Incidence and determinants of hyperkalemia among heart failure patients who used spironolactone

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Research Article

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Abstract

Background

Potassium balance in heart failure is affected by many factors including neurohormonal mechanisms and drugs used in its management. Renin–angiotensin–aldosterone system inhibitor therapies are part of heart failure therapy and have been associated with increase the risk of hyperkalemia. Currently, there are limited data on the prevalence and risk factors of hyperkalemia in heart failure patients who received spironolactone as an add-on to standard therapy which include Angiotensin-Converting Enzyme Inhibitors (ACEIs) or Angiotensin II receptor blockers (ARBs). The objective of this study is to identify Incidence and determine of hyperkalemia risk factors among heart failure patients who have been using spironolactone.

Methods

This is a retrospective chart review, from March 1, 2016 to March 31, 2019 conducted at King Abdulaziz Medical City-Riyadh. All heart failure patients with age more than 18 year who are using spironolactone were included and we excluded if they had any of the following criteria: (1) end stage renal disease on dialysis; (2) cancer; (3) history of hyperkalemia. A data collection sheet was used to collect demographics (e.g., age, gender, weight, ejection fraction, and baseline potassium), comorbidities (e.g., chronic kidney disease, and diabetes), visit history (dose of spironolactone, hyperkalemia incidence, time to the event, medication that was patient on include (ACEI, ARB, digoxin, furosemide, beta-blockers, and potassium supplements), average potassium level, average creatinine, and average BNP). An Excel-based tool (Microsoft® Excel; Version 2018) was used for systematic data sampling and analysis. The study was approved by Institutional Review Board.

Results

A total of 349 patients met the inclusion criteria. 43% of patients were men while 57% were women. The mean age of patients was 64.87 ± 14.02 years. The mean baseline of potassium before start spironolactone were 4.34 ± 3.45 mmol/L. Hyperkalemia were assessed with different dose of spironolactone (12.5 mg, 25 mg, 50 mg). 161 patients were received 12.5 mg spironolactone, 40% of those patients who had incidence of hyperkalemia. 62% of those who developed hyperkalemia were on ACEI, 28% on ARB, 14% on potassium supplements. 263 patients were received 25 mg spironolactone, 47% of patients had incidence of hyperkalemia. 49% of those who developed hyperkalemia were on ACEI, 31% on ARB, and 22% on potassium supplements. 17 patients were received 50 mg spironolactone, 53% of patients had incidence of hyperkalemia. 44% of those who developed hyperkalemia were on ACEI, 22% on ARB, and 22% on potassium supplements.

Conclusion

Our study showed that half of heart failure patients who used spironolactone developed hyperkalemia. The majority of patients who developed hyperkalemia were either on ACEIs or ARBs. Spironolactone dosing of 50 mg was associated with highest incidence of hyperkalemia. Further study with a larger sample size is required to clarify and confirm our study findings.

Introduction

Heart failure (HF) is one of the major cardiovascular disease. It is a leading cause of morbidity and mortality worldwide [1, 2]. Heart failure is associated with many serious clinical outcomes including atrial fibrillation, stroke, peripheral embolism, pulmonary embolism, hepatic dysfunction, pulmonary congestion and kidney failure. Disturbances in the potassium homeostasis are common among patients with heart failure (HF) and has been associated with unfavorable clinical outcomes [3, 4]. Potassium balance in heart failure is affected by the neurohormonal mechanisms and through the drugs that are used in its treatment [6, 7]. Patients with HF have a high prevalence of chronic kidney disease, which increases the risk of hyperkalemia [5, 21].

Spironolactone is mineralocorticoid receptor antagonist (MRA) and belongs to a class of medications known as potassium-sparing diuretics. It competitively blocks the binding of aldosterone to its cytoplasmic receptor and so increase the Na and decrease the electrically coupled K secretion [8, 9]. The most common side effects for spironolactone are gynecomastia, GI upset and hyperkalemia [10, 22, 23]. Hyperkalemia is a potentially life-threatening condition and defined as a serum potassium level more than 5 mmol/L [11, 12].

RALES trial is a landmark study supported the use of spironolactone in heart failure patients. This trial included severe heart failure patients with ejection fraction less than 35% and found that adding spironolactone to standard therapy reduced morbidity and mortality in those patients. According to American Heart Association guideline, spironolactone is recommended in patients with NYHA class II-IV with left ventricular ejection fraction (LVEF) of 35% or less and in patients after a myocardial infarction (MI) when they have an LVEF less than 40% with symptoms of HF or an LVEF less than 40% and DM [13, 14, 15].

