ISSN 1738-5997 (Print)
ISSN 2092-9935 (Online)

Electrolyte & Blood Pressure Vol. 22, No. 1, June 2024 Page 1–20, 2024

Electrolytes & Blood Pressure

Vol. 22, No. 1, June 2024

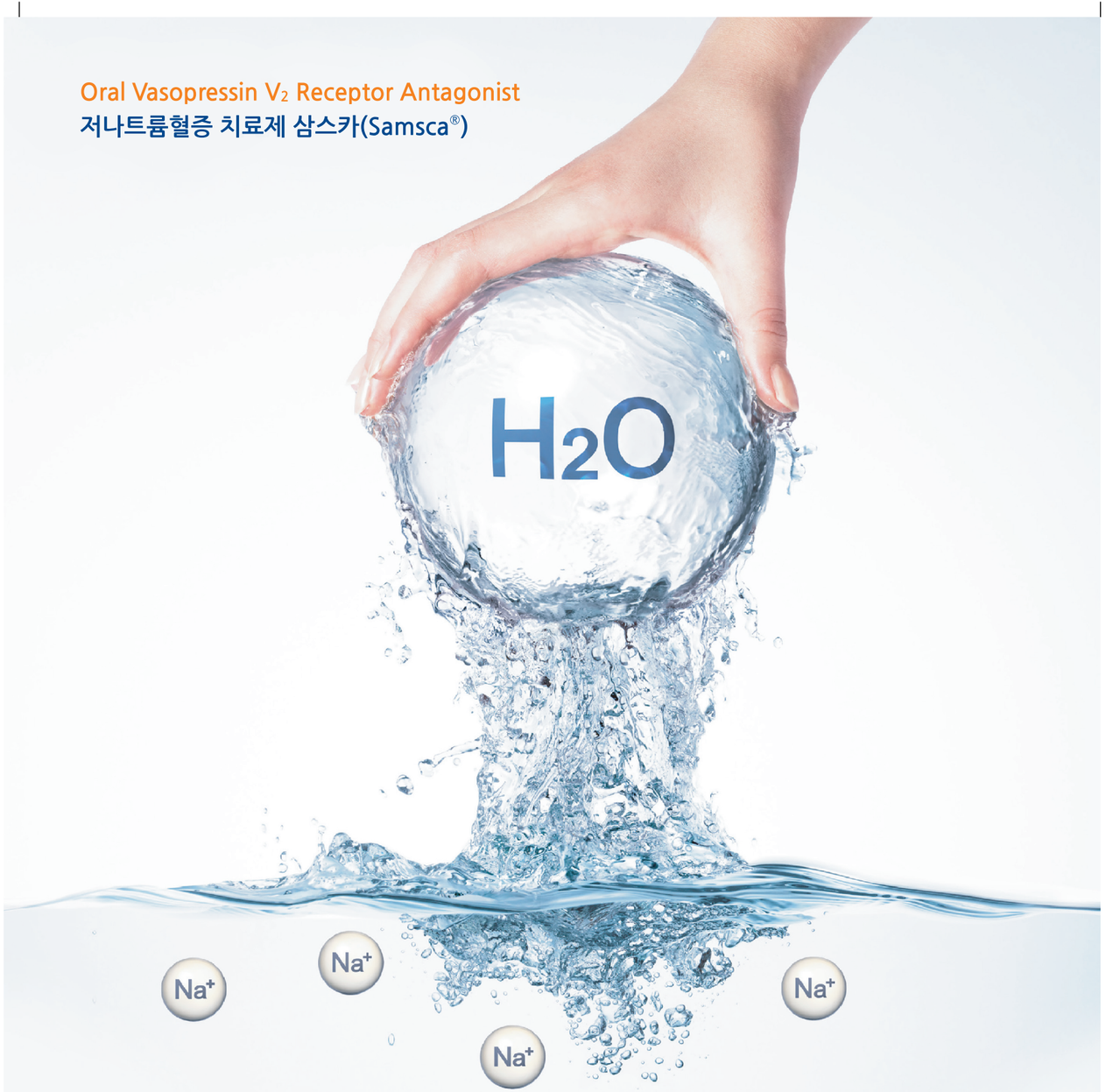
전해질고혈압연구회
E&BP
Korean Society for Electrolyte and Blood Pressure Research

전해질고혈압연구회
E&BP
Korean Society for Electrolyte and Blood Pressure Research

The Official Journal of
Korean Society for Electrolyte and Blood Pressure Research

Oral Vasopressin V_2 Receptor Antagonist

저나트륨혈증 치료제 삼스카(Samsca®)



- **Aquaretic effect** to selectively increase solute-**free water clearance** by the kidney.[1]
- In patients with **euvolemic or hypervolemic hyponatremia,** Samsca®(tolvaptan) was effective in **increasing serum sodium concentrations.**[2]

References
1. Verbalis JG, Goldsmith SR, Greenberg A, Schrier RW, Sterns RH. Hyponatremia treatment guidelines 2007: expert panel recommendations. Am J Med. 2007;120(11 Suppl 1):S1-S21.
2. Schrier RW, Gross P, Gheorghiade M, Berl T, Verbalis JG, Czerwiec FS, Orlandi C. for the SALT Investigators. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for Hyponatremia. N Engl J Med 2006;355:2099-112

Otsuka

한국오츠카제약 Under license from Otsuka Pharmaceutical Co., Ltd

06227 서울시 강남구 역삼로 226 오츠카비전빌딩
Tel 02-3287-9000 | www.otsuka.co.kr

Samsca® (tolvaptan) 15 mg 30 mg tablets

SAM-23-006 | 20230407 approved

命稟메디칼주식회사 MYOUNG POOM MEDICAL CO. LTD

칼륨억제제 이젠 우수한 품질로 편리하게 치료합니다!

카로스현탁액

경구용 현탁액 20ml
Calcium Polystyrene Sulfonate 5g

카슈트현탁액

경구용 현탁액 20ml
Calcium Polystyrene Sulfonate 5g

[제품요약정보] [전문의약품] ■ **제조회사_ (주)휴온스** ■ **제품명_ 카로스현탁액** ■ **주성분·함량_** 이 약 1포 중 폴리스티렌설폰산칼슘 5g ■ **효능·효과_** 고칼륨혈증억제
■ **용법·용량_** 성인: 폴리스티렌설폰산칼슘으로서 1일 15~30g을 2~3회 나누어 경구투여 한다. 연령증상에 따라 적절히 증감한다.
■ **금기_** 배합금기: 칼슘염과 반응하는 물질 또는 칼슘에 흡수가 저해되는 약물과의 배합은 피한다.
■ **신중투어_** 변비가 자주 발생하는 환자, 장관협착증환자, 소화관궤양환자
■ **주요이상반응_** 변비, 식용부진, 구역
■ **보험수가: 760원/포** ■ **보험코드_ 670606111** ■ **포장단위_ 90포/Box**

[제품요약정보] [전문의약품] ■ **제조회사_ DID바이오(주)** ■ **제품명_ 카슈트현탁액** ■ **주성분·함량_** 이 약 1포 중 폴리스티렌설폰산칼슘 5g ■ **효능·효과_** 고칼륨혈증억제
■ **용법·용량_** 성인: 폴리스티렌설폰산칼슘으로서 1일 15~30g을 2~3회 나누어 경구투여 한다. 연령증상에 따라 적절히 증감한다.
■ **금기_** 배합금기: 칼슘염과 반응하는 물질 또는 칼슘에 흡수가 저해되는 약물과의 배합은 피한다.
■ **신중투어_** 변비가 자주 발생하는 환자, 장관협착증환자, 소화관궤양환자
■ **주요이상반응_** 변비, 식용부진, 구역
■ **보험수가: 796원/포** ■ **보험코드_ 664101341** ■ **포장단위_ 100포/Box**

Electrolytes & Blood Pressure

Publisher : Soo Wan Kim, MD (President of the Korean Society for Electrolyte and Blood Pressure Research)

Editorial Correspondence : Sejoong Kim, MD, PhD

Editor-in-Chief of Electrolytes & Blood Pressure

Division of Nephrology, Department of Internal Medicine, Seoul National University Bundang Hospital, 82, Gumi-ro 173Beon-gil, Bundang-gu, Seongnam, Gyeonggi-do 13620, Korea

TEL : +82-31-787-7051 | FAX : +82-31-787-4052 | E-mail: junhaegil@gmail.com

Business Correspondence : Should be sent to the Korean Society for Electrolyte and Blood Pressure Research

Division of Nephrology, Department of Internal Medicine, Chonnam National University Hospital 42, Jebongro, Dong-gu, GwangJu 61469, Korea

TEL : +82-62-220-6499 | FAX : +82-62-225-8578

E-mail : junhaegil@gmail.com | Web : http://eng.kidneykorea.com

Printed by Medical Publishing

#601, Jangyang Building, 15 Eulji-ro 14-gil, Jung-gu, Seoul 04550, Korea

TEL : +82-2-713-2446 | FAX : +82-2-2279-3960 | E-mail : med2002@nate.com

Printed on June 29, 2024 | Published on June 30, 2024

Electrolytes & Blood Pressure has been indexed/tracked/covered in the following:

- Korea Citation Index (KCI)
- KoMCI Web
- PubMed Central
- Google Scholar
- CrossRef
- KoreaMed
- KoreaMed Synapse
- Western Pacific Region Index Medicus (WPRIM)
- SCOPUS EMBASE
- Chemical Abstracts (CA Search)

The Journal was supported by the Korean Federation of Science and Technology Societies Grant funded by the Korean Government (MEST).

Electrolytes & Blood Pressure

Vol. 22, No. 1, June 2024

CONTENTS

Review Article

ISSN 1738-5997 (Print) · ISSN 2092-9935 (Online)
Electrolyte Blood Press 2024;22:1-7
https://doi.org/10.5049/EBP.2024.22.1.1

Is Renal Denervation Effective in Treating Resistant Hypertension?

