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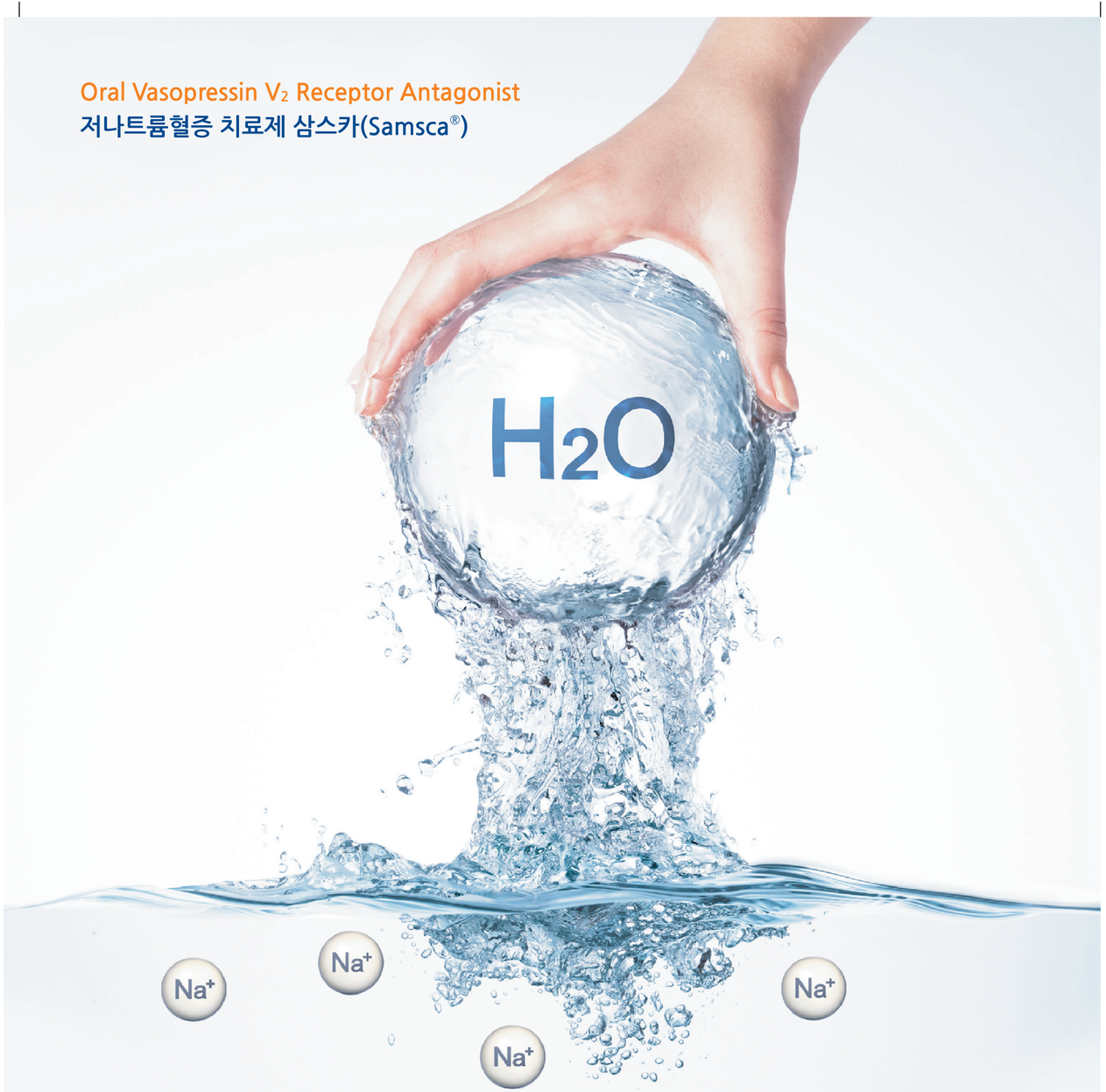

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Review Articles

Review Article

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A New Era in Diabetic Kidney Disease Treatment: The Four Pillars and Strategies to Build Beyond

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Diabetic kidney disease (DKD) is a prevalent and complex disease among patients with diabetes in Korea, requiring comprehensive treatment strategies. Traditional management strategies targeting blood pressure, blood sugar, lipid, and lifestyles are foundational approaches of DKD treatment, each of them still holding importance in current paradigms. The four pillars, renin-angiotensin system (RAS) inhibitors, sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and non-steroidal mineralocorticoid receptor antagonists (nsMRA) can enhance DKD treatment. Expanding beyond these pillars with future-oriented pillars including precision medicine, digital health, gut health, anti-inflammatory/fibrotic agents, psychosocial/behavioral health, and regenerative medicine can further advance DKD treatment strategies, offering a more cohesive framework which shifts a disease-centered approach to a patient-centered approach.

Key Words: Diabetic kidney disease, RAS inhibitors, SGLT2 inhibitors, Glucagon-like peptide-1 receptor agonists, Non-steroidal mineralocorticoid receptor antagonists, Precision medicine, Regenerative medicine

INTRODUCTION

Diabetic kidney disease (DKD) has become an increasingly prevalent and significant health burden worldwide, particularly in Korea, where rates of diabetes continue to rise.[1] With Korea's aging population and evolving lifestyle changes, the incidence of diabetes has surged, directly contributing to an increase in DKD cases[1)]. According to recent epidemiological data, nearly 40% of older patients with diabetes develop kidney complications, placing a strain on both patients and healthcare systems[1,2)]. Additionally, the high prevalence of hypertension, obesity, and metabolic syndrome among Korean adults has escalated the risk of progression from diabetes to DKD[1)].

These factors highlight the urgent need for comprehensive and effective management strategies to address the complexities of DKD. Although the traditional foundations of DKD treatment — blood pressure control[3)], glucose control[2)], cholesterol control[4)], and lifestyle modifications[5)] — provide a strong foundational approach, new pillars are required for better management. Current treatment paradigms integrate traditional foundations with new pillars of DKD treatment, but there are still remaining challenges to overcome[2)]. Expanding beyond this structure by additionally integrating rapidly advancing data science, bioengineering techniques and holistic lifestyle modifications may offer a more personalized and robust defense against the progression of DKD and its complications. The objective of this article is to explore current treatment paradigms and investigate future-oriented innovations to establish a compre-