A population-based time-series analysis has indicated that the publication of RALES trial was associated with abrupt increases in the rate of prescriptions for spironolactone and in hyperkalemia-associated morbidity and mortality [16]. Among patients with preserved ejection fraction included in TOPCAT trial, the risk of hyperkalemia associated with used of spironolactone and ACE inhibitor/ARB was 4-fold higher than placebo [17]. Furthermore, a cohort study has been done in Brazil to evaluate the risk of

hyperkalemia among heart failure patients who used angiotensin converting enzyme inhibitors (ACEIs) with or without spironolactone and they found that spironolactone group has been associated with increase the incidence of hyperkalemia [18]. A retrospective study of 125 congestive heart failure (CHF) patients showed that 30 patients developed hyperkalemia. They identified that kidney function, diabetes mellitus (DM) and heart failure medications are independent risk factors for hyperkalemia [19]. Nested case control study in Germany for HF patients who were receiving ACE or ARB in combined with spironolactone were significantly associated with increase with risk of hyperkalemia especially with age ≥70 year [20].

Currently, there are limited data on the incidence and risk factors of hyperkalemia in heart failure patients who received spironolactone as an add-on to standard therapy which include ACEIs or Angiotensin II receptor blockers (ARBs). We aimed in this study, to identify Incidence and determine of hyperkalemia risk factors among heart failure patients who have been using spironolactone.

Methods

Study design

This retrospective chart review study was carried out in King Abdulaziz Medical City (KAMC), Riyadh, Saudi Arabia from March 1, 2016 to March 31, 2019. The Medical city contains a Cardiac Center that provide patient care for heart failure. Health electronic system (Bestcare) was used to identify. All known cases of heart failure which required treatment with spironolactone, patients of both sex, and age ≥18 years were included in the study.Patient was excluded if any of the following criteria was found: (i) chronic kidney disease that requires dialysis; (ii) cancer or (iii) history of hyperkalemia (defined as if the last two readings were > 5 before start on spironolactone).

Data Collection

The data required for present study was noted down from the patients' charts in a data collection form using Excel sheet. Extracted information included demographic data (age,gender, weight ejection fraction, and baseline potassium levels), patient's comorbidities, dose of spironolactone, hyperkalemia incidence(s) if any, time to the first event, other medications (ACEI, ARB, digoxin, furosemide, beta-blockers, and potassium supplements), average potassium level, average creatinine, and average BNP).

Statistical analysis

An Excel-based tool (Microsoft® Excel; Version 2018) was used for systematic data sampling and analysis. Descriptive statistics (i.e., means and frequencies) were generated to present patients' demographic characteristics, clinical variables, study outcomes, and other variables. The study results were summarized using mean and standard deviation (SD), and percentages and proportions were used for categorical variables. The study was approved by the Ethical Review Board at King Abdullah International Medical Research Center (KAIMRC), Riyadh, Saudi Arabia. Informed consent was waived since there is no interaction with patients.

Results

A total of 429 patients records were reviewed. Of these patients, 80 subjects were excluded if at least one of the following criteria was encountered: any form of cancer, a history of hyperkalemia, hemodialysis, or lack of data. 101 patients met the inclusion criteria of this study and were included in the statistical analyses. Table 1 describes the baseline characteristics of included patients. The mean age was 64.87 ± 14.02 years, and 57% were men. The mean of the baseline potassium level before starting spironolactone was 4.34 ± 3.45 mmol/L. 75% of included patients had EF level lower than 40%. 23% of patients have CKD while 69% with DM.

Table 1. Baseline characteristics of included patients. (n = 349 patients)

Variable	*n* (%)
Age (mean ± SD)	64.87 years ±14.02
> 65 years old	194 (56)
< 65 years old	155 (44)
Weight (mean ± SD)	79.72 kg ± 19.68
Sex	
Female	148 (43)
Male	201 (57)
K baseline (mean ± SD)	4.15 ± 0.5
Type of heart failure	
EF ≥ 40%	87 (25)
EF < 40%	260 (74)
10-20%	22 (8)
20-30%	176 (68)
30-40%	61 (23)
Comorbidities	
CKD	82 (23)
DM	239 (69)

K: Potassium; EF: ejection fraction; CKD: Chronic Kidney Disease; DM: Diabetes Mellitus

A total of 164 incidences were recorded during the follow-up period. 60% of the incidences were among senior patients (65 years old or more) and 56% were male.