Ji Hye Kim[1], Soon Kil Kwon[1,2]

[1]*Department of Internal Medicine, Chungbuk National University Hospital, Cheongju, Republic of Korea;*
[2]*Department of Internal Medicine, Chungbuk National University School of Medicine, Cheongju, Republic of Korea*

Received: November 3, 2023
Revised: May 14, 2024
Accepted: May 14, 2024
Corresponding Author: Soon Kil Kwon, MD, PhD
Department of Internal Medicine, Chungbuk National University Hospital, 776, 1 Sunhwan-ro, Seowon-gu, Cheongju-si, Chungcheongbuk-do 28644, Republic of Korea
Tel: +82-43-269-6020; Fax: +82-43-269-6354
E-mail: soonkil.kwon@gmail.com

Resistant hypertension is diagnosed in patients whose blood pressure target is unmet despite the use of three or more antihypertensive medications. Systemic sympathetic hyperactivation is associated with the development of resistant hypertension. As the kidney is largely pervasive of the sympathetic nervous system renal denervation procedure was developed to control blood pressure by attenuating the renal and systemic sympathetic hyperactivity. Renal denervation is a minimally invasive procedure that uses radiofrequency or ultrasound energy waves to reduce the activity of the renal artery nerves. Previous clinical trials have shown conflicting results regarding the efficacy of the procedure. Symplicity HTN-1 and -2 trials showed effective blood pressure lowering results in the renal denervation group with a good safety profile. However, the Symplicity HTN-3 trial showed no difference in blood pressure lowering effect between the renal denervation and control Sham procedure groups. Notwithstanding, some recent clinical trials with Sham control and meta-analysis showed clinical benefits of renal denervation. Other clinical benefits of renal denervation include glucose control, cardiovascular protective effect, reduction of obstructive sleep apnea, and neuralgia control. A subset of patients with satisfactory blood pressure control response to the procedure may experience improved glucose control due to the overall reduced sympathetic activity and insulin resistance. Sympathetic activity control after renal denervation has cardioprotective effects, especially for those with arrhythmia and left ventricular hypertrophy. Also, renal denervation could be helpful in renal-origin pain control. Renal denervation is an effective, safe, non-invasive procedure with many clinical benefits beyond blood pressure control. Further development in the procedure technique and selection of target patients are needed for wider clinical use of renal denervation in resistant hypertension.

Key Words: Hypertension, Renal denervation, Cardiovascular disease, Glucose control

INTRODUCTION

Resistant hypertension is a condition in which the patient's blood pressure target is unmet despite the use of three or more antihypertensive medications including diuretics. It is estimated to affect approximately 8% of hypertensive patients. The prevalence of resistant hypertension has nearly doubled between 2005 and 2008 compared to 1998 and 2004[1)]. In the case of resistant hypertension, it is necessary to check the patient's antihypertensive medication compliance. According to a clinical study that measured the urine antihypertensive drug concentration level to objectively check the patient's medication compliance, 28.8% of the patients had poor compliance with antihypertensive medication.

Also, 23.5% of patients who were considered for renal denervation due to uncontrolled hypertension had poor compliance with antihypertensive medications[2]. In situations where it is difficult to accurately assess medication compliance the prevalence of resistant hypertension can increase up to 30%. Therefore, even though the options for antihypertensive medication have increased resistant hypertension remains a serious challenge for nephrologists.

The first surgery to remove the autonomic nerve from the human blood vessel was performed by Jaboulay in the late 19th century and surgery to remove the sympathetic nerve from the kidney for treatment of severe pain due to hydronephrosis has been attempted since the 1920s[3]. Since the 1930s, renal denervation surgery has been performed on young females with malignant hypertension which was uncontrolled with medication and a decrease in blood pressure has been confirmed[4]. However, surgical nerve block has not been widely performed due to the side effects of autonomic nerve ablation which include irreversible impotence, urinary incontinence, and orthostatic hypertension.

The association between systemic sympathetic activation to the progression of resistant hypertension is the theoretical background of renal denervation[5,6]. The kidney is an organ largely pervasive of the sympathetic nervous system and is connected to the central nervous system, which activates the systemic sympathetic nervous system when the effective circulating plasma volume is insufficient. In cases of hypotensive bleeding, hypoxia, hypercapnia, cardiac tamponade, and carotid baroreceptor unloading the kidneys suppress natriuresis by various stimuli without affecting the glomerular filtration rate. Conversely, in situations of atrial stretching, vascular volume overload, and stellate ganglion stimulation situations natriuresis is increased. All of these sympathetic responses can be blunted or eliminated by neural denervation[5].

The use of renal denervation procedures in clinical practice began in the late 2000s when catheter procedures were developed[7]. It mainly uses radiofrequency energy or ultrasound waves, but neurotoxin injection is also performed. A catheter is usually injected through the femoral artery to the renal artery, placed in the area with a diameter of 3 to 8 mm, and radiofrequency energy is given targeting to reach the adventitia. This procedure is commonly repeated 4 to 6 times by an experienced physician for effective renal denervation[8].

Clinical results of renal denervation for resistant hypertension

Symplicity HTN-1, 2, 3 studies

The 'Renal Denervation in Patients with Uncontrolled Hypertension (Symplicity HTN)' study is a multicenter, randomized trial that evaluated the efficacy of renal denervation in patients with resistant hypertension. In the 'Symplicity HTN-1' trial, 153 patients with systolic blood pressure ≥ 160 mmHg and resistant to three or more antihypertensive drugs including diuretics received renal denervation. After 24 months reduction in 32 mmHg of systolic blood pressure and 14 mmHg of diastolic blood pressure was observed[9]. Additional reductions in systolic blood pressure of 32.0 mmHg and diastolic blood pressure of 14.4 mmHg were observed after 3 years of follow-up[10]. Although this study showed that renal denervation effectively reduced both systolic and diastolic blood pressures and had few complications, the limitation of the study was that there was no control group. Therefore, researchers from Austria, Europe, and the United States conducted a similar study titled the 'Symplicity HTN-2' trial which included a control group[11]. A total of 106 resistant hypertension patients were randomized into a 1:1 ratio and 52 patients underwent renal denervation while 54 patients in the control group were treated with medication. After 6 months, the renal denervation group showed a 33 mmHg decrease in systolic blood pressure while that in the control group was 11 mmHg. The renal denervation procedure had almost no complications. In 2014 the 'Symplicity HTN-3' trial, centered in the United States, included 535 patients and compared the efficacy of the renal denervation procedure to the Sham procedure[12]. Unlike previous trials there was no difference in the reduction of both office systolic blood pressure (-14 mmHg in the renal denervation group vs. -12 mmHg in the control group, p=0.26) and ambulatory blood pressure monitoring (-6.75 mmHg in the renal denervation group vs. -4.79 mmHg in the control group, p=0.98) between the two treatment groups. This study was more reliable than previous studies

due to the larger number of enrolled patients, randomization of patients into procedure and control groups, and inclusion of 24-hour blood pressure measurements.

Other studies

A meta-analysis of 15 randomized controlled trials found no significant clinical benefits of renal denervation on resistant hypertension. There was no significant difference in both systolic blood pressure and ambulatory blood pressure monitoring between the renal denervation and control groups[13]. However, Ahmad et al. analyzed 7 larger trials totaling 1,328 patients including the Symplicity HTN-3 trial, and found that the renal denervation group showed significantly higher blood pressure lowering effect including office systolic blood pressure of -5.86 mmHg, diastolic blood pressure of -3.63 mmHg and ambulatory blood pressure monitoring of -1.85 mmHg, respectively ($p<0.001$)[14].

A Japanese study that compared 67 patients in the renal denervation group and 65 patients in the Sham treatment control group showed no significant difference in systolic blood pressure between the two groups after 3 months (-8.7 mmHg vs. -6.9 mmHg, $p=0.488$)[15]. However, the Global Symplicity Registry, which included a total of 102 resistant hypertensive patients including Korean patients, showed that the renal denervation group had a reduction in systolic blood pressure of 32.5 mmHg without significant difference between the diabetic and non-diabetic patients[16]. Also, Mahfoud et al. analyzed 80 patients with resistant hypertension over 36 months of which 38 patients in the treatment group received radiofrequency renal denervation and 42 patients in the control group received Sham treatment. After 36 months even though the number of antihypertensive medications in use was the same between the two groups, there was a significant reduction in the systolic blood pressure confirmed by ambulatory blood pressure monitoring (-18.7 mmHg vs. -8.6 mmHg, $p=0.0039$). In particular, significant reductions in both morning systolic (-11.0 mmHg) and diastolic (-11.8 mmHg) blood pressures were found. The authors suspect this would be an important factor in reducing cardiovascular complications[17]. Although this study enrolled only a small number of patients and had a short observation period, it provides evidence that renal denervation may be effective in resistant hypertension.

Benefits of renal denervation beyond refractory hypertension

Diabetes mellitus control effect of renal denervation

It is generally known that sympathetic nerve activity is increased in diabetes mellitus (DM) and hypertensive DM patients have significantly higher sympathetic nerve activity[18]. Inflammatory changes, oxidative stress, and inhibition of vascular smooth muscle cell apoptosis due to sympathetic hyperactivity are associated with insulin resistance and cardiovascular complications in diabetic patients. Therefore, inhibition of sympathetic nerve activation by renal denervation can reduce insulin resistance, prevent DM, and have a cardiovascular protective effect. According to the study by Mahfoud et al., in patients who received renal denervation, there was a significant decrease in both insulin (20.8 to 9.3 IU/mL, $p=0.006$) and C-peptide (5.3 to 3.0 ng/mL, $p=0.002$) levels respectively. After 3 months, homeostasis model assessment–insulin resistance decreased from 6.00.9 to 2.40.8 ($p=0.001$). Also, the post-prandial 2-hour glucose level was significantly reduced by 27 mg/dL ($p=0.012$)[19]. Another study by Witkowski et al. showed a reduction in glycated hemoglobin A1C level from 6.1% to 5.6% ($p<0.05$) in renal denervation patients[20]. However, as the degree of sympathetic hyperactivity or insulin resistance varies from patient to patient renal denervation may not be effective in blood sugar control in all patients. It may be helpful in a subset of patients who show good results in blood pressure control after renal denervation.

Reduction in obstructive sleep apnea after renal denervation

Obstructive sleep apnea (OSA) is associated with hypertension and is also known to cause resistant hypertension due to sympathetic hyperactivity. Therefore, it is recommended to check for the presence of OSA before treatment of resistant hypertension[21]. OSA is a risk factor for many cardiovascular diseases such as arrhythmia and left ventricular hypertrophy, which can cause vascular endothelial dysfunction and progression of arteriosclerosis due to inflammatory reactions. Witkowski et al. performed renal denervation in 10 patients with OSA and at 6 months both systolic and diastolic blood pressure significantly decreased

by 34 mmHg and 13 mmHg ($p<0.01$)[20]. The apnea-hypopnea index decreased significantly from 16.3 to 4.5 ($p=0.059$) and although there was no statistical significance sleep apnea symptoms improved along with the blood pressure reduction effect. As OSA causes excessive sympathetic hyperactivation during the day resulting in hypoactivation of sympathetic nervous response during the night even when there is hypoxia, renal denervation may be effective in improving OSA and cardiovascular complications associated with OSA.

Cardiovascular effects of renal denervation

When blood pressure and heart rate increase due to sympathetic activation left ventricular hypertrophy commonly occurs and is closely related to cardiovascular mortality. If hypertension persists, left ventricular hypertrophy occurs and left ventricular hypertrophy aggravates hypertension in a vicious cycle resulting in resistant hypertension[22]. Therefore, treatment of resistant hypertension is important to prevent cardiovascular complications.