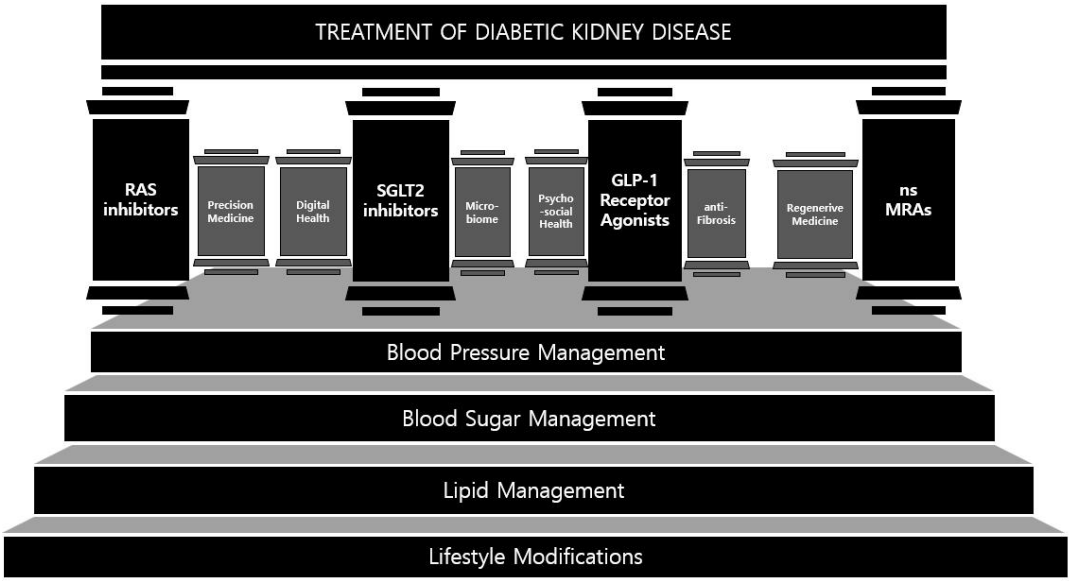

Fig. 1. An analogy illustrating the strategies of DKD treatment as pillars in a temple. Traditional managements, which are foundational approaches, are represented as stairs. The pillars include the four pillars and future-oriented pillars suggested in this article.

hensive DKD management framework (Fig. 1).

Section 1: The Unwavering Importance of Traditional Risk Factor Management

The current approach to managing DKD has evolved to incorporate a multifaceted framework that integrates both established and emerging therapies. In this approach, traditional foundations such as blood pressure management, blood sugar management, lipid management, and lifestyle modifications remain critical due to their proven roles in slowing the progression of kidney damage in diabetic patients[4-7]. These measures, aimed at maintaining cardiovascular and renal stability, emphasize lifestyle adjustments, dietary management, and medication adherence as essential components in preventing complications associated with DKD[8]. Effective management of blood pressure is particularly important, as hypertension is both a cause and a consequence of DKD[3]. Proper control of blood pressure reduces mechanical stress on the kidney's vasculature, minimizing glomerular injury and delaying progression to end-stage renal disease (ESRD)[3]. Similarly, effective blood sugar regulation plays a fundamental role in mitigating hyperglycemia-induced damage and microvascular complications[2]. Lipid regulation also plays a complementary role by lowering the risk of cardiovascular complications, which are highly prevalent among patients with DKD[4].

- **Blood Pressure Management:** Independently, managing hypertension reduces glomerular pressure and protects vascular autoregulation, mitigating renal injury and delaying progression to ESRD[3]. Maintaining target blood pressure levels has been shown to significantly reduce the risk of kidney failure in diabetic patients[6]. Cardiovascular events also have been shown to reduce with intensive blood pressure control among diabetic patients in the BPROAD trial[9]. The SPRINT trial, which tested intensive blood pressure control in patients without diabetes, showed that intensive blood pressure control can lower cardiovascular risk regardless of diabetes status[9]. Considering that cardiovascular diseases are the most common complications of DKD, blood pressure control is a key factor in DKD patient treatment. Selecting an adequate blood pressure target is important, since there is no RCT specifically determining target levels in DKD patients and excessively low blood pressure can rather cause harm[2-3].
- **Blood Sugar Management:** Effective glycemic control minimizes hyperglycemia-induced oxidative stress and renal damage, helping to reduce the incidence of mi-

crovascular complications and macrovascular complications, including diabetic nephropathy and cardiovascular events[2]. The DCCT trial showed that intensive glucose control therapy with the target of 6.05% or less glycosylated hemoglobin, can reduce the risk of nephropathy up to 34% and slow disease progression in diabetic patients[7].

- **Lipid Management:** Controlling lipid levels lowers the risk of atherosclerosis and cardiovascular complications, which are major comorbidities in DKD. Statins and other lipid-lowering agents such as ezetimibe, fibrates, bempedoic acid, and PCSK9 inhibitors are required in minimizing cardiovascular risks in these patients[4]. The CTT meta-analysis showed that statin therapy targeting LDL reduction lowered the risk of cardiovascular disease by 21%[4].
- **Lifestyle Modifications:** Lifestyle modifications such as dietary management, exercising, cessation of harmful habits are also important in DKD patients. Dietary management includes sodium restriction, protein control, and phosphorus control. Harmful habits include alcohol consumption, and smoking. These modifications address overall metabolic health, reducing inflammatory and oxidative stressors that contribute to kidney disease progression[8,10]. A systematic review of behavior change techniques used for lifestyle modifications of chronic kidney disease (CKD) patients identified that education was the most commonly used technique followed by enablement, training, persuading, and environmental restructuring[5].

In addition to these traditional measures, recent therapeutic developments focus on novel pharmacologic agents that target mechanisms of renal and cardiovascular disease progression. Key among these are renin-angiotensin system (RAS) inhibitors[6,11], sodium-glucose cotransporter-2 (SGLT2) inhibitors[12-14], Glucagon-like peptide-1 (GLP-1) receptor agonists[15,16], and non-steroidal mineralocorticoid receptor antagonists (nsMRAs)[17]. These developments address that new therapies can lead to a more tailored and advanced approach on DKD patients. However, it is crucial to emphasize that while new therapies can significantly enhance patient outcomes, the foundation of DKD management still relies on traditional risk factor management and that these traditional methods should not be overlooked.

Section 2: The Four Pillars in DKD and their Synergistic Effects with Traditional Management Therapies

The four pillars (RAS inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, nsMRAs) have been proven as significant DKD treatment choices in large-scale evidences. These pillars complement and enhance the efficacy of established practices, providing a more comprehensive approach to DKD. Each approach offers unique, independent effects in mitigating disease progression, while also demonstrating synergistic benefits when combined with traditional management strategies.

