

Brief Report

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Posted Date: 17 June 2024

doi: 10.20944/preprints202406.1114.v1

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Brief Report

The Effect of Intravenous Oxyhydrogen Nanobubble on Chronic Kidney Disease: Case Series

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Abstract: Background. Chronic kidney disease (CKD) is a progressive condition with limited treatment options that often lead to significant morbidity. Recent studies suggest that oxyhydrogen nanobubbles (HHOnb) may offer therapeutic benefits due to their antioxidative and anti-inflammatory properties. This case series examines the effects of intravenous HHOnb therapy on three patients with varying stages of CKD. **Methods.** Three patients with CKD underwent a series of ten HHOnb infusions over a period of two to three months. The patients, aged 43 to 70, presented with additional comorbidities including hypertension, diabetes mellitus, and polycystic kidney disease. Clinical parameters, including glomerular filtration rate (GFR), serum creatinine, blood pressure, and uric acid levels, were monitored alongside subjective health improvements. **Results.** Patient A. A 70-year-old woman with CKD grade 3a experienced a reduction in serum creatinine from 0.98 mg/dL to 0.82 mg/dL and an improvement in GFR from 59 mL/min/1.73 m² to 73.2 mL/min/1.73 m². She reported reduced leg swelling and increased vitality. Patient B. A 52-year-old man with CKD grade 4 and class III obesity showed a decrease in serum creatinine from 3.0 mg/dL to 2.86 mg/dL, an increase in GFR from 23 mL/min/1.73 m² to 24.4 mL/min/1.73 m², and improved sleep quality. Blood pressure reduced from 167/82 mmHg to 145/85 mmHg. Patient C. A 43-year-old man with CKD grade 4 and massive polycystic kidney disease reported reduced fatigue and normalized urination. His serum creatinine decreased from 3.26 mg/dL to 3.09 mg/dL, and his GFR improved from 22 mL/min/1.73 m² to 23.6 mL/min/1.73 m². **Conclusion.** Intravenous HHOnb therapy demonstrated potential benefits in improving renal function and overall health in CKD patients. These findings suggest that HHOnb could be a promising complementary treatment for CKD, though larger, controlled studies are needed to confirm its efficacy and safety.

Keywords: chronic kidney disease; oxyhydrogen; nanobubble; ultrafine bubble; nanomedicine; serum creatinine; glomerular filtration rate; antioxidant; anti-inflammatory; polycystic kidney disease; hypertension; diabetes mellitus

Introduction

Chronic Kidney Disease (CKD) or renal failure is a condition characterized by a decline in kidney function due to damage, which can be evidenced by albuminuria, hematuria, structural and pathological abnormalities in the kidneys, or a glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m² for at least three months (Kidney Health Australia, 2020). The prevalence of CKD in Indonesia increased from 0.2% in 2013 to 0.3% in 2018 (Hidayangsih et al., 2023; Rachmah et al., 2023). Additionally, a study found that the prevalence of CKD in Indonesia in 2018 was 0.38%, with varying rates across different provinces, such as 0.64% in North Kalimantan and 0.18% in West Sulawesi (Ro'di et al., 2023). Factors contributing to CKD in Indonesia include diabetes, hypertension, education level, living area, age, and sugary drink consumption (Hustrini et al., 2023). The burden of CKD in Indonesia is significant, with a rising number of patients undergoing kidney replacement treatment, primarily hemodialysis, and challenges in nephrology referral systems (Hustrini et al., 2023). Efforts are being made to improve kidney health in Indonesia through programs like the Uro-Nephrology Support Program.

CKD can be managed with conventional treatments, which primarily focus on controlling symptoms and slowing the progression of the disease. These treatments include medication for managing blood pressure and diabetes, dietary restrictions, and in advanced stages, dialysis or kidney transplantation. However, these treatments have limitations, including side effects, the need for long-term adherence, and limited availability of donor kidneys for transplantation. Consequently, there is a need for more effective and accessible treatments.

