

Restoration of Electrolyte Homeostasis and Microcirculatory Perfusion in End-Stage Renal Disease via Intravenous Oxyhydrogen and Gasotransmitter Nanobubble Therapy Combined with Potassium Titration: A Case Report

Aning Tyas Kusuma Dewi and Aditya Tri Hernowo *

Posted Date: 31 July 2025

doi: 10.20944/preprints202507.2558.v1

Keywords: chronic kidney disease; hemodialysis; hydrogen nanobubbles; gasotransmitters; nitric oxide; carbon monoxide; hydrogen sulfide; potassium chloride; oxidative stress; molecular therapy



Preprints.org is a free multidisciplinary platform providing preprint service that is dedicated to making early versions of research outputs permanently available and citable. Preprints posted at Preprints.org appear in Web of Science, Crossref, Google Scholar, Scilit, Europe PMC.

Copyright: This open access article is published under a Creative Commons CC BY 4.0 license, which permit the free download, distribution, and reuse, provided that the author and preprint are cited in any reuse.

Case Report

Restoration of Electrolyte Homeostasis and Microcirculatory Perfusion in End-Stage Renal Disease via Intravenous Oxyhydrogen and Gasotransmitter Nanobubble Therapy Combined with Potassium Titration: A Case Report

Aning T. K. Dewi and Aditya T. Hernowo *

Indonesian Molecule Institute, Malang, East Java 65151, Indonesia

* Correspondence: hernowo@institutmolekul.id; Tel.: +62-821-3205-2024

Abstract

Background. Chronic kidney disease (CKD) stage 5, or end-stage renal disease (ESRD), is associated with high mortality, systemic inflammation, oxidative stress, and complex metabolic derangements. Current treatments such as hemodialysis offer life-sustaining support but often fail to address these underlying molecular dysfunctions. This case explores the application of a novel molecular adjuvant therapy integrating intravenous hydrogen-oxygen (HHO) nanobubbles, gasotransmitter nanobubbles (NO, CO, H₂S), and titrated potassium chloride (KCl) in a patient undergoing maintenance dialysis. **Case presentation.** A 63-year-old male with CKD-5, type 2 diabetes, and uncontrolled hypertension received 21 sessions of post-dialysis intravenous infusions over two months (April–June 2025), comprising HHO nanobubbles, gasotransmitters, and progressively titrated KCl. Baseline symptoms included fluid intolerance (≤ 200 cc/day), post-dialysis fatigue, cutaneous hyperpigmentation, and poor appetite. Therapeutic response included increased oral fluid tolerance (400 cc/day), improved skin perfusion, appetite restoration, and normalized urination frequency. Laboratory findings showed stabilization of serum potassium (3.95 to 4.25–4.59 mmol/L), reduction in HbA1c (8.1% to 6.69%), and hs-CRP (8.0 to 2.28 mg/L), without adverse events. **Discussion.** HHO and gasotransmitter nanobubbles exhibit antioxidant, anti-inflammatory, and vasoprotective properties, while titrated KCl addresses critical electrolyte imbalances in ESRD. Together, these agents offer a multi-targeted, systems-level intervention that may mitigate oxidative stress, preserve renal microcirculation, and improve metabolic stability. This aligns with emerging literature on gasotransmitters' role in renal protection and redox modulation. **Conclusion.** This case suggests that intravenous nanobubble-based HHO and gasotransmitter therapy, when combined with controlled potassium titration, may safely improve clinical and biochemical parameters in CKD-5 patients on hemodialysis. Larger, controlled studies are warranted to validate efficacy and establish protocols for broader clinical application.

Keywords: chronic kidney disease; hemodialysis; hydrogen nanobubbles; gasotransmitters; nitric oxide; carbon monoxide; hydrogen sulfide; potassium chloride; oxidative stress; molecular therapy

Introduction

Chronic Kidney Disease (CKD) stage 5, also known as end-stage renal disease (ESRD), represents a significant global health burden, affecting millions of individuals and contributing to high mortality rates. CKD is now among the leading causes of death worldwide, with a global prevalence exceeding 800 million people and an estimated 13.4% of the population affected—of which 10.6% are in stages 3–5 (Kovesdy, 2022; Mills et al., 2015; Banerjee et al., 2019). From 1990 to

2017, the mortality rate attributable to CKD rose by 41.5%, making it a leading cause of years of life lost globally (Kovesdy, 2022).

