?	?	+	+	+	+	-
Ito2014	+	-	?	+	?	+	+
Lin2016	+	+	+	+	+	+	+
Matsumoto2014	?	?	?	?	?	+	+
NI2014	?	?	+	+	+	+	+
Raj2018	+	+	+	+	+	+	+
Taheri2009	?	?	+	+	+	+	-
Vukusich2010	?	?	+	+	+	+	+
Walsh2015	+	+	?	+	+	+	+

Figure 2

Quality of included studies

Figure 3

Forest plot for hyperkalemia (≥ 5.5 mmol/L)

Figure 4

Forest plot for hyperkalemia (≥ 6.0 mmol/L)

Figure 5

Forest plot for hyperkalemia (≥ 6.5 mmol/L)

Figure 6

Forest plot for CCV mortality

Figure 7

Forest plot for all-cause mortality

Figure 8

Forest plot for breast enlargement or tenderness

Supplementary Files

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