Oxyhydrogen nanobubbles (HHOnb) present a novel therapeutic approach for CKD. HHOnb contains three essential components: hydrogen (H_2), oxygen (O_2), and hydrogen peroxide (H_2O_2). Hydrogen and oxygen are fundamental elements of the body (Aversa et al., 2016), while hydrogen peroxide, though a type of reactive oxygen species (ROS), is required in small amounts for various bodily functions (Andrés et al., 2022). HHOnb is considered safe for CKD patients as it can improve quality of life and enhance kidney function. The nanometer-sized bubbles have several advantages, such as targeting specific sites and easily penetrating cell membranes (Ahlawat & Narayan, 2020).

The aim of this case study is to describe the effects of complementary intravenous therapy using oxyhydrogen nanobubbles in patients with chronic kidney disease. The study seeks to demonstrate how HHOnb therapy can improve the quality of life and kidney function in CKD patients. This case study aims to provide new medical insights into the positive effects of HHOnb infusion therapy on CKD, as evidenced by changes in patient health conditions before the first infusion and after the tenth infusion.

Case Descriptions

Case 1: Patient A

A 70-year-old woman presented to the author's (OI) clinic, in August 2023. She weighed 55 kg and had a height of 156 cm, resulting in a Body Mass Index (BMI) of 22.6 kg/m^2 , which is within the normal range. The patient had a history of CKD grade 1, hypertension, and anemia. She reported experiencing swelling in her right leg, fatigue, and difficulty concentrating. Despite an unhealthy diet, she was taking antihypertensive and renal medications. Previously diagnosed with diabetes mellitus, her blood glucose levels were normal without medication by August 2023. An electrocardiogram (EKG) examination indicated normal cardiac function. Before starting the HHOnb therapy, the patient's GFR was $59 \text{ mL/min/1.73 m}^2$, classifying her CKD as grade 3a. Her serum creatinine level was 0.98 mg/dL . Physical examination was normal except for edema in the right leg.

The patient underwent her first HHOnb infusion therapy in August 2023. Pre-infusion, her blood pressure was $120/67 \text{ mmHg}$, which decreased to $116/67 \text{ mmHg}$ post-infusion. Her heart rate increased from 66 beats per minute (bpm) to 70 bpm after the infusion. Laboratory results from this first infusion showed: hemoglobin 10.6 g/dL , hematocrit 30.8%, mean corpuscular volume (MCV) 96.2 fL , mean corpuscular hemoglobin (MCH) 33.1 pg , leukocytes $5370/\mu\text{L}$, platelets: $397,000/\mu\text{L}$, random blood glucose (RBG) 198 mg/dL , creatinine 0.98 mg/dL , uric acid 6.8 mg/dL , albumin 4.30 g/dL , and D-Dimer $> 3000 \text{ ng/mL}$.

The tenth infusion took place in October 2023. Before this infusion, her blood pressure was $120/115 \text{ mmHg}$, which normalized to $120/67 \text{ mmHg}$ post-infusion. Her heart rate decreased from 73 bpm to 67 bpm after the infusion. Oxygen saturation remained stable at 97-99% throughout the treatment period. Laboratory results from the tenth infusion included: hemoglobin 10.4 g/dL , hematocrit 30.7%, erythrocytes $3.37 \text{ million}/\mu\text{L}$, leukocytes: $5230/\mu\text{L}$, platelets $304,000/\mu\text{L}$, erythrocyte sedimentation rate (ESR) 14 mm/hr , RBG: 210 mg/dL , cholesterol 136 mg/dL , LDL 69 mg/dL , HDL 54 mg/dL , triglycerides 143 mg/dL , creatinine 0.82 mg/dL , uric acid 6.5 mg/dL , albumin 3.9 g/dL , SGOT/SGPT: $21/25 \text{ U/L}$, potassium 3.67 mmol/L , sodium 141.5 mmol/L , chlorine 102.8 mmol/L , and calcium 1.2 mmol/L . Physical examination after the tenth infusion was normal.

