"Quadruple whammy"- A preventable newly described syndrome of post-operative AKI in CKD II and CKD III patients on combination "Triple whammy" medications: A Mayo Clinic Health System, Eau Claire, Wisconsin experience

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Abstract

Background: The potential combination of diuretics- angiotensin-converting enzyme inhibitors- Non-steroidal anti-inflammatory drugs (diuretics-ACEIs-NSAIDs), the so-called 'triple whammy', to produce clinically significant nephrotoxicity in chronic kidney disease (CKD) is often unrecognized. In 2013, in the *British Medical Journal*, we described accelerated post-operative acute kidney injury (AKI) in CKD patients concurrently on 'triple whammy' medications, a new syndrome that we aptly named 'quadruple whammy'. **Materials and Methods:** Two case reports. **Results:** I. A 59-year-old Caucasian male, hypertensive CKD III, serum creatinine (SCr) 1.42 mg/dL, developed accelerated oliguric AKI after elective right nephrectomy. Outpatient medications included Lisinopril-Hydrochlorothiazide and Nabumetone (NSAID). SCr rapidly more than doubled with metabolic acidosis and hyperkalemia within 24 hours, peaking at 4.02 mg/dL. 'Triple whammy' medications were promptly stopped and the hypotension was corrected. SCr was 1.64 mg/dL and stable, after three months. II. A 46-year-old Caucasian male, hypertensive CKD II, SCr 1.21 mg/dL, developed accelerated AKI after elective right hip arthroplasty. Outpatient medications included Lisinopril and Hydrochlorothiazide. Celecoxib (200 mg) was given pre-operatively. Within 36 hours, SCr rapidly more than doubled to 2.58 mg/dL, with metabolic acidosis. 'Triple whammy' medications were promptly stopped and the hypotension was corrected. SCr was 0.99 mg/dL, and stable, after one month. **Conclusion:** We have described two cases of preventable accelerated AKI following post-operative hypotension in CKD patients concurrently on 'triple whammy' medications. We dubbed this new syndrome "Quadruple Whammy". It is not uncommon. 'Renoprevention', the pre-emptive withholding of (potentially nephrotoxic) medications, including 'triple whammy' medications, pre-operatively, in CKD patients, together with the simultaneous avoidance of peri-operative hypotension would help reduce, if not eliminate such AKI - a call for more pharmacovigilance.

Key words: Angiotensin converting enzyme inhibitors, acute kidney injury, chronic kidney disease, diuretics, Non-steroidal anti-infl ammatory drugs, post-operative hypotension, quadruple whammy, serum creatinine, triple whammy

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Introduction

The potential combination of diuretics-Angiotensin-converting enzyme inhibitors-Non-steroidal anti-inflammatory drugs (diuretics-ACEIs-NSAIDs), the so-called 'triple whammy' combo, to produce clinically

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significant nephrotoxicity in chronic kidney disease (CKD) patients is often unrecognized by physicians.[1] Previously, in 2000, Thomas and Boyd, both Australian physicians, had coined the expression "triple whammy" to describe the risk of renal impairment associated with the concurrent administration of the three pharmaceutical drug classes-diuretics, ACEIs/angiotensin receptor blockers (ARBs) and NSAIDs.[2,3] Later, in 2005, Loboz and Sheffield, in an observational study of the renal function of 301 patients admitted to a general medical ward of a teaching hospital in Australia demonstrated that both levels of serum creatinine and creatinine clearance were correlated to the number of drug exposures as related to diuretics, ACEIs/ARBs and NSAIDs.[4] This study reinforced previously reported observations of the 'triple whammy' effect and the authors shared concerns about the widespread use of two or more of these drugs in general practice.[4] Despite these observations, there is evidence that the physicians and healthcare providers in general continue to prescribe these potentially nephrotoxic combinations to unknowing patients. As a result, a 2003 Australian study revealed that between 4.7% and 7.9% of patients attending general practices were prescribed combinations of medications that could theoretically precipitate renal failure.[5]