A few studies analyzed the effect of blood pressure control with renal denervation on left ventricular hypertrophy suppression in resistant hypertension patients. Pisano et al. reviewed 15 studies and found that there was low-certainty evidence that renal denervation had little or no effect on the risk of myocardial infarction, ischemic stroke, unstable angina, or hospitalization. However, there was moderate-certain evidence that renal denervation may improve 24-hour ambulatory blood pressure monitoring and office diastolic blood pressure[23]. A study by Brandt et al. compared 46 bilateral renal denervation patients with 18 control patients and found that the renal denervation group had a reduction in both systolic and diastolic blood pressures by 27.8 mmHg and 8.8 mmHg after 6 months, respec-tively. Also, there was a significant decrease in the left ventricle mass from 47.0 m^2 to 44.7 m^2 ($p<0.001$)[24]. Another study by Tsioufis et al. evaluated left ventricle mass after renal denervation in 11 patients with resistant hypertension and the study results show that 70.6% of patients had a decrease in left ventricular size by at least one stage after 24 months[25]. Also, in the animal model of resistant hypertension there was more significant suppression in the ventricular fibrosis after sympathectomy compared to the control group where antihypertensive agents were used for blood pressure control[26].

Studies evaluating the cardiac function of congestive heart failure patients after renal denervation are rare, but Hopper et al. performed renal denervation on 39 patients with left ventricular ejection fraction <40% and followed up on cardiac function for 12 months. After 12 months, the N-terminal prohormone of brain natriuretic peptide (NT-pro BNP) significantly decreased from 1,530 ng/mL to 1,428 ng/mL ($p=0.006$), and the 120-minute glucose tolerance test also decreased from 201.6 mg/dL to 178.2 mg/dL ($p=0.026$). However, there was no difference in glomerular filtration rate and left ventricular contractility measured using the ejection fraction (28 vs. 29%, $p=0.536$)[27]. There is a possibility that heart failure may worsen after 12 months, so maintenance of heart function itself may confirm the effect of renal denervation on heart function preservation. Yet, observational studies with longer follow-up duration are necessary.

Effects on kidney function and blood pressure control in advanced CKD

It is difficult to find evidence that renal denervation preserves or improves the glomerular filtration rate. However, many studies show that there is no worsening of renal function and increased risk of chronic kidney disease after the procedure[28-30].

Although there is a lack of data on large patient populations there are studies that confirmed a decrease in blood pressure after renal denervation in moderate to severe chronic kidney disease patients. According to the study by Hering et al., when renal denervation was performed on 15 patients with an average estimated glomerular filtration rate of 31.2 mL/min the systolic blood pressure decreased by 25 mmHg and 32 mmHg after 3 and 6 months ($p<0.01$). Also, there was no impairment in kidney auto-regulation and electrolyte levels. However, hemoglobin levels tended to gradually increase ($p=0.08$)[29]. Ott et al. confirmed the effectiveness of renal denervation in treating hypertension in 6 hemodialysis patients. After 6 months, the systolic blood pressure decreased by 20 mmHg ($p=0.043$) and diastolic blood pressure decreased by 11 mmHg ($p=0.043$)[30]. Therefore, renal denervation can be considered in cases of refractory hypertension unresponsive to medications,

even in moderate to severe chronic kidney disease patients.

Renal denervation for neuralgia

Attempts to reduce pain through removal of sympathetic nerves have been made since the early 1920s. Recently renal denervation has been performed in an attempt to reduce pain in patients with hematuria-loin pain syndrome and polycystic kidney disease and has shown satisfactory results[31-33]. Currently, renal denervation is not recommended as the first line for pain control, however may be attempted to control renal-origin pain such as polycystic kidney disease by reducing the sympathetic nerve activity of the kidney.

Future perspectives of renal denervation

Renal denervation has shown some satisfactory clinical outcomes, but data regarding its long-term effects are still insufficient for clinical application. In 2022, the Thailand Society of Nephrology established a guideline for renal denervation for the treatment of hypertension[34]. The guideline recommends considering renal denervation in cases of refractory hypertension unresponsive to conventional antihypertensive treatments and may be beneficial for a subset of resistant hypertension patients with cardiovascular complications. However, based on the results of previous clinical trials including Symplicity HTN-3, the 2022 Korean Society of Hypertension guideline suggests that although renal denervation is a relatively safe procedure there is still a lack of evidence for the clinical benefits in blood pressure control and therefore is not currently recommended in clinical practice[35].

According to the results of Symplicity HTN-3, blood pressure was significantly reduced even in patients who received Sham procedure. Therefore, the overall sympathetic nerve activity of the patient as well as that of renal arteries have an important role in controlling resistant hypervascularization. Sardar et al. conducted a meta-analysis of 6 clinical studies with the Sham procedure control group. Blood pressure was statistically significantly reduced in the renal denervation group and the effect was greater in second-generation studies compared to the first-generation studies[36]. Additionally, in resistant hypertension, blood pressure is effectively decreased after sympathetic nerve blockade, but rebounds over time. This is believed to be due to incomplete blockade or the subsequent increase in the activity of the remaining sympathetic nerves leading to the overall increase in blood pressure. If the sympathetic nerves around the tunica adventitia are blocked with higher radiofrequency or ultrasound energy to increase the effectiveness of sympathetic nerve blockade a more sustained antihypertensive effect may be expected. However, there may be an increase in the side effect rates. In addition, as suggested by Hart et al., if a more specific standard for measuring human sympathetic nerve activity is established, the safety of renal denervation is expected to be highly improved[37].

The next thing to consider is how to predict which patients will have an effective response to renal nerve denervation. The degree of sympathetic nerve activity varies among patients with resistant hypertension and the response to renal nerve denervation may vary depending on previous beta-blocker or renin-angiotensin blockade use[38]. A previous study by Zuern et al. showed that cardiac baroreceptor sensitivity was highly associated with response to renal denervation[39]. Therefore, it is predicted that patients who have higher sympathetic activity and sensitivity will respond better to renal denervation.

CONCLUSIONS

Although renal denervation is not yet the current standard treatment for resistant hypertension the benefits of the procedure including effective blood pressure control and cardioprotective effects via sympathetic blockade are warranted with relatively good safety profile. With further development of technical devices and treatment protocols we can expect promising results of renal denervation with increased use in the real world clinical practice. Furthermore, by selecting patients who are expected to have effective responses to the procedure and establishing optimal treatment program renal denervation may become one of the standard treatments for resistant hypertension in the future.

Conflict of Interest

The authors have no conflicts of interest to declare.

REFERENCES

1. Egan, B.M., et al.: Uncontrolled and apparent treatment resistant hypertension in the United States, 1988 to 2008. Circulation, 2011;124(9):1046-1058.
2. Tomaszewski, M., et al.: High rates of non-adherence to antihypertensive treatment revealed by high-performance liquid chromatography-tandem mass spectrometry (HP LC-MS/MS) urine analysis. Heart, 2014;100(11):855-861.
3. Laios, K., et al.: Mathieu Jaboulay (1860-1913) and His Innovations in Vascular and General Surgery. Surg Innov, 2020; 27(1):120-123.
4. Page, I.H. and G.J. Heuer, The Effect of Renal Denervation On The Level of Arterial Blood Pressure and Renal Function in Essential Hypertension. J Clin Invest, 1935;14(1):27-30.
5. DiBona, G.F., Physiology in perspective: The Wisdom of the Body. Neural control of the kidney. Am J Physiol Regul Integr Comp Physiol, 2005;289(3):R633-641.
6. DiBona, G.F. and M. Esler, Translational medicine: the antihypertensive effect of renal denervation. Am J Physiol Regul Integr Comp Physiol, 2010;298(2):R245-253.
7. Krum, H., et al.: Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet, 2009;373(9671):1275-1281.
8. Krum, H., et al.: Device-based antihypertensive therapy: therapeutic modulation of the autonomic nervous system. Circulation, 2011;123(2):209-215.
9. Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. Hypertension, 2011;57(5):911-917.
10. Krum, H., et al.: Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study. Lancet, 2014;383(9917):622-629.
11. Esler, M.D., et al.: Renal sympathetic denervation for treatment of drug-resistant hypertension: one-year results from the Symplicity HTN-2 randomized, controlled trial. Circulation, 2012;126(25):2976-2982.
12. Bhatt, D.L., et al.: A controlled trial of renal denervation for resistant hypertension. N Engl J Med, 2014;370(15):1393-1401.
13. Agasthi, P., et al.: Renal Denervation for Resistant Hypertension in the contemporary era: A Systematic Review and Meta-analysis. Sci Rep, 2019;9(1):6200.
14. Ahmad, Y., et al.: Renal Denervation for Hypertension: A Systematic Review and Meta-Analysis of Randomized, Blinded, Placebo-Controlled Trials. JACC Cardiovasc Interv, 2021;14(23): 2614-2624.
15. Kario, K., et al.: Catheter-based ultrasound renal denervation in patients with resistant hypertension: the randomized, controlled REQUIRE trial. Hypertens Res, 2022;45(2): 221-231.
16. Kim, B.K., et al.: Long-term outcomes after renal denervation in an Asian population: results from the Global SYMPLICITY Registry in South Korea (GSR Korea). Hypertens Res, 2021; 44(9):1099-1104.
17. Mahfoud, F., et al.: Long-term efficacy and safety of renal denervation in the presence of antihypertensive drugs (SPYRAL HTN-ON MED): a randomised, sham-controlled trial. Lancet, 2022;399(10333):1401-1410.
18. Huggett, R.J., et al.: Impact of type 2 diabetes mellitus on sympathetic neural mechanisms in hypertension. Circulation, 2003;108(25):3097-3101.
19. Mahfoud, F., et al.: Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension: a pilot study. Circulation, 2011;123(18):1940-1946.
20. Witkowski, A., et al.: Effects of renal sympathetic denervation on blood pressure, sleep apnea course, and glycemic control in patients with resistant hypertension and sleep apnea. Hypertension, 2011;58(4):559-565.
21. Baguet, J.P., G. Barone-Rochette, and J.L. Pépin, Hypertension and obstructive sleep apnoea syndrome: current perspectives. J Hum Hypertens, 2009;23(7):431-443.
22. Aeschbacher, B.C., et al.: Diastolic dysfunction precedes myocardial hypertrophy in the development of hypertension. Am J Hypertens, 2001;14(2):106-113.
23. Pisano, A., et al.: Renal denervation for resistant hypertension. Cochrane Database Syst Rev, 2021;11(11):Cd011499.
24. Brandt, M.C., et al.: Renal sympathetic denervation reduces left ventricular hypertrophy and improves cardiac function in patients with resistant hypertension. J Am Coll Cardiol, 2012;59(10):901-909.
25. Tsioufis, C., et al.: Long-term effects of multielectrode renal denervation on cardiac adaptations in resistant hypertensive patients with left ventricular hypertrophy. J Hum Hypertens, 2016;30(11):714-719.
26. Perlini, S., et al.: Sympathectomy or doxazosin, but not propranolol, blunt myocardial interstitial fibrosis in pressure-overload hypertrophy. Hypertension, 2005;46(5):1213-1218.
27. Hopper, I., et al.: Sympathetic Response and Outcomes Following Renal Denervation in Patients With Chronic Heart Failure: 12-Month Outcomes From the Symplicity HF Feasibility Study. J Card Fail, 2017;23(9):702-707.
28. Sanders, M.F., et al.: Renal safety of catheter-based renal