Table 2. at least one incidence of hyperkalemia* during the follow-up period. n (%)

164 (47)	
≥ 65 years old	99 (60)
< 65 years old	65 (40)
Female	72 (44)
Male	92 (56)

* hyperkalemia is defined as a serum potassium level > 5 mmol/L

We were looking at different doses of spironolactone (12.5 mg, 25 mg, and 50 mg). 40% of patients who received 12.5 mg spironolactone developed hyperkalemia. 62% of those patients were on ACEI, 28% on ARB and 14% on potassium supplements. 263 patients were received 25 mg spironolactone, 47% of patients had incidence of hyperkalemia. 49% of those who developed hyperkalemia were on ACEI, 31% on ARB, and 22% on potassium supplements. 17 patients were received 50 mg spironolactone, 53% of patients had incidence of hyperkalemia. 44% of those who developed hyperkalemia were on ACEI, 22% on ARB, and 22% on potassium supplements. (Table 3).

Table 3. Incidence of hyperkalaemia among included patients who received 12.5 mg, 25 mg, 50 mg of spironolactone during the follow-up period

	12.5 mg (n = 161)	25 mg (n = 263)	50 mg (n =17)
Incidence hyperkalemia no. (%)	65 (40)	124 (47)	9 (53)
Medications	Patients no. (%)		
ACEI	40 (62)	61 (49)	4 (44)
ARBs	18 (28)	38 (31)	2 (22)
Furosemide	65 (100)	117 (94)	9 (100)
Digoxin	7 (11)	22 (18)	0
Beta blockers	63 (97)	108 (87)	9 (100)
K supplements	9 (14)	27 (22)	9 (53)

Discussion

Potassium imbalance in heart failure is affected by many factors including neurohormonal mechanisms and medications used in its management and has been associated with unfavorable clinical outcomes [3, 4, 6, 7]. Several studies have been shown that spironolactone utilization in HF patients has been associated with increase the risk of hyperkalemia, specifically when ACEI/ARB is coadministered or other risk factors are present [16, 17, 18]. A limited evidence was found in the literature on assessing the risk of hyperkalemia with concomitant use of ACE inhibitor/ARB and spironolactone therapy in HF patients. Despite the previous studies, much uncertainty still exists about the risk of hyperkalemia associated with spironolactone use in patients with heart failure [23]. Therefore, the objective of this study is to identify the incidence and determine of hyperkalemia risk factors among heart failure patients who have been using spironolactone.

An initial objective of the study was to identify the incidence of hyperkalemia among HF patients who have been using spironolactone. The present study found that 164 patients (53 %) had incidence of hyperkalemia. This result is consistent with data obtained in previous studies that the incidence is increased with using spironolactone [17, 18]. Another important finding showed that 60% of the incidence were among senior patients (65 years old or more) which indicate that is advancing in age was associated with increase the risk of hyperkalemia incidence which is consistent with Juurlink study finding [15]. Another important finding that the majority of patients who had hyperkalemia were either on

ACEi or ARBs which is consistent with previous study finding [19]. Moreover, the present study was designed to look at different doses of spironolactone and the rate of hyperkalemia incidence. The study showed that the incidence rate of hyperkalemia was increasing with increased the dose of spironolactone. The highest incidence rate was associated with spironolactone 50 mg. however, only 9 patients were receiving this dose.

Several limitations of our study should be noted. First, it's retrospective design and reliance on medical record documentation for data collection, and it was done in single setting. Moreover, the study has a small sample size which may limit the generalizability of the findings to Saudi patients.

Conclusion

Our study showed that half of heart failure patients who used spironolactone developed hyperkalemia. The majority of patients who developed hyperkalemia were either on ACEIs or ARBs. Spironolactone dosing of 50 mg was associated with highest incidence of hyperkalemia. Further study with a larger sample size is required to clarify and confirm our study findings.

Declarations

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Declaration of conflicting interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article

Ethics approval

The study was approved by the Institutional Review Board (IRB) of King Abdullah International Medical Research Canter (KAIMRC), National Guard Health Affairs, Riyadh, Saudi Arabia, in February 2019. The informed consent was waived due to minimal risk associated with design of retrospective studies.

Consent to participate

Not applicable

Availability of data and material

The data used to support the finding of this study are restricted by the KAIMRC in order to protect patient privacy. Data are available from KAIMRC for researchers who meet the criteria for access to confidential data.

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Author contributions

MN, AA, ZQ and MM have written the paper; MM has supervised the research; ZQ and MN have analyzed and interpreted the data; MN and AA has worked on data collection.

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Abbreviations

HF	Heart Failure
MRA	Mineralocorticoid Receptor Antagonist
NYHA	New York Heart Association
DM	Diabetes Mellitus
ACEI	Angiotensin-Converting Enzyme Inhibitors
ARB	Angiotensin II Receptor Blocker
CHF	Congestive Heart Failure
CKD	Chronic Kidney Disease