In early 2013, we had briefly described our experience of managing accelerated post-operative AKI in two CKD (II and III stages, respectively) patients on 'triple whammy' medications in the *British Medical Journal* and had aptly named this syndrome 'quadruple whammy'.[6,7] In this report, we discuss these two case reports, in a lot greater detail, revisit the phenomenon of 'triple whammy' medications seen against an increasing global AKI pandemic,[8,9] emphasize the need for more preventative nephrology, or 'renoprevention', a term we introduced to the medical literature in 2009,[10] and in conclusion renew calls for more pharmacovigilance with respect to the potential for causing iatrogenic renal failure with prescription and over-the-counter medications.[11-13]

Materials and Methods

Case Reports-The two case presentations are described in the results section.

Results

Case I

In February 2013, in a Northwestern Wisconsin ICU, our Renal Service was consulted on a 59-year old morbidly obese hypertensive Caucasian male patient, with a baseline serum creatinine of 1.42 mg/dL (eGFR 54 ml/min/1.73 sq. m BSA), who had developed accelerated oliguric acute kidney injury (AKI) following an elective right nephrectomy that was complicated by peri-operative hypotension and anemia [Figure 1]. His outpatient medications prior to the elective procedure included Lisinopril-Hydrochlorothiazide 20/25 taken daily for hypertension, and Nabumetone (NSAID) 1000 mg daily, for symptomatic osteoarthritis. Within 24-hours following the operation, his serum creatinine had more than doubled to 3.2 mg/dL (eGFR 22 ml/min/1.73 sq. m BSA), together with the concurrent development of metabolic acidosis and hyperkalemia [Figures 2 and 3]. The 'triple whammy' medications, Lisinopril, Hydrochlorothiazide and Nabumetone, were promptly discontinued. He received intravenous infusions of normal saline together with intravenous pressors to correct hypotension and was transfused for anemia. Subsequently, he indeed needed intravenous Furosemide to treat worsening oliguria and associated volume overload. Serum creatinine peaked at 4.02 mg/dL (eGFR 15 ml/min/1.73 sq. m BSA), about 48 hours after the nephrectomy [Figure 2]. Afterward, his kidney function started to improve with falling serum creatinine [Figures 3 and 4]. His blood pressure normalized and he in fact became hypertensive again, requiring the institution of oral Metoprolol and Furosemide for hypertension control. He was discharged after about a week on Metoprolol and Furosemide, together with as needed Acetaminophen, Tramadol and Hydrocodone,

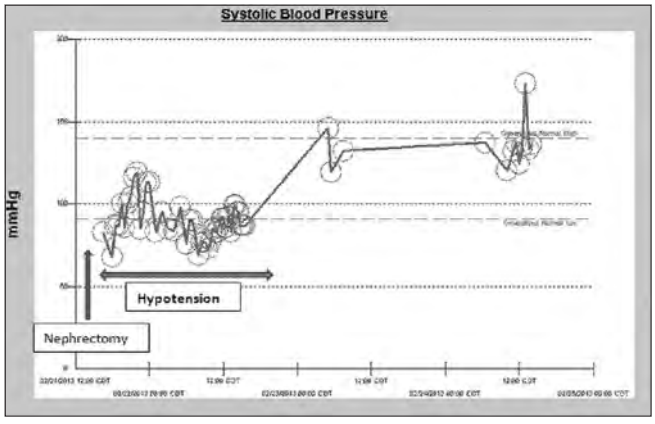

Figure 1: Peri-operative hypotension in a 59-year-old CKD male patient following elective right nephrectomy