denervation: systematic review and meta-analysis. Nephrol Dial Transplant, 2017;32(9):1440-1447.
29. Hering, D., et al.: Renal denervation in moderate to severe CKD. J Am Soc Nephrol, 2012;23(7):1250-1257.
30. Ott, C., et al.: Effects of renal denervation on blood pressure in hypertensive patients with end-stage renal disease: a single centre experience. Clin Exp Nephrol, 2019;23(6):749-755.
31. Prasad, B., et al.: Renal Denervation in Patients With Loin Pain Hematuria Syndrome. Am J Kidney Dis, 2017;69(1):156-159.
32. Riccio, E., et al.: Catheter-based renal denervation in ADPKD: just for pain control? Am J Kidney Dis, 2014;64(6):999.
33. Valente, J.F., et al.: Laparoscopic renal denervation for intractable ADPKD-related pain. Nephrol Dial Transplant, 2001; 16(1):160.
34. Roubsanthisuk, W., et al.: 2022 Renal denervation therapy for the treatment of hypertension: a statement from the Thai Hypertension Society. Hypertension Research, 2023; 46(4):898-912.
35. Kim, H.-L., et al.: The 2022 focused update of the 2018 Korean Hypertension Society Guidelines for the management of hypertension. Clinical Hypertension, 2023;29(1):11.
36. Sardar, P., et al.: Sham-Controlled Randomized Trials of Catheter-Based Renal Denervation in Patients With Hypertension. J Am Coll Cardiol, 2019;73(13):1633-1642.
37. Hart, E.C., et al.: Recording sympathetic nerve activity in conscious humans and other mammals: guidelines and the road to standardization. Am J Physiol Heart Circ Physiol, 2017;312(5):H1031-h1051.
38. Bakris, G.L., et al.: Impact of renal denervation on 24-hour ambulatory blood pressure: results from SYMPLICITY HTN-3. J Am Coll Cardiol, 2014;64(11):1071-1078.
39. Zuern, C.S., et al.: Impaired cardiac baroreflex sensitivity predicts response to renal sympathetic denervation in patients with resistant hypertension. J Am Coll Cardiol, 2013; 62(22):2124-2130.

Original Article

ISSN 1738-5997 (Print) · ISSN 2092-9935 (Online)
Electrolyte Blood Press 2024;22:8-15
https://doi.org/10.5049/EBP.2024.22.1.8

Use of Fludrocortisone for Hyperkalemia in Chronic Kidney Disease Not Yet on Dialysis

Eun Kyoung Lee[1], Won Seok Yang[2]

[1]Division of Nephrology, Department of Internal Medicine, Dankook University Hospital, Dankook University College of Medicine, Cheonan, Republic of Korea; [2]Division of Nephrology, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Received: December 7, 2023
Revised: June 23, 2024
Accepted: June 24, 2024
Corresponding Author: Won Seok Yang, MD
Division of Nephrology, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Republic of Korea
Tel: +82-2-3010-3260; Fax: +82-2-3010-6963
E-mail: wsyang@amc.seoul.kr

Background: Hyperkalemia is a frequent and potentially lethal complication of chronic kidney disease (CKD). We retrospectively examined the potassium-lowering effect of oral fludrocortisone and its adverse effects in hyperkalemic CKD patients not yet on dialysis.
Methods: Thirty-three patients (23 men and 10 women, ages 69±14 years) were included. To control hyperkalemia at the outpatient clinic, twenty-one patients (Group 1) received fludrocortisone (0.05–0.1 mg/day) without changes in angiotensin II receptor blockers (ARBs) and calcium polystyrene sulfonate (CPS), while twelve patients (Group 2) were treated with fludrocortisone in addition to stopping ARBs and/or adding low-dose CPS.
Results: Fludrocortisone was administered for a median of 169 days (interquartile range, 47–445). At the first follow-up after fludrocortisone administration, serum potassium dropped from 6.14±0.32 mEq/L to 4.52±1.06 mEq/L ($p<0.001$) in Group 1 and from 6.37±0.35 mEq/L to 4.08±0.74 mEq/L ($p<0.01$) in Group 2. Ten patients in Group 1 and five patients in Group 2 measured serum potassium levels at four outpatient visits before and after fludrocortisone administration, respectively. The frequency of serum potassium ≥6.0 mEq/L decreased from 19/40 (48%) to 2/40 (5%) ($p<0.001$) in Group 1 and from 11/20 (55%) to 0/20 (0%) ($p<0.001$) in Group 2. Eleven patients experienced sodium retention-related problems after fludrocortisone administration: 7 with worsening leg edema, 2 with pleural effusions, and 2 with pulmonary edema.
Conclusion: In pre-dialysis CKD patients, fludrocortisone at low doses effectively reduced serum potassium levels; however, sodium retention was a common adverse effect.

Key Words: Calcium polystyrene sulfonate, Chronic kidney disease, Fludrocortisone, Hyperkalemia

INTRODUCTION

Hyperkalemia is a common complication of chronic kidney disease (CKD), since potassium is primarily eliminated through the kidneys[1]. Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) that are used to reduce proteinuria also contribute to decreased potassium excretion. Clinically, hyperkalemia may cause life-threatening arrhythmias, especially when the serum potassium exceeds 6.5 mEq/L[2]. As a result, hyperkalemia is a potentially serious issue for CKD patients.

Cation-exchange resins, such as sodium polystyrene sulfonate (SPS) and calcium polystyrene sulfonate (CPS), have been extensively used to control hyperkalemia in CKD outpatients[3,4]. In the gastrointestinal tract, SPS and CPS take potassium in exchange for sodium or calcium ions, respectively,

and promote potassium excretion. However, many patients find the drugs intolerable because of their adverse effects, which are most commonly nausea and constipation[4]. Loop diuretics may lower serum potassium by increasing renal potassium excretion, but their use may be inappropriate in the absence of volume overload since they could exacerbate renal dysfunction[5]. Sodium bicarbonate may decrease serum potassium by transferring potassium into the cells, but its effectiveness is limited[6]. Most recently, sodium zirconium cyclosilicate and patiromer have been introduced[7]. Like SPS and CPS, these drugs take up potassium in exchange for sodium or calcium ions in the gastrointestinal tract. These new agents have been shown to effectively reduce serum potassium and have fewer side effects. However, they are not yet available in many countries, including Korea.

Despite dietary education for potassium restriction and administration of a potassium-binding agent, hyperkalemia is frequent in CKD outpatients, and it is a tough problem to control. If hyperkalemia is severe, referral to the emergency room is required for rapid correction of it with intravenous insulin/glucose infusions, repeated enemas with a potassium-binding agent, or even hemodialysis.

Fludrocortisone is a synthetic mineralocorticoid receptor agonist that lowers potassium levels by increasing potassium and hydrogen excretion instead of sodium reabsorption[8]. Due to sodium retention, however, fludrocortisone may have adverse effects such as peripheral edema, congestive heart failure, and hypertension. In addition, activation of mineralocorticoid receptors may contribute to interstitial inflammation, fibrosis, and proteinuria in CKD patients[9,10]. Mineralocorticoid receptor antagonists, on the other hand, have been shown in animal models of diabetic kidney disease to reduce mesangial expansion, interstitial fibrosis, and proteinuria[9,10]. Thus, sodium retention and the potential adverse mineralocorticoid effects on the kidney make fludrocortisone unattractive for chronic therapy, and fludrocortisone has not traditionally been used for hyperkalemia in CKD patients.

However, fludrocortisone may be used if there are no other effective ways to prevent fatal, severe hyperkalemia. The use of fludrocortisone as a potassium-lowering agent has been reported in hemodialysis patients[11-14] and organ transplant recipients receiving calcineurin inhibitors[15-19], but there has been little data regarding the use of fludrocortisone for hyperkalemia control in patients with CKD who are not yet on dialysis.

In this study, we retrospectively examined the potassium-lowering effect of oral fludrocortisone and its adverse effects in hyperkalemic pre-dialysis CKD patients who did not tolerate adding CPS or increasing the dose of CPS.

Materials and Methods

1. Patients

We reviewed the medical records of patients registered at Asan Medical Center, a tertiary hospital in Seoul, Korea, and included adult CKD patients (≥18 years) who received oral fludrocortisone at the outpatient clinic to control hyperkalemia (K^+ >5.1 mEq/L) between January 1, 2011, and December 31, 2022. Patients with CKD who have hyperkalemia have been treated with CPS. The included patients were given oral fludrocortisone, mostly because they were unable to tolerate adding CPS or increasing the CPS dosage.

Patients with normal renal function or patients with end-stage renal disease on hemodialysis or peritoneal dialysis were excluded. Patients who received fludrocortisone to manage orthostatic hypotension but not hyperkalemia were also excluded.

In cases of severe hyperkalemia (K^+ ≥6.0 mEq/L), some patients received 10 g of CPS three times per day for the first five days. ACEI/ARBs were prescribed at the divisions of nephrology, cardiology, and endocrinology and the department of neurology. ACEI/ARBs were stopped or reduced in some patients but not in others, especially in those who received them from departments other than nephrology.

This study was approved by the Institutional Review Board (IRB) of Asan Medical Center (IRB No. S2022-1461-0001).

2. Clinical and laboratory parameters

We collected data from the medical records, such as age, gender, underlying renal disease, medication use (including CPS and antihypertensive drugs), weight, blood pressure, and laboratory data, including creatinine, potassium, and

estimated glomerular filtration rate (eGFR). The CKD-EPI 2021 equation was used to calculate eGFR using sex, age, and serum creatinine[20]. The normal range of serum potassium was 3.5-5.1 mEq/L.

3. Statistical analyses

Results are expressed as mean±SD or median (interquartile range), depending on the data type. Serum potassium levels, body weights, and blood pressure before and after fludrocortisone administration were compared using Wilcoxon signed rank test. The frequency of serum potassium ≥6.0 mEq/L was compared before and after fludrocortisone administration using the chi-squared test. Statistical analyses were performed using SPSS version 21 (IBM Co., Armonk, NY, USA). P values less than 0.05 were considered statistically significant.

Results

1. Patient characteristics

Thirty-three patients (23 men and 10 women) with a mean age (±SD) of 69±14 years were included. Serum creatinine was 2.84 (2.01-4.49) mg/dl and estimated GFR was 23±12 ml/min/1.73m^2. Fludrocortisone was administered at doses of 0.05-0.1 mg/day for a median of 169 (47-445) days.

Baseline demographic and clinical characteristics are presented in Table 1. One patient had liver transplantation, and another had lung transplantation, receiving tacrolimus as an immunosuppressant.