Following ten HHOnb infusions, the patient reported improvements in her health, including reduced swelling in her right leg and an overall feeling of increased vitality. These subjective improvements were supported by laboratory results showing a decrease in serum creatinine from 0.98 mg/dL to 0.82 mg/dL , which indicated an improvement in her GFR from $59 \text{ mL/min/1.73 m}^2$

(CKD grade 3a) to 73.2 mL/min/1.73 m² (CKD grade 2). Additionally, her uric acid levels decreased from 6.8 mg/dL to 6.5 mg/dL. These results suggest a positive impact of HHOnb infusion therapy on her renal function and overall health.

Case 2: Patient B

The patient is a 52-year-old man weighing 120 kg and standing 165 cm tall, resulting in a BMI of 44.1 kg/m², which is classified as class III obesity. He was diagnosed with CKD grade 4, type 2 diabetes mellitus (DM2), and hypertension. His treatment regimen included antihypertensive medications and insulin injections (both long and rapid-acting) for diabetes management. Despite regulating his diet, he did not engage in regular physical exercise. His primary complaint was excessive daytime sleepiness, leading to sudden sleep episodes.

At the presentation, the patient reported normal urinary frequency. Physical and EKG examinations were normal. However, he had a history of high blood pressure. His first HHOnb infusion was administered in October 2023. Pre-infusion, his blood pressure was 167/82 mmHg, which increased to 175/94 mmHg post-infusion. His heart rate increased from 67 beats per minute (bpm) to 73 bpm following the infusion. Laboratory results from the first infusion included: GFR 23 mL/min/1.73 m², creatinine 3.0 mg/dL, hemoglobin 10.8 g/dL, erythrocytes 3.82 million/ μ L, hematocrit 33%, ESR 90 mm/hr, fasting blood glucose (FBG) 140 mg/dL, blood urea nitrogen (BUN) 41.5 mg/dL, uric acid 7.2 mg/dL, potassium 5.0 mmol/L, sodium 140 mmol/L, phosphorus 4.4 mmol/L, albumin/protein +4, and microalbumin 4.9320 g/dL.

The patient received his tenth HHOnb infusion at the end of November 2023. Before the infusion, his blood pressure was 162/81 mmHg, which dropped to 145/85 mmHg post-infusion. His heart rate decreased from 64 bpm to 60 bpm following the infusion. His oxygen saturation levels were consistently good, ranging between 97-99%. Laboratory results from the tenth infusion included: GFR 24.4 mL/min/1.73 m², creatinine: 2.86 mg/dL, uric acid 6.9 mg/dL, hemoglobin 10.3 g/dL, hematocrit 30.2%, erythrocytes 3.57 million/ μ L, leukocytes 8680/ μ L, platelets 312,000/ μ L, RBG 179 mg/dL, cholesterol 192 mg/dL, LDL 106 mg/dL, HDL 47 mg/dL, triglycerides 212 mg/dL, albumin 4.2 g/dL, SGOT/SGPT: 27/15 U/L, potassium 6.03 mmol/L, sodium 141.8 mmol/L, chloride 109.04 mmol/L, calcium 1.19 mmol/L, protein: +3, and glucose: +3. Urinalysis revealed the presence of granular casts, bacteria, and amorphous deposits.

Following the tenth infusion, the patient reported improvements in his condition, including better sleep quality. Objective measures also showed significant improvements: serum creatinine decreased from 3.0 mg/dL to 2.86 mg/dL; GFR increased from 23 mL/min/1.73 m² to 24.4 mL/min/1.73 m²; blood pressure reduced from 167/82 mmHg to 145/85 mmHg; uric acid levels decreased from 7.2 mg/dL to 6.9 mg/dL; and urine protein levels decreased from +4 to +3. These changes indicate a positive response to the HHOnb therapy, with marked improvements in renal function and overall health.

Case 3: Patient C

The patient is a 43-year-old man who presented to OI's clinic in October 2023 for his first HHOnb infusion therapy. He weighs 79 kg and has a height of 172 cm, resulting in a BMI of 26.7 kg/m², which classifies him as overweight. He was diagnosed with CKD grade 4, massive polycystic kidney disease, and glomerulonephritis. He reported fatigue and cloudy, frothy urine. In 2021, he experienced hematuria and a significant drop in hemoglobin levels, with an ASTO level of around +200 IU.