- **Renin-Angiotensin System (RAS) Inhibitors:** RAS inhibitors such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin ii receptor blockers (ARB) directly protect the kidneys by reducing intraglomerular pressure and proteinuria, addressing specific pathways involved in renal injury[6,11]. The IDNT study demonstrated that irbesartan has renoprotective benefits independent of achieved systolic blood pressure in diabetic patients[11]. However, combination of ACEi and ARB therapy is not recommended because it can increase the risk of adverse events[3,18].
- **Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors:** SGLT2 inhibitors reduce hyperfiltration and improve metabolic control, exerting renoprotective effects through mechanisms beyond glucose reduction[12]. The CREDENCE trial[12] and the CANVAS trial[14] showed improved kidney outcomes with canagliflozin in DKD patients. The EMPA-REG OUTCOME trial demonstrated the effect of empagliflozin on improving kidney outcomes in DKD patients[13]. Through these evidences, SGLT2 inhibitors stand as an important pillar in preventing kidney function decline in DKD patients.
- **Glucagon-like Peptide-1 (GLP-1) Receptor Agonists:** GLP-1 receptor agonists were first recognized to control glucose level, decrease body weight, and reduce cardiovascular risk in diabetic patients[16]. Recent trials on DKD patients demonstrated that GLP-1 receptor agonists have additional renoprotective benefits along with previously known effects. GLP-1 receptor agonists can improve kidney functions in DKD patients in-

directly by preventing hyperglycemia, hypertension, obesity and also directly, by reducing oxidative stress and inflammation[19,20]. Liraglutide and dulaglutide have been demonstrated to lower albuminuria, slow eGFR decline, and reduce risk of kidney function loss in the LEADER trial[15] and the REWIND trial[20], respectively. Semaglutide was shown to induce 24% reduction of kidney related outcomes (albuminuria, low eGFR, initiation of RRT, kidney related death) in the FLOW trial[16] and the SUSTAIN 6 trial[15]. Other novel GLP-1 receptor agonists showed similar promising results. Tirzepatide showed renoprotective effects by slowering eGFR decrease and stabilizing urine albumin-creatinine ratio (UACR) in the SURPASS-4 trial[21,22]. Efpeglenatide also mitigated kidney related outcomes such as albuminuria in the AMPLITUDE-O trial[23]. These evidences support the position of GLP-1 receptor agonists as a promising new pillar in DKD treatment.

- **Non-steroidal Mineralocorticoid Receptor Antagonists (nsMRAs):** Novel nsMRAs act to reduce inflammation and fibrosis within the kidney, targeting mechanisms that are not adequately addressed by traditional therapies or other agents such as SGLT2 inhibitors and GLP-1 receptor agonists[17]. By limiting the fibrotic response, these agents help preserve kidney function over time. In the FIDELIO-DKD study and the FIGARO-DKD study, finerenone reduced disease progression and the risk of cardiovascular diseases in DKD patients[8,17]. The additive effect of finerenone on patients treated with SGLT2 inhibitors and GLP-1 receptor agonists needs further investigation[8].

Synergistic Effects between the Four Pillars and Traditional Management Therapies

While each of the four pillars has independent effects, a synergistic benefit arises when traditional risk factor management is combined with the four pillars. For instance, blood pressure control alongside RAS inhibition provides an enhanced protective effect on glomerular pressure. The RENAAL study demonstrated that combining losartan with other BP management therapy can slow ESRD progression[6]. Similarly, blood sugar regulation such as use of metformin complements the glucose-lowering effect of SGLT2 inhibitors and GLP-1 receptor agonists, together offering greater metabolic control and reduced renal workload[2,8,24].

The combination of lipid management with GLP-1 receptor agonists also results in reduced cardiovascular risk, a major cause of morbidity and mortality among patients with DKD[8]. Lifestyle interventions, such as diet and exercise, have shown synergistic effects with pharmacological therapies, helping to maximize therapeutic outcomes[2,10,24]. This suggests that significant lifestyle modifications are required to patients undergoing treatment[24].

In sum, traditional risk factor management and the four pillars work in concert to provide a multi-layered defense against DKD progression. The independent and synergistic effects underscore the importance of a holistic and comprehensive approach to DKD management, leveraging each component to achieve optimal renal and cardiovascular outcomes for patients.

Section 3: Future-Oriented Expansion of DKD Treatment Pillars

As DKD continues to evolve in both prevalence and complexity, expanding beyond the current paradigm is called for. These future pillars aim to address gaps in treatment and embrace advancing technologies, precision medicine, and comprehensive patient-centered care. The following potential pillars could reshape the DKD treatment landscape:

1. Precision Medicine

Future treatments may incorporate genetic profiling and biomarker-based diagnostics, allowing therapies tailored to each patient's unique genetic and biological profile[25].

In terms of genetic profile, current studies perform genome-wide association studies (GWAS) or investigate experimental models to identify differentially expressed genes (DEG) in DKD groups using bioinformatic technologies[26]. Therapeutic strategies for disease-mediating genes include small molecules or oligonucleotides such as antisense oligonucleotides, small interfering RNA, and micro RNA[27].

In terms of biological profile, kidney biopsy provides histopathological biomarkers, aiding in personalized treatment plans[28]. Also, assay-based biomarkers of DKD including neu-

trophil gelatinase-associated lipocalin (NGAL)[29], kidney injury molecule-1 (KIM-1)[30], and advanced glycation end products (AGEs)[2,31] can act as diagnostic tools as well as treatment targets[25]. Proteomics, metabolomics, and transcriptomics methods can be further used for identifying novel biomarkers for risk stratification. Proteomics has been used to identify proteins such as uromodulin, progranulin, clusterin, α1 acid glycoprotein, and haptoglobin. Metabolomics identified metabolites including octanol, oxalic acid, phosphoric acid, and benzamide. Transcriptomics identified various types of micro RNAs. These identified proteins, metabolites, and micro RNAs have been actively studied for their predictive effects[25].

AI-based predictive models can also be used to identify patients at higher risk for DKD progression, facilitating early intervention and prevention strategies[32]. Based on these comprehensive profiles, a more personalized approach could optimize responses to specific medications and minimize adverse effects, particularly among diverse patient populations[25].

2. Digital Health

- **Continuous Glucose and Blood Pressure Monitoring:** Wearable devices and sensors for real-time monitoring could allow patients to manage blood glucose and blood pressure levels with unprecedented accuracy, enhancing adherence and early detection of dysregulation[8,33].
- **Telemedicine and Remote Care Platforms:** As digital health solutions evolve, patients could access continuous medical support, enabling timely adjustments to treatment plans based on remote monitoring data, which is particularly beneficial for those in remote or underserved regions.

3. Microbiome and Gut Health

Research on the gut microbiome's role in kidney health suggests that there is a close interplay between the gut microbiome and DKD. Targeting the microbiome could reduce systemic inflammation and improve metabolic regulation, indirectly benefiting kidney function. Researches suggest elevated levels of gut-microbiota derived metabolites (such as PBUTs) in circulation increase inflammation and exert negative effects including fibrosis[34]. Specific dietary supplements or probiotic interventions could become standard practices for managing the gut-kidney axis, providing a novel, non-invasive means of supporting renal health[34].