To control hyperkalemia, twenty-one patients received

Table 1. Clinical and laboratory data of the study population at the time of initiating fludrocortisone

	Group 1# (n=21)	Group 2## (n=12)
Age (years)	70±15	67±12
Male/female	14/7	9/3
Creatinine (mg/dL)	2.84 (1.77-4.68)	3.04 (2.45-4.48)
eGFR (mL/min/1.73m^2)	24±13	21±10
Potassium (mEq/L)	6.14±0.32	6.37±0.35
Total CO_2 (mEq/L)	19.3±3.1	18.7±3.7
Underlying Kidney Diseases		
Diabetes nephropathy	5	4
IgA nephropathy	2	-
Membranous nephropathy	1	-
Polycystic kidney disease	1	-
Reflux nephropathy	1	-
Myeloma kidney	1	-
Chronic kidney disease of unknown etiology	10	8
Comorbidities		
Hypertension	16	8
Diabetes mellitus	9	6
Medications at the time of fludrocortisone administration		
ARB	8	10
ACEI	1	-
CCB	15	9
Beta blocker	8	2
CPS dose (g/day)	15 (10-17.5)	7.5 (0-15)
Furosemide	2	1
Thiazide	1	1
K-sparing diuretic	-	-
Sodium bicarbonate	13	7

#Patients in Group 1 received fludrocortisone with no changes in ARB or CPS.
##Patients in Group 2 were given fludrocortisone as well as the discontinuation of ARBs and/or the addition of low-dose CPS.
ARB; angiotensin II receptor blocker, ACEI; angiotensin-converting enzyme inhibitor, CCB; calcium channel blocker, CPS; calcium polystyrene sulfonate

fludrocortisone without changes in ARB and CPS (Group 1), while the remaining twelve patients received fludrocortisone as well as discontinuation of ARBs and/or addition of low-dose CPS (Group 2).

At the time of fludrocortisone initiation, furosemide was maintained at the current dose in 2 patients in Group 1, increased in 1 patient in Group 2, and not prescribed in the other patients.

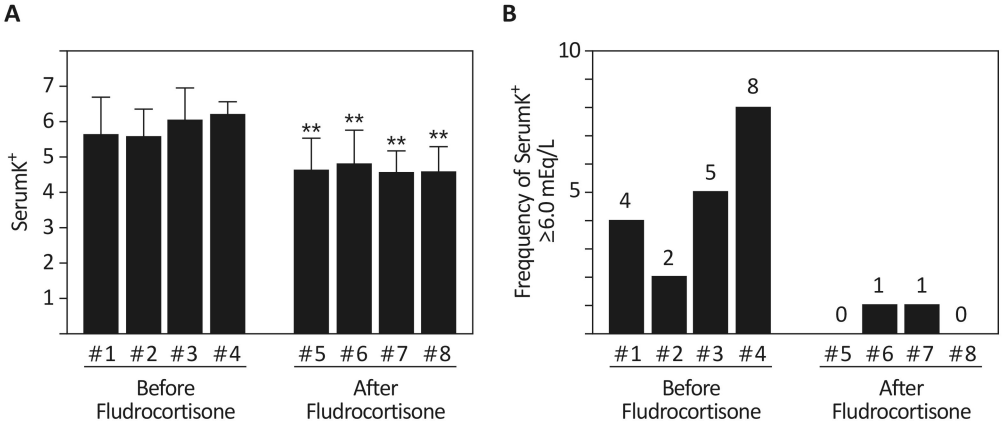
2. Changes in serum potassium after fludrocortisone administration

The serum potassium in Group 1 dropped from 6.14±0.32 mEq/L to 4.52±1.06 mEq/L ($p<0.001$) at the first follow-up after a median of 35 (18-60) days. Similarly, in Group 2, it dropped from 6.37±0.35 mEq/L to 4.08±0.74 mEq/L at the first follow-up after a median of 30 (19-42) days ($p<0.01$).

To evaluate whether the potassium-lowering effect is sustained while fludrocortisone is taken, we analyzed 15 patients (10 patients in Group 1 and 5 patients in Group 2) in whom serum potassium levels were measured at four outpatient visits before and after fludrocortisone administration. The intervals between the measurements are shown in Figs. 1 and 2.

In Group 1, the four consecutive serum potassium levels were 5.63±1.06 mEq/L, 5.56±0.79 mEq/L, 6.02±0.93 mEq/L, and 6.18±0.37 mEq/L before fludrocortisone administration, and 4.60±0.91 mEq/L, 4.79±0.96 mEq/L, 4.55±0.60 mEq/L, and 4.56±0.72 mEq/L after fludrocortisone administration, respectively (Fig. 1A). The frequency of serum potassium ≥6.0 mEq/L was 4/10, 2/10, 5/10, and 8/10 before fludrocortisone administration and 0/10, 1/10, 1/10, and 0/10 after fludrocortisone administration (Fig. 1B); thus, it decreased from 19/40 measurements (48%) to 2/40 measurements (5%) after fludrocortisone administration ($p<0.001$).

In Group 2, the four consecutive serum potassium levels were 5.74±0.63 mEq/L, 5.66±0.55 mEq/L, 5.84±0.36 mEq/L, and 6.48±0.48 mEq/L before fludrocortisone administration, and 4.20±0.88 mEq/L, 4.66±0.51 mEq/L, 5.32±0.58 mEq/L,



C

eGRF (ml/min/1.73m²; mean with standard deviation)

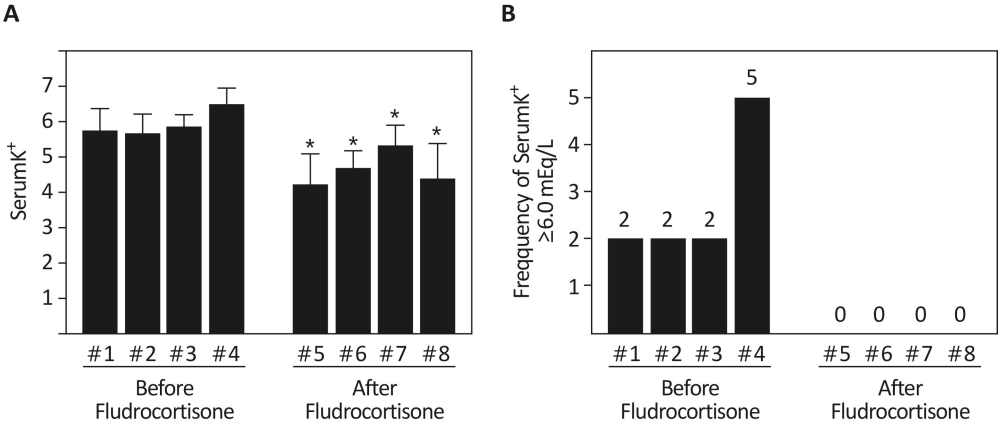
#1	#2	#3	#4	#5	#6	#7	#8
27.3±12.9	25.8±14.7	23.5±14.1	26.2±13.9	27.8±16.9	25.9±16.5	24.6±17.5	22.7±15.9

D

Intervals between measurements (days; median with interquartile range)

#1~#2	#2~#3	#3~#4	#4~#5	#5~#6	#6~#7	#7~#8
59 (21~95)	59 (26~92)	28 (8~63)	30 (19~54)	49 (26~63)	50 (30~56)	60 (45~67)

Fig. 1. Serum potassium levels (**A**) and the frequency of serum potassium ≥6.0 mEq/L (**B**) in patients who received fludrocortisone without changes in ARB and CPS, and measured serum potassium at four outpatient visits before and after fludrocortisone administration (n=10, **p<0.01 compared with #4 before fludrocortisone).



C

eGRF (ml/min/1.73m²; mean with standard deviation)

#1	#2	#3	#4	#5	#6	#7	#8
21.4±11.7	21.0±14.0	19.2±14.4	17.2±12.3	18.2±14.6	14.0±9.1	13.2±10.7	12.2±9.8

D

Intervals between measurements (days; median with interquartile range)

#1~#2	#2~#3	#3~#4	#4~#5	#5~#6	#6~#7	#7~#8
91 (66~109)	91 (57~105)	92 (77~138)	27 (13~71)	66 (49~92)	45 (22~93)	41 (33~77)

Fig. 2. Serum potassium levels (**A**) and the frequency of serum potassium ≥6.0 mEq/L (**B**) in patients who received fludrocortisone as well as discontinuation of ARBs and/or the addition of low-dose CPS to control hyperkalemia, and measured serum potassium at four outpatient visits before and after fludrocortisone administration (n=5, *p<0.05 compared with #4 before fludrocortisone).

and 4.36±1.01 mEq/L after fludrocortisone administration, respectively (Fig. 2A). The frequency of serum potassium ≥6.0 mEq/L was 2/5, 2/5, 2/5, 5/5 before fludrocortisone administration and 0/5, 0/5, 0/5, 0/5 after fludrocortisone administration (Fig. 2B); thus, it decreased from 11/20 measurements (55%) to 0/20 measurements (0%) after fludrocortisone administration (p<0.001).

3. Changes in body weight and blood pressure after fludrocortisone administration

In 15 patients, blood pressure and body weight were measured at four outpatient visits before and after fludrocortisone administration.

Body weight was 67.5±10.8 kg, 67.2±10.3 kg, 67.1±10.4 kg, and 67.3±10.3 kg before fludrocortisone administration, and 68.6±10.3 kg, 68.2±10.9 kg, 68.6±11.1 kg, and 68.1±10.1 kg after fludrocortisone administration, with small but significant increases after fludrocortisone administration (Fig. 3).

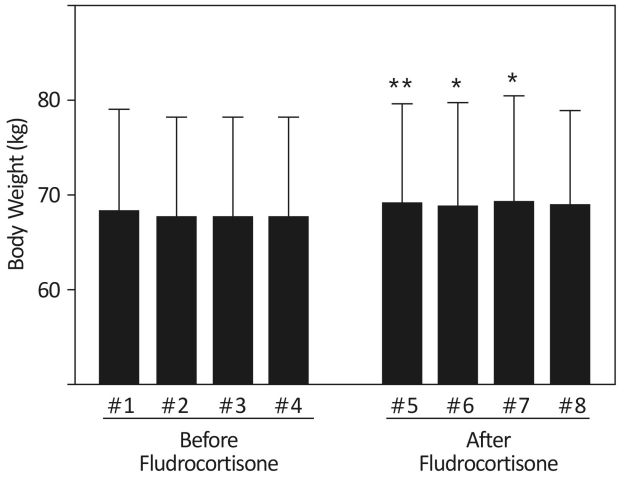


Fig. 3. Body weight changes in patients who were measured at four outpatient visits before and after fludrocortisone administration (n=15, *p<0.05 and **p<0.01 compared with #4 before fludrocortisone)

Systolic blood pressure was 129±18 mmHg, 130±20 mmHg, 131±17 mmHg, and 133±15 mmHg prior to the administration of fludrocortisone and 134±15 mmHg, 134±16 mmHg, 141±

16 mmHg, and 136±19 mmHg after fludrocortisone administration. Diastolic blood pressure was 72±10 mmHg, 74±12 mmHg, 72±7 mmHg, and 74±10 mmHg before fludrocortisone administration, and 74±9 mmHg, 76±11 mmHg, 76±10 mmHg, and 74±10 mmHg after fludrocortisone administration. There were no differences in systolic and diastolic blood pressures before and after fludrocortisone administration. During this time, antihypertensive medications were not changed in 13 patients, the dose of a calcium channel blocker was reduced in one patient, and an ARB was added in another patient.