At the time of his first infusion in October 2023, his blood pressure was 122/88 mmHg, which slightly increased to 127/89 mmHg post-infusion. His heart rate decreased from 80 bpm to 72 bpm after the infusion. Oxygen saturation improved from 95% to 96%. Renal ultrasound revealed massive polycystic changes in both kidneys. Laboratory tests indicated elevated creatinine (3.26 mg/dL) and reduced GFR (22 mL/min/1.73 m²). Despite normal EKG and physical examination results, he had elevated ASTO (+200 IU) and decreased HDL levels (33 mg/dL). Additional laboratory results included: uric acid 5.8 mg/dL, CRP 0.5 mg/L, FBG 95 mg/dL, HbA1c 5.6%, cholesterol 134 mg/dL,

LDL 103 mg/dL, triglycerides 84 mg/dL, and SGOT/SGPT: 14/12 U/L. Dietary modifications were implemented to limit potassium and high-protein intake.

The patient received his tenth HHOnb infusion in December 2023. Post-infusion, his blood pressure was 150/100 mmHg, heart rate was 68 bpm, and oxygen saturation was 100%. Laboratory tests from this session included: GFR 23.6 mL/min/1.73 m², creatinine 3.09 mg/dL, uric acid 5.8 mg/dL, hemoglobin 12 g/dL, hematocrit 34.6%, erythrocytes 4.1 million/ μ L, leukocytes 5700/ μ L, platelets 283,000/ μ L, ESR 32 mm/hr, FBG 94 mg/dL, cholesterol 165 mg/dL, LDL 103 mg/dL, HDL 37 mg/dL, triglycerides 125 mg/dL, albumin 4.1 g/dL, SGOT/SGPT: 15/15 U/L, potassium 5.09 mmol/L, sodium 143.3 mmol/L, chloride 107 mmol/L, and calcium 1.21 mmol/L. Complete urinalysis showed: leukocytes +2, 8-10/LPF, erythrocytes +1, 4-6/LPF, blood +1, protein +2, epithelial cells 2-4/HPF, and presence of bacteria.

Following the tenth infusion, the patient reported feeling less fatigued and noted that his urine had returned to normal, with no recurrence of hematuria. Objective improvements included a decrease in creatinine levels from 3.26 mg/dL to 3.09 mg/dL, and a slight increase in GFR from 22 mL/min/1.73 m² to 23.6 mL/min/1.73 m². Additionally, his HDL levels improved from 33 mg/dL to 37 mg/dL. These results suggest a positive response to HHOnb therapy, with improvements in both renal function and overall health.

Discussion

The three cases discussed in this series highlight the potential benefits of intravenous oxyhydrogen nanobubble therapy for patients with chronic kidney disease. According to Kidney Health Australia (2020), CKD is characterized by a decline in kidney function due to damage, indicated by albuminuria, hematuria, structural and pathological kidney abnormalities, or a GFR of less than 60 mL/min/1.73 m² for three months or more. Risk factors for CKD include diabetes, hypertension, cardiovascular disease, a family history of kidney failure, obesity (BMI $\geq$ 30 kg/m²), smoking, age over 60, and a history of acute kidney injury (AKI). Kidney health can be assessed through blood tests (serum creatinine and GFR), urine tests (albumin/creatinine ratio), and blood pressure measurements.