4. Anti-Inflammatory and Anti-Fibrotic Therapies

- **Targeting Inflammatory Pathways:** Future therapies are likely to focus on renal inflammation reduction, as inflammation contributes significantly to DKD progression. Upregulation of cytokines such as IL-6, IL-1 are suggested to be associated with decline in kidney function. Anti-inflammatory drugs or biologics targeting key inflammatory mediators could slow kidney damage[35].
- **Targeting Fibrosis Pathways:** Tubulointerstitial fibrosis is highly associated with DKD and various fibrotic factors play a key role in the pathogenesis of DKD[35]. Emerging drugs that specifically inhibit renal fibrosis pathways could directly prevent the scarring that leads to kidney dysfunction, offering an alternative mechanism to traditional therapies. Adding on to nsMRAs, endothelin receptor antagonists are being studied on their effects of reducing fibrosis and kidney inflammation. Atrasentan, avosentan, and zibotentan were studied in the ASCEND trial, the SONAR trial, and the ZENITH-CKD trial, respectively[35].

5. Comprehensive Psychosocial and Behavioral Health Support

- **Psychosocial Health Support:** Mental health support may become an integral part of DKD management. Patients with diabetes and CKD have higher risk of depression, and as a combination of these two diseases, DKD is expected to increase risk of depression[36]. It is important to acknowledge stress and depression in diabetic patients due to its association with treatment adherence[37]. One way to improve mental health status in DKD patients is changing weight to optimal level through lifestyle modifications[36]. Additional holistic approaches for depression are required to enhance patient engagement and treatment adherence.

- **Patient Education and Self-Management Tools:** Digital applications for patient education, tailored lifestyle coaching, and enhanced self-management would empower patients to actively engage in their health, addressing lifestyle factors crucial to DKD management[8].

6. Regenerative Medicine

- **Stem Cell Therapy:** Stem cell-based therapies, aimed at repairing damaged kidney tissue or regenerating functional kidney cells, hold future promise for halting or even reversing DKD progression. Strategies for regenerating kidney cells include decellularized scaffold technology, 3D bioprinting, and kidney organoid fabrication. Strategies for repairing kidney cells include injection of stem cells or secretome such as growth factors[38,39].
- **Bioengineered Renal Tissue:** Advances in microphysiological systems and bioengineered kidney tissues could provide functional alternatives or support to damaged kidneys, delaying or potentially eliminating the need for dialysis[40].

Looking forward, the integration of these future pillars could revolutionize DKD management by expanding from a disease-centered approach to a comprehensive, patient-centered approach. Precision medicine, digital health tools, advanced anti-inflammatory and anti-fibrotic therapies, comprehensive psychosocial support, and regenerative treatments represent forward-oriented paths that hold the potential to mitigate DKD progression and improve quality of life. Together, these future-oriented approaches form a cohesive framework that supports early intervention, personalized treatment, and holistic patient care.

CONCLUSION

In summary, continued research and collaboration among healthcare providers will be crucial to successfully integrate these treatment pillars into everyday clinical practice. A multi-dimensional approach that integrates traditional risk factor management, the four pillars, and emerging future pillars is needed for effective DKD management. Traditional foundations —control of blood pressure, blood sugar, and cholesterol along with lifestyle modifications—remain foundational to slowing DKD progression. The four pillars—RAS inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, and nsMRAs—have added crucial, targeted therapies that address both renal and cardiovascular risks.

Future-oriented pillars such as precision medicine, digital health innovations, microbiome modulation, advanced anti-inflammatory, anti-fibrotic therapies, behavioral and psychosocial support, and regenerative medicine offer promising new avenues to further enhance DKD management. Combining these pillars creates a comprehensive framework that addresses the complex and evolving needs of DKD patients. Developing these pillars and discussing ways to effectively and safely integrate them will be essential.

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Management Strategies for Potassium Levels During Non-steroidal Mineralocorticoid Receptor Antagonist Therapy: A Comprehensive Review

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Diabetic kidney disease (DKD) is a leading cause of chronic kidney disease (CKD). Recent advancements highlight the role of finerenone, a non-steroidal mineralocorticoid receptor antagonist (nsMRA), in DKD management. Studies like FIDELIO-DKD, FIGARO-DKD, and FIDELITY have demonstrated finerenone's efficacy in reducing CKD progression and cardiovascular risks in DKD patients. Trials reveal higher incidence of hyperkalemia in finerenone groups compared to controls. Asian populations are noted to have a higher risk, emphasizing the need for close monitoring. To manage hyperkalemia, evidence-based protocols suggested starting finerenone with potassium level below 4.8 mEq/L, discontinuing if potassium level exceed 5.5 mEq/L. Strategies include dietary potassium restriction, potassium binders, and frequent monitoring. While these managements help mitigate risks, real-word challenges call for further evidence to refine practical guidelines. Finerenone emerges as a promising therapy for DKD but requires careful management to prevent hyperkalemia, ensuring optimal patient outcomes.

Key Words: Dabetic kidney disease, Non-steroidal mineralocorticoid receptor antagonists, Finerenone, Hyperkalemia

INTRODUCTION

Principles of pharmacological treatment for diabetic kidney disease

Diabetic kidney disease (DKD) affects nearly 25.4% of adult patients with diabetes mellitus, according to a recent factsheet released in South Korea[1]. Globally, diabetes mellitus (DM) is well known as the most common cause of progressive chronic kidney disease (CKD). As the average age of patients with diabetes increases, the incidence of DKD is also expected to increase[2]. Currently, DKD refers not only to diabetic nephropathy but also to CKD with diabetes[3]. It has classically been known that DKD results from hyperfiltration of nephrons and hypertrophy of nephrons, leading to nephron loss and fibrosis via metabolic and inflammatory process[4]. In terms of hemodynamics, tubuloglomerular feedback triggered by reduced sodium delivery to the macula densa in DKD leads to glomerular hyperfiltration[5]. The renin-angiotensin-aldosterone system (RAAS) plays a crucial role in the progression of DKD. In DKD, RAAS activation causes hemodynamic changes, glomerular hyperfiltration, endothelial-mesenchymal transition, and renal fibrosis.