4. Other adverse effects of fludrocortisone administration

Eleven patients experienced problems related to sodium retention following a median of 71 (51-435) days of fludrocortisone administration. Seven patients had worsening leg edema. Two patients suffered pleural effusions, while the other two developed pulmonary edemas. Diuretics were used to treat pleural effusion and pulmonary edema, and fludrocortisone was discontinued.

Three of the 21 patients in Group 1 and three of the 12 patients in Group 2 experienced hypokalemia (K^+ <3.5 mEq/L) at the first follow-up.

Discussion

In pre-dialysis CKD patients who are unable to tolerate adding CPS/SPS or increasing the dose of CPS/SPS, hyperkalemia detected in the outpatient clinic is a difficult problem to manage. The present study suggests that oral fludrocortisone may be an option in this situation.

So far, there has been little data on the use of fludrocortisone to control hyperkalemia in pre-dialysis CKD patients except a case report[21] in which fludrocortisone was safe and effective in preventing hyperkalemia and maintaining renal function in a woman with type 2 diabetes and CKD stage 3. Despite the lack of data, it has been suggested that CKD patients may require high doses of fludrocortisone (up to 0.4 mg daily) to reduce serum potassium due to aldosterone resistance in damaged renal tubules[22]. In the present study, however, low-dose fludrocortisone (0.05-0.1 mg daily) effectively decreased serum potassium level at 1st follow-up and significantly decreased the frequency of serum potassium ≥6.0 mmol/L from 30/60 (50%) to 2/60 (3%) ($p<0.001$) in 15 patients who measured serum potassium levels at four outpatient visits before and after fludrocortisone administration, respectively, reducing the risk of developing fatal arrhythmia.

Fludrocortisone has previously been studied to prevent hyperkalemia in hemodialysis patients. In a study of 19 hemodialysis patients[11], fludrocortisone (0.1-0.3 mg/day) decreased serum potassium from 5.6±0.1 mEq/L to 4.9±0.1 mEq/L. In another study of 15 patients[12] on hemodialysis receiving fludrocortisone with its dosage gradually increased from 0 to 0.2 mg/day, serum potassium was observed for five successive 4-week periods. The serum potassium concentration decreased from 5.57±0.05 mEq/L to 4.89±0.11 mEq/L at 0.15 mg administration. Such a decrease in serum potassium concentration was more significant in patients with low plasma aldosterone concentrations. In another study[13], 13 hemodialysis patients were treated with fludrocortisone (0.1 mg/day), and fludrocortisone lowered serum potassium levels from 6.1 (5.3-6.8) mEq/L to 5.2 (4.4-6.0) mEq/L at 10 months of treatment. In the other study of 37 hemodialysis patients[14], however, oral fludrocortisone (0.1 mg/day for 3 months) did not significantly reduce serum potassium levels. Thus, fludrocortisone demonstrated modest potassium-lowering effects in hemodialysis patients.

Because the primary sites of action for fludrocortisone are the collecting ducts of the kidneys, the potassium-lowering effect of fludrocortisone may vary depending on the presence of renal function. The majority of the hemodialysis patients included in the previous studies were oliguric or anuric, and thus fludrocortisone could not increase urinary potassium loss, and the decrease in serum potassium values was considered to occur via extrarenal losses, including gastrointestinal potassium excretion[23]. Fludrocortisone consequently had a limited effect on potassium elimination in HD patients and was well tolerated with no significant adverse effects, such as hypertension and volume overload. In contrast, the current study shows that fludrocortisone significantly lowers serum potassium levels in pre-dialysis CKD patients and, in some cases, even results in hypokalemia. On the other hand, the adverse effects seem to be more common in patients with CKD who are not yet on dialysis. Although the blood pressure was not significantly raised,

fludrocortisone caused pleural effusion and pulmonary edema in some patients. Thus, it may be necessary to co-administer a loop diuretic to prevent sodium retention.

Calcineurin inhibitors are one of the major components of immunosuppressants in patients with a kidney or liver transplant. Calcineurin inhibitors can result in type 4 renal tubular acidosis and hyperkalemia. Fludrocortisone, on the other hand, increases sodium resorption and facilitates potassium excretion in the distal convoluted renal tubule. As a result, fludrocortisone has been used to treat calcineurin inhibitor-induced hyperkalemia. A study[15] of 9 liver transplantation patients receiving tacrolimus has shown that fludrocortisone (0.14±0.08 mg/day) decreased serum potassium from 5.7±1 to 4.3±0.5 mEq/L within 48 h. In another study[16] of 10 renal transplant patients with hyperkalemic metabolic acidosis who were taking calcineurin inhibitors, such as tacrolimus, fludrocortisone decreased potassium from 6.1±0.4 to 5.3±0.3 mEq/L. However, fludrocortisone had no significant effects on blood pressure or serum sodium. Consistent with the previous reports, serum potassium was well controlled in two of our patients, one of whom had liver transplantation and another had lung transplantation, receiving tacrolimus as an immunosuppressant.

After oral administration, fludrocortisone is promptly absorbed and exhibits a two- to three-hour half-life. In normal subjects, fludrocortisone (0.2 mg) was shown to increase the transtubular potassium gradient (TTKG) within 3 h after oral administration[24]. Fludrocortisone may thus be useful for acutely lowering serum potassium. It is unknown, however, how quickly it reduces serum potassium levels in CKD patients. The findings in this study warrant further research into the acute effect of fludrocortisone on serum potassium in pre-dialysis CKD.

The traditionally used potassium-lowering agents, CPS and SPS, are unpalatable and cause constipation. Sodium zirconium cyclosilicate and patiromer, two newly introduced potassium-lowering agents, are known to be effective and have fewer adverse reactions[7]. These agents, however, should also be avoided in patients with severe constipation[25], are significantly more expensive than CPS and SPS[5,26], and are not available in many countries. In this study, low-dose fludrocortisone caused sodium retention-related problems in some patients but effectively lowered serum potassium. Our findings suggest that fludrocortisone may be used selectively in pre-dialysis hyperkalemic CKD patients if no other appropriate option to lower serum potassium levels is available. In CKD patients, renin-angiotensin system (RAS) inhibitors, including ARBs, are often discontinued due to hyperkalemia, but withdrawing RAS inhibitors is associated with a higher risk of mortality[27]. Our data suggest that fludrocortisone may also lower serum potassium levels in ARB-treated patients.

However, because of the retrospective study design, this study has a number of limitations. First, because fludrocortisone has not traditionally been utilized for hyperkalemia in CKD patients, the sample size was limited. Second, evidence of increases in urine potassium or TTKG following fludrocortisone administration is useful in supporting the potassium-lowering effect of the drug, but the data on urinary potassium levels are lacking. Third, the absence of a control group made it impossible to assess the impact of fludrocortisone on cardiovascular events and renal function.

In conclusion, low-dose oral fludrocortisone may be a useful short-term option for lowering high potassium levels in hyperkalemic pre-dialysis CKD patients if CPS/SPS is not tolerated and other potassium-binding agents are not available. However, it should be used with caution due to the potential for adverse effects such as pulmonary edema.

Conflict of Interest

The authors have no conflicts of interest to declare.

REFERENCES

1. Gilligan S, Raphael KL: Hyperkalemia and Hypokalemia in CKD: Prevalence, Risk Factors, and Clinical Outcomes. Adv Chronic Kidney Dis 2017;24:315-318.
2. Montford JR, Linas S: How Dangerous Is Hyperkalemia? J Am Soc Nephrol 2017;28:3155-3165.
3. Yu MY, Yeo JH, Park JS, Lee CH, Kim GH: Long-term efficacy of oral calcium polystyrene sulfonate for hyperkalemia in CKD patients. PLoS One 2017;12:e0173542.
4. Lepage L, Dufour AC, Doiron J, et al.: Randomized Clinical Trial of Sodium Polystyrene Sulfonate for the Treatment of Mild Hyperkalemia in CKD. Clin J Am Soc Nephrol 2015; 10:2136-2142.
5. Larivée NL, Michaud JB, More KM, Wilson JA, Tennankore