Hemodialysis, while life-sustaining, presents its own clinical challenges. Fatigue is a common and debilitating complaint, frequently resulting from metabolic disturbances and muscle deconditioning, and it leads to reduced functional capacity (Sakkas & Karatzaferi, 2012). Electrolyte abnormalities, including hyperkalemia and hyponatremia, are prevalent and are linked to higher mortality risks (Pirklbauer, 2020). Poor tissue perfusion, often exacerbated by hemodynamic instability during dialysis, may precipitate ischemic injury—especially in patients with comorbid diabetes—underscoring the need for targeted, mechanism-based interventions (Eldehni et al., 2022).

In this context, the implementation of a multi-modal adjuvant therapy that combines hydrogen-oxygen nanobubbles (HHO), gasotransmitter nanobubbles—namely nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide (H₂S)—with titrated potassium chloride (KCl), offers a promising therapeutic strategy. This approach leverages the synergistic antioxidative, anti-inflammatory, and cytoprotective properties of its molecular components to counteract the fundamental pathophysiological drivers of CKD progression. By targeting oxidative stress, inflammation, vascular dysfunction, and electrolyte imbalance, the therapy aims to stabilize systemic physiology and preserve renal function in patients with advanced CKD.

Molecular hydrogen (H₂) exhibits selective antioxidant, anti-apoptotic, and mitochondrial-supportive properties. It neutralizes hydroxyl radicals and reduces cellular oxidative burden, contributing to improved renal cellular integrity (Hirano et al., 2023; Lu et al., 2023). Intravenous administration of oxyhydrogen nanobubbles (HHOnb) has demonstrated benefits in CKD patients, including improved glomerular filtration rate (GFR) and reduced serum creatinine, suggesting enhanced renal function (Indrajani et al., 2024). Similarly, gasotransmitters such as NO, CO, and H₂S are key regulators of vascular tone, antioxidative signaling, and anti-inflammatory responses. Carbon monoxide, in particular, has been shown to attenuate ischemia-reperfusion injury and reduce oxidative stress in preclinical kidney models (Nishida et al., 2018).

Complementing these effects, potassium chloride (KCl) plays a pivotal role in maintaining electrolyte homeostasis. CKD patients on dialysis are especially vulnerable to shifts in serum potassium, and carefully titrated KCl administration can help prevent both hypo- and hyperkalemia. It also supports neuromuscular stability and cellular membrane potential (Canaud et al., n.d.). The integration of HHO, gasotransmitters, and KCl offers a multi-targeted intervention that addresses both systemic manifestations and cellular-level dysfunction in CKD. Emerging evidence suggests that this approach may not only reduce symptom burden but also slow disease progression (Nakayama et al., 2016; Nakayama et al., 2024; Indrajani et al., 2024). The application of nanotechnology in nephrology, though promising, presents technical challenges related to nanoparticle synthesis, biodistribution, and kidney-specific targeting. Overcoming these barriers will be critical to translating this innovative approach into standardized clinical care (Roointan et al., 2024).

Case Description

A 63-year-old male patient was diagnosed with stage 5 chronic kidney disease (CKD-5), with a history of type 2 diabetes mellitus and uncontrolled hypertension. He had been undergoing maintenance hemodialysis twice weekly as renal replacement therapy. As an adjuvant intervention, the patient received a combination of intravenous infusion therapy consisting of HHO and gasotransmitter nanobubbles and potassium chloride (KCl). The therapy was administered 21 times over a two-month period (April–June 2025), immediately following each dialysis session.

At baseline, prior to initiation of the adjuvant therapy, the patient exhibited several clinical features commonly observed in long-term hemodialysis patients. These included a strict limitation in oral fluid intake to a maximum of 200 cc/day due to fluid intolerance and risk of overload; hyperpigmentation and darkening of the skin, particularly on the face and lower extremities,

suggestive of peripheral perfusion disturbance; profound fatigue following dialysis sessions; and reduced appetite affecting overall nutritional intake.

The infusion protocol commenced with intravenous administration of 15 ml HHO and 1 ml KCl per session. From the third session onward, GASO was added at a dose of 5 ml and maintained through the remainder of the therapy. KCl dosage was progressively titrated in accordance with laboratory parameters and clinical tolerance, reaching a maximum dose of 8.5 ml per session by sessions 15 to 21. By the 12th session (KCl dose of 7.5 ml), the patient demonstrated a marked increase in fluid intake capacity, reaching 400 cc/day without signs of fluid overload. Concurrently, improvement in skin coloration, increased appetite, and normalized urinary frequency were noted. No new complaints or adverse events were reported throughout the course of the therapy.