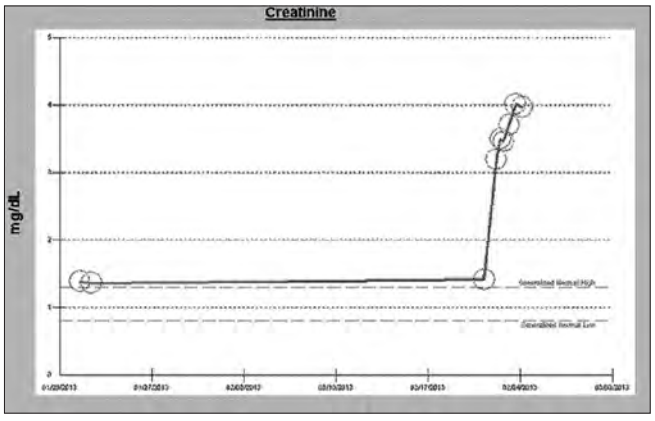

Figure 2: Accelerated AKI within 24 hours following elective right-sided nephrectomy

for treatment of his symptomatic ostoearthritis. Serum creatinine improved to 2.00 mg/dL (eGFR 34 ml/min/1.73 sq. m BSA) after two weeks, and was stable at 1.64 mg/dL (eGFR 43 ml/min/1.73 sq. m BSA). On May 21, 2013, exactly three months following the elective right nephrectomy procedure he continues to feel better. Surgical pathology of the removed right kidney confirmed renal cell carcinoma, papillary type, Fuhrman grade 3.

Case II

Within a week of treating the patient (Case I), we had another nephrology consultation in the same ICU, this time on a 46-year old morbidly obese hypertensive Caucasian male patient with a baseline serum creatinine of 1.21 mg/dL (eGFR 70 ml/min/1.73 sq. m BSA), who had developed accelerated AKI after an elective right hip arthroplasty, again complicated by peri-operative hypotension and anemia [Figure 5]. His outpatient medications prior to the elective procedure included Lisinopril 40 mg daily and Hydrochlorothiazide 25 mg daily, both taken for hypertension. In addition, he had been administered a pre-operative Orthopedic Unit analgesic protocol dose of 200 mg Celecoxib (Cox II inhibitor). The latter ofcourse completed the "triple whammy" circle. Within 36 hours, his serum creatinine had again more than doubled to 2.58 mg/dL (eGFR 28 ml/min/1.73 sq. m BSA), together with the simultaneous development of metabolic acidosis [Figures 6 and 7]. Yet again, following the nephrology consultation, Lisinopril and Hydrochlorothiazide were discontinued. Hypotension was rapidly corrected with intravenous infusions of normal saline. He subsequently required intravenous Furosemide for worsening oliguria. Urine output later improved and serum creatinine started to decrease. Similar to Case I, following the correction of hypotension, he in fact became hypertensive, thus requiring the initiation of antihypertensive therapy with oral Amlodipine and Furosemide. His serum creatinine continued to improve post-discharge, and was down to 0.99 mg/dL (eGFR 85 ml/min/1.73 sq. m BSA), one month later, a level of improved kidney function much better than he ever had, prior to the right hip arthroplasty procedure [Figure 8].

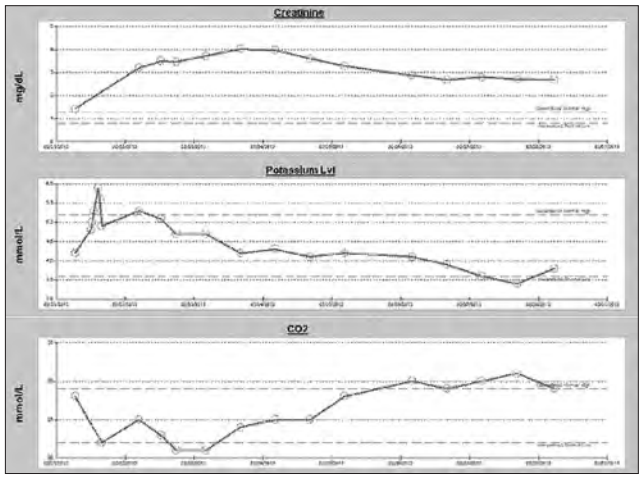

Figure 3: Simultaneous development of metabolic acidosis and hyperkalemia accompanying accelerated AKI after right-sided nephrectomy