KK: Hyperkalemia: Prevalence, Predictors and Emerging Treatments. Cardiol Ther 2023;12:35-63.
6. Rossignol P, Legrand M, Kosiborod M, et al.: Emergency management of severe hyperkalemia: Guideline for best practice and opportunities for the future. Pharmacol Res 2016;113:585-591.
7. Meaney CJ, Beccari MV, Yang Y, Zhao J: Systematic Review and Meta-Analysis of Patiromer and Sodium Zirconium Cyclosilicate: A New Armamentarium for the Treatment of Hyperkalemia. Pharmacotherapy 2017;37:401-411.
8. Quinkler M, Oelkers W, Remde H, Allolio B: Mineralocorticoid substitution and monitoring in primary adrenal insufficiency. Best Pract Res Clin Endocrinol Metab 2015;29:17-24.
9. Barrera-Chimal J, Lima-Posada I, Bakris GL, Jaisser F: Mineralocorticoid receptor antagonists in diabetic kidney disease - mechanistic and therapeutic effects. Nat Rev Nephrol 2022;18:56-70.
10. Epstein M, Kovesdy CP, Clase CM, Sood MM, Pecoits-Filho R: Aldosterone, mineralocorticoid receptor activation, and CKD: A review of evolving treatment paradigms. Am J Kidney Dis 2022;80:658-666.
11. Singhal PC, Desroches L, Mattana J, Abramovici M, Wagner JD, Maesaka JK: Mineralocorticoid therapy lowers serum potassium in patients with end-stage renal disease. Am J Nephrol 1993;13:138-141.
12. Furuya R, Kumagai H, Sakao T, Maruyama Y, Hishida A: Potassium-lowering effect of mineralocorticoid therapy in patients undergoing hemodialysis. Nephron 2002;92:576-581.
13. Kim DM, Chung JH, Yoon SH, Kim HL: Effect of fludrocortisone acetate on reducing serum potassium levels in patients with end-stage renal disease undergoing haemodialysis. Nephrol Dial Transplant 2007;22:3273-3276.
14. Kaisar MO, Wiggins KJ, Sturtevant JM, et al.: A randomized controlled trial of fludrocortisone for the treatment of hyperkalemia in hemodialysis patients. Am J Kidney Dis 2006;47:809-814.
15. Dick TB, Raines AA, Stinson JB, Collingridge DS, Harmston GE: Fludrocortisone is effective in the management of tacrolimus-induced hyperkalemia in liver transplant recipients. Transplant Proc 2011;43:2664-2668.
16. Gama RM, Makanjuola D, Wahba M, Quan V, Phanish M: Fludrocortisone is an effective treatment for hyperkalaemic metabolic acidosis in kidney transplant recipients on tacrolimus: A case series. Nephron 2022;146:190-196.
17. Sahu MK, Singh SP, Das A, et al.: High blood tacrolimus and hyperkalemia in a heart transplant patient. Ann Card Anaesth 2017;20:270-271.
18. Gheith OA, Dahab M, Nagib AM, et al.: Fludrocortisone among adult renal transplant recipients with persistent hyperkalemia: Single-center experience. Exp Clin Transplant 2022;20(Suppl 1):69-73.
19. Hamrahian SM, Fülöp T: Hyperkalemia and hypertension post organ transplantation - A management challenge. Am J Med Sci 2021;361:106-110.
20. Inker LA, Eneanya ND, Coresh J, et al.: Chronic kidney disease epidemiology collaboration. New creatinine- and cystatin C-based equations to estimate GFR without race. N Engl J Med 2021;385:1737-1749.
21. Dobbin SJH, Petrie JR, Lean MEJ, McKay GA: Fludrocortisone therapy for persistent hyperkalaemia. Diabet Med 2017;34:1005-1008.
22. DeFronzo RA: Hyperkalemia and hyporeninemic hypoaldosteronism. Kidney Int 1980;17:118-134.
23. Imbriano LJ, Durham JH, Maesaka JK: Treating interdialytic hyperkalemia with fludrocortisone. Semin Dial 2003;16:5-7.
24. Kamel KS, Ethier JH, Quaggin S, et al.: Studies to determine the basis for hyperkalemia in recipients of a renal transplant who are treated with cyclosporine. J Am Soc Nephrol 1992;2(8):1279-1284.
25. Rosano GMC, Spoletini I, Agewall S: Pharmacology of new treatments for hyperkalaemia: patiromer and sodium zirconium cyclosilicate. Eur Heart J 2019;Suppl 21(Suppl A):A28-A33.
26. Bounthavong M, Butler J, Dolan CM, et al.: Cost-effectiveness analysis of patiromer and spironolactone therapy in heart failure patients with hyperkalemia. Pharmacoeconomics 2018;36:1463-1473.
27. Nakayama T, Mitsuno R, Azegami T, Sato Y, Hayashi K, Itoh H: A systematic review and meta-analysis of the clinical impact of stopping renin-angiotensin system inhibitor in patients with chronic kidney disease. Hypertens Res 2023;46:1525-1535.

Case Report

ISSN 1738-5997 (Print) · ISSN 2092-9935 (Online)
Electrolyte Blood Press 2024;22:16-20
https://doi.org/10.5049/EBP.2024.22.1.16

A Case of Recurrent Renal Infarction Following Transient Resolution: Evidence From Serial Computed Tomography

In Hong Choi, Chang Seong Kim, Eun Hui Bae, Seong Kwon Ma, Soo Wan Kim and Hong Sang Choi[1,2]

[1]*Department of Internal Medicine, Chonnam National University Medical School, Gwangju, Republic of Korea;*
[2]*Department of Internal Medicine, Chonnam National University Hospital, Gwangju, Republic of Korea*

Received: December 27, 2023
Revised: April 10, 2024
Accepted: April 16, 2024
Corresponding Author: Hong Sang Choi, MD, PhD
Department of Internal Medicine Chonnam National University Medical School 42 Jebongro, Gwangju 61469, Republic of Korea
Tel: +82-62-220-6296; Fax: +82-62-225-8578
E-mail: choihs@jnu.ac.kr

Although renal infarction (RI) is not a rare disease, its outcomes have not been well-documented. Furthermore, transient resolution and recurrence of RI have not been captured through imaging. We report a case of idiopathic RI that recurred within a short period following transient resolution, as demonstrated by serial computed tomography (CT). A 53-year-old man diagnosed with RI was transferred to the emergency room. An abdominal CT scan at the local hospital revealed a segmental wedge-shaped perfusion defect in the left kidney and a focal thrombotic filling defect in the anterior segmental branch of the left renal artery. Since his left flank pain improved, another CT scan was performed again 6 hours after the initial CT scan. A repeat CT scan showed that the thrombus in the renal artery remained, but the perfusion defect had spontaneously resolved. We initiated anticoagulant therapy using unfractionated heparin. On the sixth day of hospitalization, the left flank pain recurred, prompting another CT scan. The follow-up CT scan confirmed that RI had recurred in the same area as before. We continued anticoagulant therapy and switched to warfarin. After treatment, his symptoms improved, and he was discharged. RI can recur at any time, even after it has spontaneously resolved, as evidenced by our case. Therefore, it is crucial to closely monitor patients who experience resolution of RI for any recurrence of symptoms, and repeat radiological evaluation should be performed even within a short period.

Key Words: Renal infarction, Transient resolution, Recurrence, Computed tomography

INTRODUCTION

Renal infarction (RI) is an uncommon condition that can result from acute occlusion of blood flow in the renal arteries or their segmental branches[1-6]. Many risk factors are known to cause RI, including cardiogenic factors, such as atrial fibrillation, valvular heart disease, and endocarditis, as well as renal artery injury, hypercoagulation disorders, and hematologic diseases[1,2]. However, in some cases, the cause is unknown[1,2].

The outcomes of RI can include acute kidney injury, progression to chronic kidney disease or end-stage renal disease, and death[1] Moreover, thromboembolic events are likely to recur in other organs, including the kidneys[3,7]. However, to our knowledge, there have been no published large-scale retrospective studies investigating the outcomes of RI, so these have not been well reported[1]. Furthermore, there have been no reports demonstrating the recurrence of RI after transient resolution through imaging. We report a case of idiopathic RI that recurred within a short period after transient resolution, as demonstrated by serial computed tomography (CT).

CASE REPORT

A 53-year-old man suspected of having RI based on an abdominal CT scan was transferred to our emergency room (ER) from a local hospital. He complained of Lt flank pain about five hours ago, and the symptom persisted until he was at the local hospital, but gradually improved after arriving at our hospital. He was taking 80 mg of valsartan, 5 mg of amlodipine, and 0.2 mg of tamsulosin per day for hypertension and benign prostatic hyperplasia diagnosed 10 years ago and was not taking any other medications such as antiplatelet agents or anticoagulants. He was a current smoker for about 15 pack-years and a social alcohol drinker. His blood pressure was 150/80 mmHg, his pulse rate was 82 beats/min, and his body temperature was 36.6℃. Laboratory studies showed a white blood cell count of $12.9 \times 10^3/\mu L$ and an elevated lactate dehydrogenase (LDH) level (640 IU/L), while his C-reactive protein level (0.15 mg/dL) was normal. Additionally, he had a normal creatinine level (0.95 mg/dL) and a normal eGFR (91.02 mL/min/1.73 m^2). No hematuria or pyuria was observed; however, mild proteinuria (1+) was detected in the urinalysis. An abdominal CT scan at the local hospital revealed a segmental wedge-shaped perfusion defect in the left kidney and a focal thrombotic filling defect in the anterior segmental branch of the left renal artery (Fig.1A, 2A). Since his flank pain improved after admission to our ER, another abdominal CT scan was performed 6 hours after the initial CT scan at the local hospital. The thrombus in the anterior segmental branch of the left renal artery remained, but the segmental wedge-shaped perfusion defect in the left kidney had spontaneously resolved in the repeated CT scan (Fig. 1B, 2B). We initiated anticoagulant therapy with intravenous unfractionated heparin and adjusted the dose to target activated partial thromboplastin time of 60-90 seconds. We tested his blood for hypercoagulability and autoimmune diseases and performed electrocardiography and echocardiography to investigate the cause of the RI. The blood tests for hypercoagulability such as protein C, protein S, antithrombin and homocysteine, and tests for antiphospholipid syndrome did not reveal any abnormal findings. Electrocardiography did not detect any arrhythmias during his hospitalization, and there was no evidence of thromboembolic sources such as thrombi or vegetations on the echocardiogram. We, therefore, diagnosed him with idiopathic RI. On the sixth day of hospitalization, he again complained of left flank pain similar to his previous pain. He did not have a fever, and there was no evidence of a urinary tract infection, so another abdominal CT scan was performed to ascertain the possibility of recurrent RI. The follow-up abdominal CT scan showed that the segmental wedge-shaped perfusion defect had recurred in the same area as previously observed, and the thrombus in the anterior segmental branch remained (Fig. 1C, 2C). We continued anticoagulant therapy with unfractionated heparin for a week and transitioned to warfarin 6-7 mg/day for the goal of prothrombin time 2-3 INR, with a period of overlap between the two

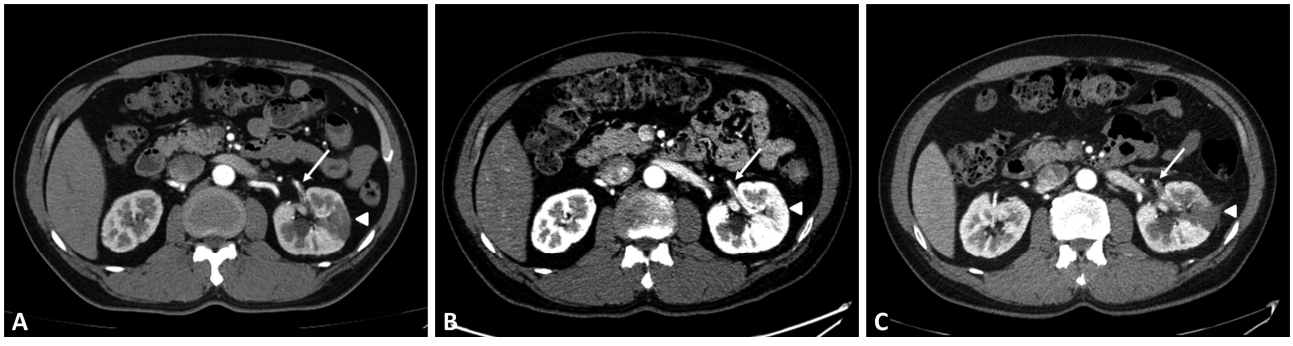


Fig. 1. Serial transverse views of abdominal CT scans of the patient with renal infarction. (**A**) An abdominal CT scan at the local hospital revealed a perfusion defect in the left kidney (arrowhead); (**B**) The perfusion defect spontaneously resolved (arrowhead) in our emergency room; (**C**) The perfusion defect recurred (arrowhead) on the sixth day of hospitalization. A thrombus in the anterior segmental branch of the left renal artery (arrow) persisted on all serial abdominal CT scans.