Recent evidence suggests that finerenone may be effective in treating DKD with microalbuminuria. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) help suppress RAAS hyperactivation[6-8]. After

Table 1. Serum potassium levels in previous studies related to finerenone

Trial	Definition of hyperkalemia	Incidence of hyperkalemia	
		Placebo	Finerenone
FIDELIO-DKD	>5.5 mmol/L	9.0%	18.3%
FIGARO-DKD	>5.5 mmol/L	5.3%	10.8%
FIDELITY	>5.5 mmol/L	5.9%	12.0%
FIDELIO-Asian	>5.5 mmol/L	17.0% (Non-Asian group: 6.6%)	26.0% (Non-Asian group: 15.9%)

the use of medications such as SGLT2 inhibitors and GLP1 agonists in DKD, finerenone has emerged as a novel treatment for DKD and heart failure[9-11]. Finerenone is a non-steroidal mineralocorticoid receptor antagonist with higher sensitivity and selectivity compared to steroidal mineralocorticoid receptor antagonists (MRAs) such as spironolactone and eplerenone[12]. Studies on the efficacy of spironolactone and eplerenone demonstrated the effect of reducing blood pressure and proteinuria, however, failed to reveal reno-protective effect because of the development of acute kidney injury and/or hyperkalemia[13]. Due to its bulky structure and independent mechanism of action, finerenone has a 500-fold higher specificity compared to other steroidal MRAs, with fewer side effects, such as gynecomastia.

Pivotal studies on finerenone

Three key trials—FIDELIO-DKD[14], FIGARO-DKD[15], and FIDELITY[16]—reported improved renal and cardiovascular outcomes in DKD patients with microalbuminuria. All participants received maximum tolerable renin-angiotensin system blockade in these trials. The FIDELIO-DKD trial included 5,734 patients with type 2 diabetes and CKD characterized by reduced kidney function (eGFR between 25 to 60 ml/min/1.73m^2) with microalbuminuria (UACR ≥300 and <5,000 mg/g), and followed up for 2.7 years. The FIGARO-DKD trial involved 7,437 participants whose eGFR between 25 to 90 ml/min/1.73m^2) with microalbuminuria (UACR ≥30 to <300 mg/g), or albuminuria between 300 to 5,000 mg/g with an eGFR over 60 ml/min/1.73 m^2), and followed up for 3.4 years. The FIDELIO-DKD, the FIGARO-DKD, and the pooled FIDELITY trial showed improved cardiovascular outcome and reduced CKD progression. Pooling data from both trials (over 13,000 patients) showed a 14% reduction in the composite cardiovascular outcome and a 23% reduction of CKD progression.

Hyperkalemia in finerenone

Hyperkalemia is a common complication in DKD patients, particularly in those with progressive kidney disease[17,18]. Aldosterone plays a crucial role in potassium homeostasis by regulating renal outer medullary potassium channel in the kidney collecting duct[15]. When aldosterone acts in the kidneys, sodium reabsorption and potassium secretion are accelerated in the collecting ducts. In the hyperglycemic state, the RAAS is activated, leading to hyperfiltration, inflammation, and fibrosis in the kidneys of diabetes patients. To slow the progression of chronic kidney dysfunction, ACE inhibitors, ARBs, and finerenone suppress the RAAS. However, due to their pharmacological effects, MRAs can cause hyperkalemia[19]. For instance, the incidence of hyperkalemia was higher in the finerenone group in three large trials: FIDELIO-DKD, FIGARO-DKD, and FIDELITY (Table 1)[14-16]. In these trials, participants with serum potassium levels of 4.8 mEq/L or higher were excluded at baseline. Although there were no differences in severe hyperkalemia, 18.3% of participants taking finerenone developed hyperkalemia compared to 9.0% of those not taking finerenone in the FIDELIO-DKD trial. In the FIGARO-DKD trial, which included patients with better kidney function, the incidence of hyperkalemia was 10.8% in the finerenone group and 5.3% in the control group. The FIDELITY trial showed similar results regarding the development of hyperkalemia.

Ways to manage hyperkalemia

Unified guidelines for managing hyperkalemia are scarce,

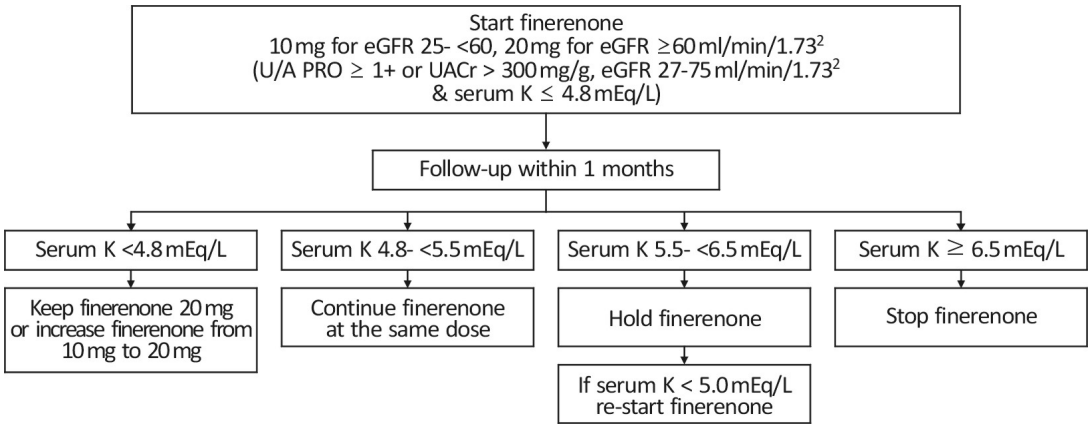

Fig. 1. Flowchart for hyperkalemia management when prescribing finerenone.

partly due to the varying definitions of the condition. In heart failure, intervention is recommended when serum potassium exceeds 5.0 mEq/L[20], which is stricter than that recommended in kidney disease. According to the KDIGO guidelines[21], the FIDELIO-DKD and FIGARO-DKD trials defined hyperkalemia as a serum potassium level above 5.5 mEq/L, with severe hyperkalemia considered as levels over 6.5 mEq/L, associated with serious complications such as arrhythmia. Furthermore, a post-hoc analysis of the FIDELIO-DKD trial showed higher rates of hyperkalemia-related adverse events in Asian patients compared to non-Asian patients[22], giving caution to preventing hyperkalemia in Asian groups. Hyperkalemia can be influenced by several factors, including underlying comorbidities, age, food intake, and medications. Identifying factors that contribute to increased serum potassium in individual patients and ensuring close follow-up are practical strategies. It would be rational to follow protocols whose results have been validated by previous studies. In a post-hoc analysis from the FIDELIO-DKD trial[23], the authors suggested that close monitoring and management strategies for hyperkalemia would minimize its impact on patients' outcomes. Based on large studies with finerenone[14-16], it is recommended to initiate finerenone treatment when the serum potassium level is less than 4.8 mEq/L, with follow-up at 1 and 4 months (± 7 days). Finerenone should be discontinued if potassium exceeds 5.5 mEq/L, alongside other strategies to manage hyperkalemia (Fig. 1). Methods to control hyperkalemia include reducing dietary potassium intake and using medications such as potassium binders, with or without finerenone. Serum potassium levels should be monitored repeatedly within 72 hours after discontinuing finerenone. However, certain aspects of these protocols, such as the follow-up duration, may be challenging to implement in real-world clinical settings. Further evidence is needed to establish practical and comprehensive guidelines for the use of finerenone.