Serial laboratory assessments revealed stable increases in serum potassium levels, rising from an initial value of 3.95 mmol/L to within the physiological range of 4.25–4.59 mmol/L during the treatment period. Other electrolytes, including sodium and chloride, remained within normal limits. Ionized calcium and total calcium levels also remained stable throughout the intervention. Hemoglobin A1c (HbA1c) levels decreased from 8.1% at baseline to 6.69% by the end of the observation period. High-sensitivity C-reactive protein (hs-CRP) levels declined from 8.0 mg/L to 2.28 mg/L. Uric acid, serum albumin, and liver enzymes (SGOT, SGPT) remained within normal limits during the entire treatment course.

Discussion

Hydrogen-oxygen nanobubbles and gasotransmitters have garnered increasing attention for their therapeutic potential in CKD. These endogenously produced gaseous molecules are involved in essential physiological functions, including vascular tone regulation, glomerular filtration, and cellular redox homeostasis—all of which are frequently disrupted in CKD. Their dysregulation has been linked to disease progression, particularly in diabetic nephropathy and hypertensive nephrosclerosis.

Among these gasotransmitters, H₂S has been notably studied for its renoprotective roles. Synthesized locally in renal tissues, H₂S contributes to the maintenance of renal blood flow, electrolyte balance, and glomerular hemodynamics. A deficiency of H₂S in CKD has been associated with increased oxidative stress, inflammation, and vascular dysfunction (Kasinath and Lee, 2021; Sun et al., 2019). In preclinical models, administration of H₂S donors has been shown to restore physiological H₂S levels, modulate autophagy and apoptosis, suppress renal inflammation, and improve structural and functional renal outcomes (Ngowi et al., 2020; Aziz et al., 2020).

Similarly, NO and CO are well-established gasotransmitters with vasodilatory, anti-inflammatory, and cytoprotective effects. Both have demonstrated efficacy in reducing renal injury across models of acute and chronic kidney disease (Hsu et al., 2021). Importantly, NO and H₂S signaling converge in the regulation of vascular tone and blood pressure, both of which are commonly dysregulated in CKD (Лобов and Соколова, 2020). Emerging evidence further suggests that these gasotransmitters may act synergistically, where their co-modulation offers enhanced protection of renal microcirculation and cellular integrity (Aziz et al., 2020).

Unlike conventional treatments for CKD—such as ACE inhibitors, angiotensin receptor blockers, and diuretics—which primarily aim to manage systemic manifestations like hypertension, proteinuria, and volume overload, gasotransmitter-based therapies offer a mechanistic approach that targets the root molecular and cellular drivers of disease progression. These include oxidative stress, chronic inflammation, mitochondrial dysfunction, and endothelial injury—domains not directly addressed by current pharmacologic standards (Xu, 2022; Hsu and Tain, 2018).

Despite their promise, the translation of gasotransmitter therapies into clinical nephrology faces several challenges. Chief among these are the need to elucidate precise molecular mechanisms, optimize dosage and exposure timing, and develop reliable, targeted delivery systems to minimize off-target effects (Sun et al., 2019; Chen et al., 2023). Furthermore, inter-individual variability in

response and concerns regarding systemic toxicity due to non-specific biodistribution must be carefully managed in future development efforts (Hsu et al., 2022).

In summary, gasotransmitters such as H₂S, NO, and CO represent a promising new class of therapeutic agents capable of addressing key molecular mechanisms in CKD pathogenesis. With further validation through rigorous mechanistic and clinical studies, these agents hold the potential not only to complement existing treatments but also to redefine therapeutic paradigms in the management of chronic kidney disease.

Conflicts of Interest: The authors declare no conflicts of interest.