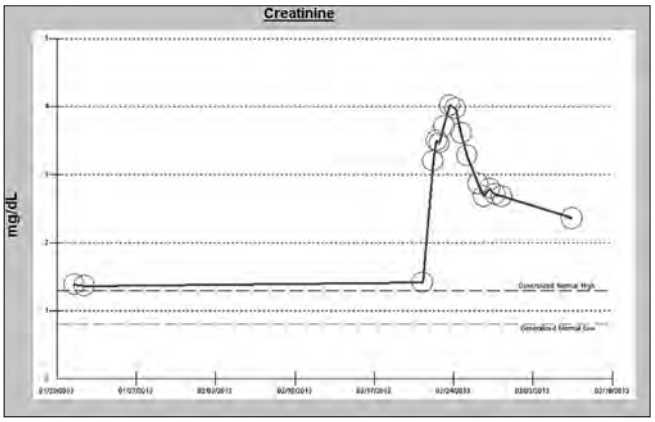

Figure 4: Serum creatinine trajectory following discontinuation of 'triple whammy' medications and correction of hypotension and anemia

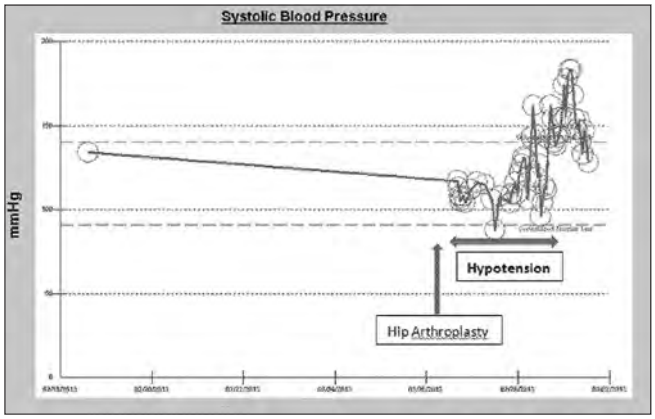

Figure 5: Peri-operative hypotension in a 46-year-old CKD male patient following elective right hip arthroplasty

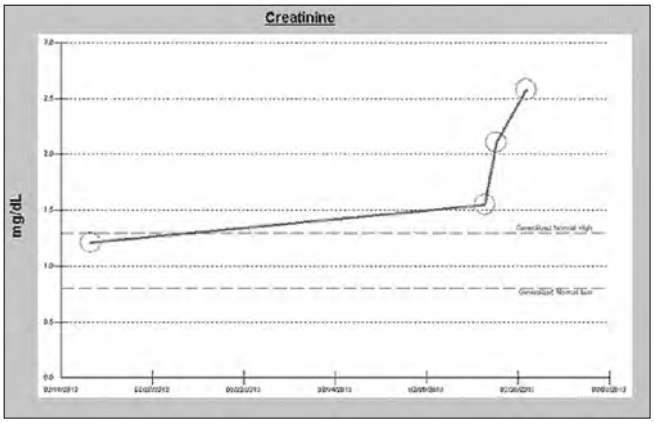

Figure 6: Accelerated AKI within 24 hours following elective right hip arthroplasty