CONCLUSIONS

Finerenone is a novel agent for treating DKD and potentially heart failure. However, caution is required when prescribing it to patients with hyperkalemia. Therefore, hyperkalemia should be managed and prevented before starting finerenone.

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None

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Efficacy and Renal Safety of Protocol-based 11.7% Hypertonic Saline Infusion Compared with 20% Mannitol in Patients with Elevated Intracranial Pressure: A Study Protocol for a Randomized Clinical Trial

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Background: Elevated intracranial pressure (ICP) is a potentially life-threatening condition requiring prompt intervention. While both mannitol and hypertonic saline (HTS) are commonly used hyperosmotic agents for treating elevated ICP, there is insufficient evidence comparing their renal safety profiles and overall effectiveness. This study protocol outlines a pragmatic randomized trial to compare protocol-based 11.7% HTS with 20% mannitol in patients with elevated ICP, focusing particularly on renal outcomes and treatment efficacy.

Methods: This single-center, pragmatic randomized trial will enroll 116 intensive care unit patients with elevated ICP. Participants will be randomly assigned to receive either 11.7% HTS or 20% mannitol following a schedule-based randomization approach, with HTS administration during odd-numbered months and mannitol during even-numbered months. The study will regularly monitor serum electrolytes, osmolarity, and renal function, with brain CT evaluations conducted on days 3 and 7. Comprehensive clinical assessments, including neurological evaluations and laboratory tests, will be performed at specified intervals throughout the study period.

Measured Outcomes: Primary outcomes include the incidence of acute kidney injury within 7 days according to KDIGO guidelines, requirement for mechanical ventilation, development of pulmonary edema, and significant fluid retention. Secondary outcomes encompass ICU and hospital length of stay, 30- and 90-day mortality rates, and neurological outcomes assessed by Glasgow Coma Scale scores at days 7 and 30. The study hypothesizes that protocol-based HTS administration will demonstrate a lower incidence of acute kidney injury and related complications while maintaining comparable efficacy in managing elevated ICP.

Conclusion: This study aims to provide definitive evidence regarding the relative efficacy and safety profiles of HTS compared to mannitol in managing elevated ICP. The findings will help establish clearer clinical guidelines for selecting appropriate hyperosmotic agents, potentially improving patient care outcomes and reducing treatment-related complications. This research will address a significant gap in current clinical knowledge and practice by focusing on treatment efficacy and renal safety considerations in patients with elevated ICP.

Key Words: Intracranial pressure, Acute kidney injury, Hypernatremia, Study protocol, Pragmatic clinical trial

BACKGROUND

Elevated intracranial pressure (ICP) presents as an acute, potentially fatal condition, leading to cerebral edema and further clinical deterioration[1-3]. Normal ICP values generally range from 5 to 15 mm Hg. Intracranial hypertension is characterized by a sustained ICP exceeding 20 mmHg[4,5]. Elevated ICP can precipitate serious consequences such as cerebral hypoxia, coma, brain herniation, and in severe cases, potentially fatal outcomes[6,7]. Despite limited practical evidence for the selection and monitoring of therapies aimed at elevated ICP management, the administration of hyperosmotic solutions is a widely adopted therapeutic strategy for patients with elevated ICP[8,9]. Mannitol and hypertonic saline (HTS) are employed as hyperosmotic agents in the treatment of elevated ICP[10]. These agents facilitate osmotic fluid shifts, dehydrate endothelial cells, and improve perfusion in ischemic areas. Mannitol and HTS share underlying mechanisms in the reduction of increased ICP[11,12]. Recent attention has been drawn to the adverse effects associated with the administration of mannitol. Notable among these are hypotension and dehydration, primarily resulting from over-diuresis, along with the development of hypernatremia and acute kidney injury (AKI)[13,14]. The pathophysiological mechanisms potentially contributing to these outcomes include elevated plasma oncotic pressure, a reduction in the glomerular filtration rate due to tubular lumen constriction, and pronounced vacuolization in the renal tubules[15,16].

HTS therapy, a method used to reduce intracranial pressure, employs sodium—a physiological substance—in concentrations of 3% or higher[17-19]. This approach increases the osmotic pressure within the extracellular fluid (ECF), resulting in the withdrawal of water from brain cells. Unlike mannitol, HTS intravenous administration does not cause systemic dehydration[20]. It selectively enhances the osmotic pressure on the vascular side of the blood-brain barrier. In animal models, the gradient effect of HTS on osmotic pressure is observed to last approximately 1 to 4 hours. Additionally, hypertonic solutions have been found to improve oxygen delivery and cerebral perfusion[21,22].

Owing to these characteristics, recent clinical studies have been conducted to assess the efficacy and safety of HTS as an alternative treatment to mannitol in patients with elevated intracranial pressure[22-25]. The findings from these studies indicate that HTS offers comparable or superior results in comparison to mannitol[26,27]. This includes aspects such as mortality rates, effectiveness in reducing intracranial pressure, and overall safety in patients experiencing increased intracranial pressure[17,28].

However, there is a lack of comprehensive studies comparing the renal side effects, electrolyte balance, and body fluid homeostasis between HTS and mannitol therapy in the context of high osmotic pressure treatment. Consequently, most clinical guidelines currently recommend the use of both mannitol and HTS in patients with cerebral edema or elevated intracranial pressure. Yet, there is insufficient evidence to clearly define specific indications for each medication or to identify a more suitable patient group[29,30].

In this study, for this purpose, we plan to conduct a randomized controlled clinical trial and a randomized controlled clinical trial as a preliminary study. The purpose of the present study was to investigate the safety and efficacy of HTS compared with mannitol in patients with elevated intracranial pressure by randomized controlled clinical trial.

METHODS

Hypothesis

In patients with elevated intracranial pressure, the administration of protocol based HTS will reduce the incidence of acute kidney injury, edema, and metabolic acidosis. Additionally, HTS treatment will result in improvements in patient consciousness and mortality rates that are comparable to those achieved with mannitol administration. This hypothesis aims to address the gap regarding the differential impacts of these two treatments on complex clinical outcomes in patients with elevated intracranial pressure.