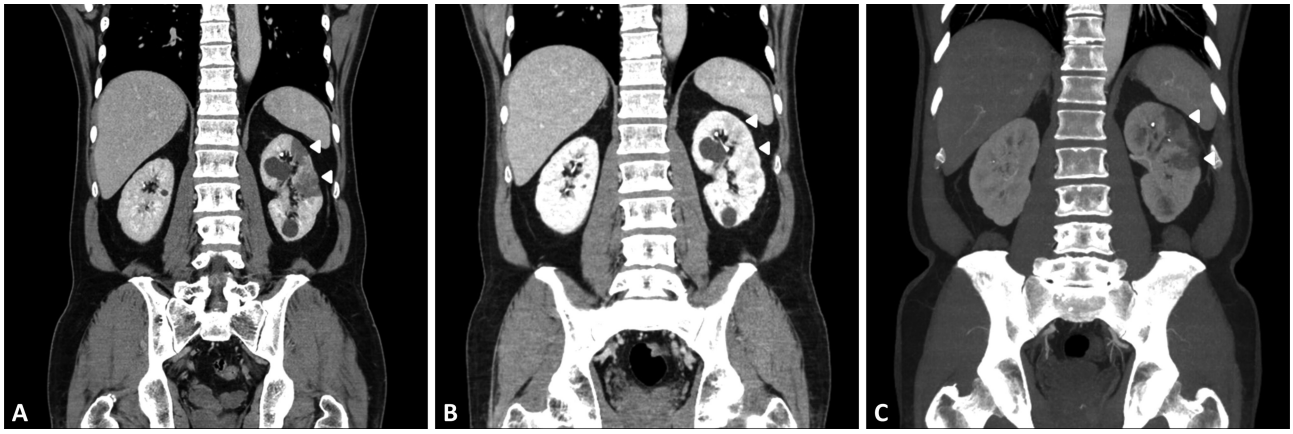


Fig. 2. Serial coronal views of abdominal CT scans of the patient with renal infarction. (**A**) An abdominal CT scan at the local hospital showed a perfusion defect in the left kidney (arrowhead); (**B**) The perfusion defect spontaneously resolved (arrowhead) in our emergency room; (**C**) The perfusion defect recurred (arrowhead) on the sixth day of hospitalization.

anticoagulants. After treatment, his symptoms improved, and he was discharged on the eighth day of hospitalization with ongoing anticoagulant therapy. Six months after discharge, low-dose aspirin was prescribed instead of warfarin, and it was planned to be maintained lifelong to prevent recurrence of RI. One year after the event, he had not experienced any symptoms associated with RI such as flank pain, and his renal function remained within the normal range of eGFR 96 mL/min/1.73 m^2.

DISCUSSION

The incidence of RI is not yet clearly known[8]. Domanovits et al. and Huang et al. reported that 0.007% (17 of 248,842) and 0.004% (20 of the 481,540), respectively, of patients who visited the ER were diagnosed with RI[3,8]. Korzets et al. also found that 11 of 151,914 patients (0.007%) admitted to their hospital were diagnosed with RI[9]. However, the actual prevalence is thought to be higher because RI is often misdiagnosed owing to its non-specific symptoms[9]. Additionally, as the use of contrast-enhanced CT increases as a diagnostic tool for abdominal problems of unknown origins, the number of patients diagnosed with RI is also increasing[9]. The symptoms and signs of RI include abdominal or flank pain, nausea, vomiting, fever, and hypertension [1,2,4,9,10]. However, because of these non-specific features, RI is often misdiagnosed as other more common diseases, such as urolithiasis, acute pyelonephritis, and back pain of musculoskeletal origin, leading to delayed diagnosis[8,9]. Increased serum LDH is the most sensitive laboratory finding, and inflammation markers, such as white blood cells and C-reactive protein, are sometimes elevated[1-3,10]. Hematuria and proteinuria are also sometimes present[3,10]. However, these same laboratory findings and urinalysis results can be associated with other diseases[3,10]. Therefore, imaging tools, such as CT, magnetic resonance imaging, renal angiography, and/or scintigraphy, are required to confirm RI[1,3]. Since contrast-enhanced CT is non-invasive and can be performed within 24 hours, it is currently the gold standard for diagnosing RI[3].

Treatment options for RI include radiologic or surgical percutaneous endovascular therapy, anticoagulant therapy, and antiplatelet therapy[1,2]. However, there are currently no prospective randomized clinical trials to determine which treatment is superior[2,3]. Thus, there is still no established definitive treatment for RI[2,3]. Treatment for RI should be chosen considering various factors such as the time taken to diagnose the infarction, the underlying cause of the infarction, and the severity of the infarction[2,3,7,8]. If revascularization is deemed to be more beneficial, radiologic or surgical percutaneous endovascular therapy may be considered as the initial intervention[2,3,7,8]. If revascularization is not deemed beneficial, antiplatelet therapy or anticoagulant therapy may be selected based on the underlying cause of the RI[2,3,7,8]. In cases diagnosed as idiopathic renal infarction, like our case, anticoagulant therapy is typically initiated.

If the diagnosis of RI is delayed, appropriate treatment cannot be administered, which may result in deterioration of renal function and even death[6,8]. Therefore, early diagnosis is important for improving outcomes[3]. Domanovits et al. suggest that contrast-enhanced CT should be performed early for all patients exhibiting the triad of high risk for thromboembolic events: persistent back pain, elevated serum LDH, and/or hematuria within 24 hours of the onset of pain[3]. However, this triad has limitations: many patients diagnosed with RI have a low risk of thromboembolism and often do not have hematuria[5,8]. Huang et al. also proposed a flow chart for the diagnosis and treatment of RI[8]. Due to the current lack of established guidelines for the early diagnosis of RI, further studies are needed. It is also important for physicians to be aware that RI is not a rare disease[8].

The outcomes of RI are not yet clearly known[1]. Specifically, there are few studies that have reported the frequency and timing of recurrent thromboembolic events in RI[1,5]. Oh et al. found that 2.8% (12 of 438) of patients diagnosed with RI experienced recurrence, and the median time to recurrence was 11.5 months (range, 1-108 months)[1]. García-García et al. reported that 11.9% (7 of 59) of patients diagnosed with RI had recurrent arterial thrombosis (three with RI, two with cerebrovascular disease, and three with ischemic heart disease) and 3.4% (2 of the 59 patients) had recurrent venous thromboembolism[5]. While Oh et al. found that there was no significant difference in the recurrence rate based on the cause of RI, García-García et al. determined that the recurrence rate of arterial thrombosis was higher in the group with clear underlying pathogenetic mechanisms compared with the idiopathic group[1,5]. Additional studies are needed to understand the frequency, timing, and risk factors associated with recurrent RI.

There is a lack of established guidelines for monitoring patients following the initiation of treatment for RI. Our case demonstrated that thromboembolic events can recur during treatment, and the recurrence interval can be remarkably short. As early diagnosis and appropriate treatment are important for the prognosis of RI[3,4,6-8], it is also crucial to detect the recurrence of thromboembolic events early. To achieve this, proper monitoring of the patient's status following treatment is required. This entails ongoing assessment of their clinical condition, laboratory findings, and urinalysis. Physicians' alertness to the possibility of recurrent RI is also crucial for early detection. If there is suspicion of recurrence of RI during monitoring, it is necessary to actively perform radiologic examinations (especially contrast-enhanced CT) to confirm recurrence.

The first is the presence of undetected arrhythmias such as paroxysmal atrial fibrillation (Af). Af is one of the main causes of RI, and it is important to suspect the presence of paroxysmal Af even if arrhythmia is not found when RI occurs (cereus paper). Although we were monitoring the patient very closely and maintaining anticoagulation, this possibility cannot be completely ruled out. Second, the patient's thrombotic risk may have been higher than we expected. The patient was a long-term current smoker. Smoking is known to be one of the risk factors for RI. Huang et al. reported that current smoking had a significant adverse impact on thromboembolic complications after RI[11]. Therefore, continuous monitoring of the expression of Af will be very important in determining the treatment policy for patients with renal infarction, and educating current smokers such as our patient to quit smoking will likely improve the patient's prognosis.

As we experienced during the management of this patient, the recurrence of RI may be observed during the administration of anticoagulation therapy despite the prior spontaneous resolution of the RI. Furthermore, RI recurrence can occur within a short period following spontaneous resolution. Radiologically documented cases of spontaneous resolution and recurrence of RI during initial anticoagulation are rare. Therefore, physicians' awareness of the potential for recurrent thromboembolic events is essential. Also, if recurrence is suspected, it is important to actively perform radiologic examinations for early diagnosis.

Acknowledgements

This work was supported by a National Research Foundation of Korea (NRF) grant funded by the Korean government (Ministry of Science and ICT) (NRF-2022R1C1C1007573)

Disclosure

The authors have no potential conflicts of interest to disclose.

REFERENCES

1. Oh YK, Yang CW, Kim YL, et al.: Clinical Characteristics and Outcomes of Renal Infarction. Am J Kidney Di 2016;67(2): 243-250.
2. Bourgault M, Grimbert P, Verret C, et al.: Acute renal infarction: a case series. Clin J Am Soc Nephrol 2013;8(3): 392-398.
3. Domanovits H, Paulis M, Nikfardjam M, et al.: Acute renal infarction. Clinical characteristics of 17 patients. Medicine (Baltimore) 1999;78(6):386-394.
4. Bae EJ, Hwang K, Jang HN, et al.: A retrospective study of short- and long-term effects on renal function after acute renal infarction. Ren Fail 2014;36(9):1385-1389.
5. García-García A, Demelo-Rodríguez P, Ordieres-Ortega L, et al.: Idiopathic versus Provoked Renal Infarction: Characteristics and Long-Term Follow-Up of a Cohort of Patients in a Tertiary Hospital. Kidney Blood Press Res 2019;44(6):1432-1440.
6. Antopolsky M, Simanovsky N, Stalnikowicz R, et al.: Renal infarction in the ED: 10-year experience and review of the literature. Am J Emerg Med 2012;30(7):1055-1060.
7. Hazanov N, Somin M, Attali M, et al.: Acute renal embolism. Forty-four cases of renal infarction in patients with atrial fibrillation. Medicine (Baltimore) 2004;83(5):292-299.
8. Huang CC, Lo HC, Huang HH, et al.: ED presentations of acute renal infarction. Am J Emerg Med 2007;25(2):164-169.
9. Korzets Z, Plotkin E, Bernheim J, et al.: The clinical spectrum of acute renal infarction. Isr Med Assoc J 2002;4(10):781-784.
10. Chu PL, Wei YF, Huang JW, et al.: Clinical characteristics of patients with segmental renal infarction. Nephrology (Carlton) 2006;11(4):336-340.
11. Huang CW, Lee MJ, Hsu CY et al.: Clinical outcomes associated with anti-coagulant therapy in patients with renal infarction. QJM 2018;111(12):867-873.