References

- Aziz, N.M., Elbassuoni, E.A., Kamel, M.Y. and Ahmed, S.M., 2020. Hydrogen sulfide renal protective effects: possible link between hydrogen sulfide and endogenous carbon monoxide in a rat model of renal injury. *Cell Stress and Chaperones*, 25(2), pp.211-221.
- Banerjee, D. and Jha, V., 2019. Vitamin D and cardiovascular complications of CKD: what's next?. *Clinical Journal of the American Society of Nephrology*, 14(6), pp.932-934.
- Canaud, B., Stephens, M.P., Nikam, M., Etter, M. and Collins, A., 2021. Multitargeted interventions to reduce dialysis-induced systemic stress. *Clinical Kidney Journal*, 14(Supplement_4), pp.i72-i84.
- Chen, C.J., Cheng, M.C., Hsu, C.N. and Tain, Y.L., 2023. Sulfur-containing amino acids, hydrogen sulfide, and sulfur compounds on kidney health and disease. *Metabolites*, 13(6), p.688.
- Cheng, J., Shi, M., Sun, X. and Lu, H., 2024. Therapeutic effect of hydrogen and its mechanisms in kidney disease treatment. *Medical Gas Research*, 14(2), pp.48-53.
- Eldehni, M.T., Crowley, L.E. and Selby, N.M., 2022. Challenges in Management of Diabetic patient on Dialysis. *Kidney and Dialysis*, 2(4), pp.553-564.
- Hirano, S.I., Ichikawa, Y., Sato, B., Takefuji, Y. and Satoh, F., 2023. Medical Application of Molecular Hydrogen to Diabetic Kidney Disease: Therapeutic Potential through Improvements in Mitochondrial Function.
- Hsu, C.N., Chen, W.L., Liao, W.T., Chang-Chien, G.P., Lin, S. and Tain, Y.L., 2022. Hydrogen Sulfide-to-Thiosulfate Ratio Associated with Blood Pressure Abnormalities in Pediatric CKD. *Journal of Personalized Medicine*, 12(8), p.1241.
- Hsu, C.N. and Tain, Y.L., 2018. Hydrogen sulfide in hypertension and kidney disease of developmental origins. *International journal of molecular sciences*, 19(5), p.1438.
- Indrajani, P.O., Hernowo, A.T., Ekasari, C.P., Yudhanata, R. and Sumitro, S.B., 2024. The Effect of Intravenous Oxyhydrogen Nanobubble on Chronic Kidney Disease: Case Series.
- Kasinath, B.S. and Lee, H.J., 2021. Hydrogen sulfide and the kidney. *Advances in Hydrogen Sulfide Biology*, pp.17-50.
- Kovesdy, C.P., 2022. Epidemiology of chronic kidney disease: an update 2022. *Kidney international supplements*, 12(1), pp.7-11.
- Лобов, Г.И. and Соколова, И.Б., 2020. Роль NO и H₂S в регуляции тонуса церебральных сосудов при хронической болезни почек. *Российский физиологический журнал им. ИМ Сеченова*, 106(8), pp.1002-1015.
- Mills, K.T., Xu, Y., Zhang, W., Bundy, J.D., Chen, C.S., Kelly, T.N., Chen, J. and He, J., 2015. A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. *Kidney international*, 88(5), pp.950-957.
- Nakayama, M., Kabayama, S. and Ito, S., 2016. The hydrogen molecule as antioxidant therapy: Clinical application in hemodialysis and perspectives. *Renal Replacement Therapy*, 2, pp.1-10.

- Nakayama, M., Kabayama, S. and Miyazaki, M., 2024. Application of Electrolyzed Hydrogen Water for Management of Chronic Kidney Disease and Dialysis Treatment—Perspective View. *Antioxidants*, 13(1), p.90.
- Ngowi, E.E., Sarfraz, M., Afzal, A., Khan, N.H., Khattak, S., Zhang, X., Li, T., Duan, S.F., Ji, X.Y. and Wu, D.D., 2020. Roles of hydrogen sulfide donors in common kidney diseases. *Frontiers in pharmacology*, 11, p.564281.
- Nishida, T., Hayashi, T., Inamoto, T., Kato, R., Ibuki, N., Takahara, K., Takai, T., Yoshikawa, Y., Uchimoto, T., Saito, K. and Tanda, N., 2018, January. Dual gas treatment with hydrogen and carbon monoxide attenuates oxidative stress and protects from renal ischemia-reperfusion injury. In *Transplantation proceedings* (Vol. 50, No. 1, pp. 250-258). Elsevier.
- Pirklbauer, M., 2020. Hemodialysis treatment in patients with severe electrolyte disorders: Management of hyperkalemia and hyponatremia. *Hemodialysis International*, 24(3), pp.282-289.
- Roointan, A., Xu, R., Corrie, S., Hagemeyer, C.E. and Alt, K., 2024. Nanotherapeutics in kidney disease: innovations, challenges, and future directions. *Journal of the American Society of Nephrology*, pp.10-1681.
- Sakkas, G.K. and Karatzaferi, C., 2012. Hemodialysis fatigue: just “simple” fatigue or a syndrome on its own right?. *Frontiers in physiology*, 3, p.306.
- Sun, H.J., Wu, Z.Y., Cao, L., Zhu, M.Y., Liu, T.T., Guo, L., Lin, Y., Nie, X.W. and Bian, J.S., 2019. Hydrogen sulfide: recent progression and perspectives for the treatment of diabetic nephropathy. *Molecules*, 24(15), p.2857.

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.