Objective of the Study

The primary objective of this study is to compare the efficacy and frequency of side effects between mannitol and protocol-based HTS administration in patients with elevated intracranial pressure. The study aims to provide clear,

Table 1. Inclusion and Exclusion Criteria
Abbreviations: ICU, intensive care unit; CNS, central nervous system; ARDS, acute respiratory distress syndrome.

Inclusion Criteria	Exclusion Criteria
1. Adults aged 18 to 80. 2. Diagnosed with conditions requiring intracranial pressure management in the ICU 3. Closed traumatic brain injury, intracranial hemorrhage, acute stroke, brain neoplasm, CNS infection, encephalitis, pseudotumor cerebri. 4. Agreement to participate in the study.	1. Receiving osmotic therapy prior to observation. 2. Acute kidney injury stage>3 (eGFR<15 ml/min or requiring RRT) 3. Heart failure (ejection fraction<40% on echocardiography). 4. Liver cirrhosis with ascites 5. PaO_2/FiO_2 ratio<200, indicating moderate to severe ARDS 6. Serum sodium<130 meq/L or >150 meq/L 7. Do not agree to participate in the study or cancel 8. Difficult to carry out the study by the principal investigator.

evidence-based insights into which of these treatments is more effective in managing the critical aspects of elevated intracranial pressure.

Study Participants and Measurements

Patients admitted to the intensive care unit (ICU) at the research medical institution who meet the selection criteria will be approached for participation in this study. The study will be proposed to eligible patients or their guardians, and their consent to participate in the clinical trial will be sought before the administration of any osmotic agents. Eligibility for the study is contingent upon participants meeting all the inclusion criteria, not being subject to any of the exclusion criteria, and providing written informed consent. (Table 1) The study is designed as a clinical trial with a total enrollment of 116 participants, divided equally into two groups of 58 each. This sample size is calculated to be the minimum required to confirm the statistical effects and side effects of the treatments under investigation.

Sample size estimates

In patients with brain hemorrhage, the predictive incidence of AKI is 10.5% when mannitol is administered according the previous study[13]. The frequency and severity of AKI increase with high dose of mannitol. Moreover, the presence of advanced age (≥70 years), along with pre-existing conditions such as hypertension and chronic kidney disease (CKD), further exacerbates the risk, leading to a substantial increase in the incidence of AKI. Additionally, hypernatremia occurs in approximately 16-40% of cases when mannitol is used[13]. The null hypothesis (H0) is that there is no difference in renal outcome, including electrolyte imbalance and renal dysfunction, 7 days after admission among patients with elevated intracranial pressure treated with mannitol or hypertonic saline. The alternative hypothesis (HA) is that there is a difference in renal outcome 7 days after admission among patients randomized to mannitol or hypertonic saline. A total sample size of 116 (58 per group) participants with increased intracranial pressure is required, assuming overall significance (alpha) = 0.05, power (1- beta) = 0.80. In this trial, the aim is to decrease renal-related side effects, such as AKI and hypernatremia, another electrolyte imbalance by 25%.

Randomization

In this clinical trial, the randomization process is designed as a pragmatic, schedule-based approach to ensure the integrity and scientific validity of the study (Fig. 1). The participants will be allocated based on the month of their admission. Patients admitted during odd-numbered months will receive HTS, while those admitted during even-numbered months will receive mannitol. This allocation is implemented immediately after obtaining informed consent and is coordinated by the research team. By using a monthly assignment strategy, the study maintains an impartial and transparent allocation process. Although blinding the clinical observers is impractical—given the distinct treatment protocols and monitoring indicators required for mannitol versus HTS—the pragmatic monthly allocation ensures that all participants receive prompt and appropriate treatment upon hospital admission, while preserving the scientific rigor and

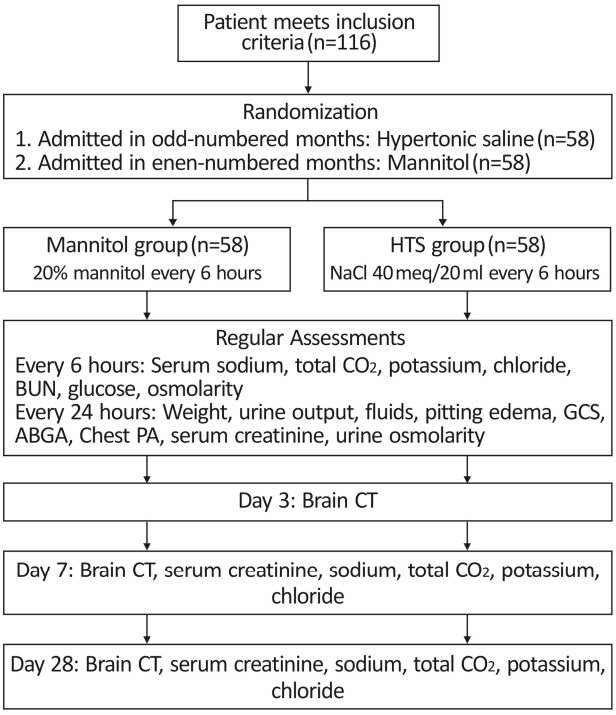

Fig. 1. Study protocol for HTS and mannitol group.
Abbreviations: HTS, hypertonic saline; GCS, Glasgow coma scale; ABGA, arterial blood gas analysis; CT, computed tomography.

fairness of the trial design.

Study Algorithm for HTS and Mannitol Groups

In this study, a total of 116 eligible patients, meeting inclusion criteria and without any exclusion criteria, were enrolled. These patients were randomly assigned to receive either hypertonic saline or mannitol treatment based on a pragmatic schedule-based randomization approach, with treatment alternating between odd (HTS) and even (mannitol) months. The mannitol group received 20% mannitol 100cc every 6 hours, while the hypertonic saline group received NaCl 120 mEq, 60 cc every 6 hours.

Serum sodium, osmolarity, blood urea nitrogen (BUN), and glucose levels were measured every 6 hours, while assessments of body weight, urine output, presence of pitting edema, serum creatinine, and urine osmolarity were performed every 24 hours. During the 3rd, 7th, and 28th days of the study period, participants undergo brain CT for neurological evaluation and serum levels of creatinine, sodium, potassium, chloride, and total CO_2 were assessed. biochemical analyses are performed to assess serum levels of creatinine, sodium, potassium, chloride, and total CO_2, providing valuable insights into renal function and electrolyte balance. On the 3rd day, a brain CT evaluation was performed, and on the 7th day, 28th day, assessments included serum creatinine, serum sodium, potassium chloride, and total CO_2. Furthermore, on the 28th day, evaluations were conducted for mortality, the duration of ICU admission, and other clinical parameters.