In Case 1, a 70-year-old woman with CKD grade 3a, hypertension, and anemia, experienced significant improvements after ten HHOnb infusions. Her serum creatinine levels decreased from 0.98 mg/dL to 0.82 mg/dL, resulting in an improved GFR from 59 mL/min/1.73 m² to 73.2 mL/min/1.73 m², indicating a shift from CKD grade 3a to grade 2. Additionally, her uric acid levels decreased from 6.8 mg/dL to 6.5 mg/dL. These improvements were accompanied by reduced leg swelling and increased vitality. The anti-inflammatory effects of hydrogen, which enhances the release of anti-inflammatory cytokines and inhibits pro-inflammatory cytokines (such as IL-1 β , IL-6, IL-8, IL-10, TNF- α , and NF- κ B), likely contributed to these positive outcomes (Wang et al., 2015; Liu et al., 2013; Chen et al., 2013). Case 2 involved a 52-year-old man with CKD grade 4, diabetes mellitus, hypertension, and class III obesity. His lifestyle factors, including an unhealthy diet and lack of exercise, contributed to his condition. After ten HHOnb infusions, his serum creatinine levels decreased from 3.0 mg/dL to 2.86 mg/dL, and his GFR increased from 23 mL/min/1.73 m² to 24.4 mL/min/1.73 m². Blood pressure improved from 167/82 mmHg to 145/85 mmHg, and uric acid levels decreased from 7.2 mg/dL to 6.9 mg/dL. The therapy also led to better sleep quality and reduced protein levels in his urine. Hydrogen's ability to lower systolic blood pressure through the reduction of angiotensin II, cortisol, aldosterone, and plasma renin levels (Liu et al., 2021) and its selective scavenging of harmful radicals without affecting physiologically important radicals (Wang et al., 2022) are likely mechanisms underlying these benefits. Case 3 describes a 43-year-old man with CKD grade 4, massive polycystic kidney disease, and glomerulonephritis. Following ten HHOnb infusions, his serum creatinine levels decreased from 3.26 mg/dL to 3.09 mg/dL, and his GFR increased from 22 mL/min/1.73 m² to 23.6 mL/min/1.73 m². He reported reduced fatigue and normalized urination, with no recurrence of hematuria. Hydrogen's selective reduction of hydroxyl radicals ($\bullet$ OH) and peroxynitrite (ONOO⁻), which cause oxidative damage (Ohsawa et al., 2007), and its enhancement of endogenous antioxidants like superoxide dismutase (SOD) and catalase (CAT)

(Wang et al., 2011), support these improvements. Additionally, dietary modifications to limit potassium and protein intake likely contributed to his overall health improvement.

Traditional CKD treatments focus on managing symptoms and slowing disease progression through medications, dietary modifications, dialysis, and kidney transplantation in severe cases. While effective, these treatments have limitations, including side effects, the need for long-term adherence, and limited availability of donor kidneys. Previous studies on hydrogen-rich water have demonstrated its antioxidative and anti-inflammatory effects, providing renal protection (Wang et al., 2022; Liu et al., 2021). HHOnb therapy aligns with these findings, showing potential as a complementary treatment for CKD by addressing oxidative stress and inflammation, common contributors to CKD progression.

HHOnb therapy benefits CKD patients through several mechanisms. **Antioxidant properties;** hydrogen in HHOnb selectively scavenges harmful ROS such as hydroxyl radicals and peroxynitrite, reducing oxidative stress, a major factor in CKD. **Anti-inflammatory effects;** hydrogen enhances the release of anti-inflammatory cytokines and inhibits pro-inflammatory cytokines, reducing kidney inflammation (Wang et al., 2015; Liu et al., 2013; Chen et al., 2013). **Improved cellular function;** oxygen in HHOnb enhances cellular respiration and energy production, improving kidney function. **Enhanced tissue repair;** small amounts of hydrogen peroxide in HHOnb act as signaling molecules that promote tissue repair and regeneration. These mechanisms collectively contribute to the observed improvements in renal function and overall health in the patients.

The study has several limitations: 1) the study includes only three patients, limiting the generalizability of the findings; 2) the observation period was relatively short (two to three months), potentially missing long-term effects and sustainability of treatment benefits; 3) without a control group, it is difficult to attribute improvements solely to HHOnb therapy; and 4) patients had different CKD stages and comorbidities, making standardization of results challenging. Future research should address these limitations by: 1) conducting larger, randomized controlled trials to confirm the efficacy and safety of HHOnb therapy in a more diverse patient population; 2) extending the duration of studies to evaluate long-term benefits and potential side effects; 3) investigating specific biochemical pathways through which HHOnb exerts its therapeutic effects; and 4) exploring optimal dosage and frequency of HHOnb infusions for different CKD stages and comorbid conditions.

In conclusion, the initial findings from these case studies suggest that HHOnb therapy could be a promising complementary treatment for CKD. However, more extensive research is needed to fully understand its potential and integrate it into standard CKD management protocols.

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