If serum sodium exceeds 155 meq/L, HTS administration is discontinued and serum sodium is reassessed after 6 hours. If the serum sodium remains elevated, it leads to replacement with 5% dextrose fluid or 0.45% saline. The Mannitol Group receives 20% mannitol every 6 hours, with serum osmolarity evaluated prior to each dose to ensure proper management. Fluid replacement is adjusted based on clinical judgment, using 5% dextrose fluid or 0.45% saline as needed. This algorithm ensures that both groups receive appropriate interventions to correct and stabilize serum sodium and osmolarity levels, thereby minimizing the risk of complications associated with hypernatremia and hyperosmolarity.

Observations and Assessments

In this clinical trial, patients undergo extensive clinical and laboratory evaluations to assess treatment effects and overall health. Initial assessments at enrollment include clinical measurements (weight, height, age, medical history), neurological evaluation (Modified Glasgow Coma Scale score), and various laboratory tests (serum sodium, BUN, creatinine, glucose, osmolarity, ABGA, CO_2, potassium, chloride, BNP), along with urinalysis and imaging/cardiac assessments (Chest PA, Brain CT, Electrocardiogram, Echocardiography within 72 hours). Regular assessments are conducted every 6 hours (serum levels and osmolarity) and every 24 hours (weight, urine output, administered fluids, pitting edema, Glasgow Coma Scale (GCS) score, ABGA, Chest PA, serum creatinine, urine osmolarity). Specific timepoint assessments include Brain CT scans on Day 3 and Day 7. Additional assessments and data collection cover cardiomegaly suspicion (echocardiography) and comprehensive history and follow-up (medication history, surgical history, infectious history, hospitalization and ICU period, time of death, sur-

Table 2. Observations and Assessments Schedule during study protocol
Abbreviations: GCS, Glasgow coma scale; BUN, blood urea nitrogen; BNP, brain natriuretic peptide; CT, computed tomography; ECG, electrocardiogram; ABGA, arterial blood gas analysis.

Assessment Type	Frequency	Parameters
Initial Assessments	At Enrollment	Weight, height, age, medical history, GCS, serum levels (sodium, BUN, creatinine, glucose, osmolarity, CO_2, potassium, chloride, BNP), urinalysis, Chest PA, Brain CT, ECG, Echocardiography
Regular Assessments	Every 6 Hours	Serum sodium, CO_2, potassium, chloride, BUN, glucose, osmolarity
	Every 24 Hours	Weight, urine output, fluids, pitting edema, GCS, ABGA, Chest PA, serum creatinine, urine osmolarity
Timepoint Assessments	Day 3, 7, 28	Brain CT
Additional Assessments	Indicated	Echocardiography, comprehensive medical history, hospitalization details

vival after 30 days) (Table 2).

Outcome Evaluation

The primary outcome of our study defined as composite clinical events of acute kidney injury (stage 1 to 3) and hypernatremia (serum sodium > 150 mEq/L). These include the incidence of acute kidney injury within the 7 days of observation according to the 2012 KDIGO guidelines. The secondary outcomes include the duration of ICU admission, which reflects the severity of the patient's condition and the effectiveness of the treatment. The total hospitalization period is also recorded. Mortality is a critical measure, with specific time to death, and death occurrences within 30 and 90 days of treatment. Additionally, the GCS scores are assessed on the 7^{th} and 30^{th} days to evaluate neurological outcomes. Additionally, the need for mechanical ventilator application is monitored as an indicator of severe patient condition progression. In addition, pulmonary edema and fluid accumulation in pleural or pericardial spaces reflect potential complications in fluid management. The outcome of edematous event defined as composite event of the presence of Grade 3 or higher pretibial pitting edema, more than 10% of weight gain compared to the baseline, or significant pulmonary edema or pleural effusion on chest images.

Safety issues

Adverse reactions are closely monitored, with their details, severity, and causal relationship evaluated and reported to the principal investigator. This includes assessing the likelihood of the reaction being related to the study, ranging from certain to unrelated. Serious adverse reactions warrant immediate reporting to the principal investigator, who then notifies the participant protection center in compliance with their standards. This protocol ensures an ethical approach to handling adverse reactions, maintaining standards of participant safety and research integrity in clinical trials.

Data Analysis and Statistical Methods

The Kolmogorov-Smirnov Z Test is first used to check the normality of numeric variables. Primary categorical outcomes are analyzed using the Chi-square Test, with Fisher's Exact Test as an alternative for non-normal distributions. Secondary outcomes are examined using the Student's T-test and Chi-square Test, with non-normal distributions handled by the Mann-Whitney U Test and Fisher's Exact Test. For time-to-event data like mortality, neurologic recovery time, and ICU duration, we use the Kaplan-Meier Plot and Cox-Proportional Hazard Model.

Adverse Effects, Precautions, and Measures

In our clinical trial, significant adverse reactions are defined following Naranjo's criteria, encompassing severe outcomes like death, life-threatening situations, extended hospitalization, or serious disability. If any severe drug-related

adverse reactions occur, the trial will be immediately stopped and reported to the Institutional Review Board (IRB). The principal investigator is responsible for regular data and safety monitoring, adhering to strict guidelines and conducting monthly reviews. Unanticipated safety issues identified through various tests are reported to the IRB within 72 hours. All adverse reactions during the study are documented and communicated to the principal investigator. These reactions are evaluated at specific time points, particularly 7 days after randomization. Serious adverse reactions are thoroughly assessed to determine if they meet the criteria for reporting to the IRB and other relevant authorities, ensuring safety management throughout the study.

DISCUSSION

Elevated ICP presents as an acute, potentially fatal condition that can lead to cerebral edema and adverse outcomes. Hyperosmotic solutions like mannitol and HTS are commonly used to reduce ICP by facilitating fluid shifts and improving perfusion. While each treatment shares mechanisms in reducing ICP, recent attention has focused on mannitol's adverse effects, such as hypotension and dehydration. Although both mannitol and HTS have been shown to effectively reduce intracranial pressure in randomized controlled trials, there is a lack of studies comparing their safety profiles, including major side effects such as hypernatremia and acute renal injury, during treatment[1)]. As a result, current guidelines recommend the use of both mannitol and HTS for patients with elevated ICP, but specific indications for each medication remain unclear. In this study, led by nephrologists, a sufficient number of patients with elevated ICP will be enrolled using a pragmatic randomization approach to compare the outcomes of mannitol and HTS. It is anticipated that this will provide important evidence supporting the safe of elevated ICP using HTS, potentially reducing the occurrence of AKI, complications, and mortality rates.

Declaration of conflicting interests

The authors declared no potential conflicts of interest for the research, authorship, and publication of this article.

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