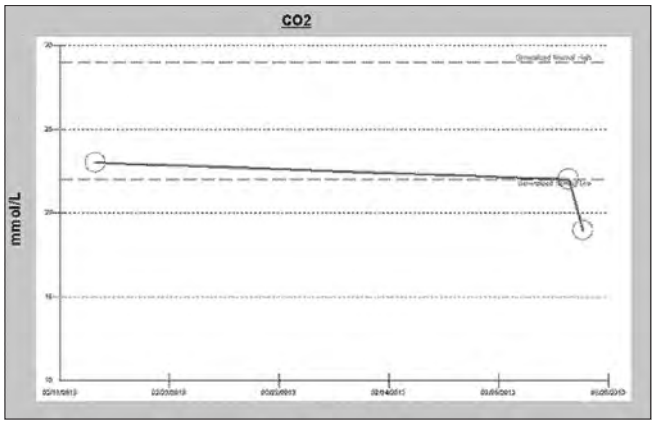

Figure 7: Simultaneous development of metabolic acidosis accompanying accelerated AKI after right hip arthroplasty

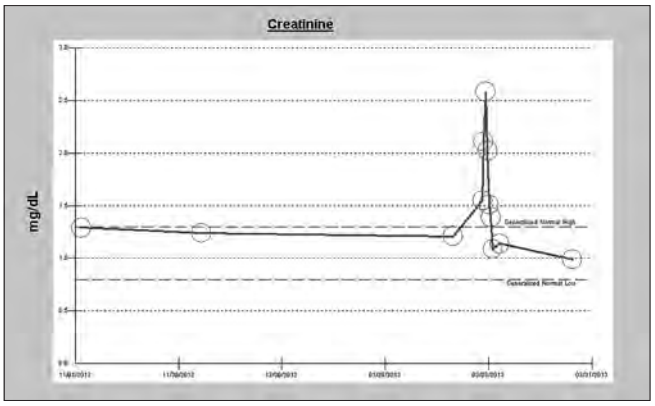

Figure 8: Serum creatinine in Case II normalized to below pre-operative levels, one month following elective right hip arthroplasty

Discussion

In one week in February-March of 2013, our Renal Service had managed two patients with rapidly accelerated AKI on CKD (II and III stages, respectively) following surgery that was complicated by peri-operative hypotension and anemia, while concurrently on 'triple whammy' medications.[6,7] We had therefore coined the new term "Quadruple Whammy" to describe this new syndrome of preventable AKI on CKD in patients on 'triple whammy' resulting from the superimposition of peri-operative stressors, especially hypotension in a patient with *a priori* stable CKD on 'triple whammy' medications following a surgical intervention.[6,7] We submit and have argued that in these two instances of elective surgical procedures, if the ACEI (+Diuretic + NSAID) had been temporarily withdrawn 4-7 days prior to the surgical operation, and if peri-operative hypotension had been more aggressively prevented or minimized, that both patients would have left the hospital sooner, without developing such severe degrees of AKI on CKD as so reported herein. This would have translated to less AKI, reduced length of hospital stay, reduced patient morbidity, and concomitant huge dollar savings for all.[14] Our recent analysis, published in the Journal *Renal Failure* clearly demonstrated the utility of such preventative nephrology practices in the ICU.[14]

A recent 2012 US study reported a rapidly increasing incidence of serious AKI requiring dialysis with the incidence rising from 222 cases per million person years in 2000 to 533 cases per million person years in 2009, averaging a 10% increase each year.[8] Furthermore, Lapi and colleagues in 2013, had identified 2215 cases of AKI during follow-up using the Clinical Practice Research Datalink (CPRD), previously known as the General Practice Research Database, and the Hospital Episodes Statistics repository from the UK, representing an overall AKI incidence rate of 7 in 10 000 (95% CI 7/10 000 to 8/10 000) person years.[9] Whilst the reasons for these increases in the global AKI epidemic remain unclear and must be multifactorial, in previous analyses and reports, we and other investigators have demonstrated that the increasing use of angiotensin inhibition in older patients with later stage CKD, at least in part, may help explain this global pandemic.[15-22] Indeed, in our 2008 report on 100 CKD patients who developed worsening AKI while on concurrent angiotensin inhibition and who were recruited into a prospective angiotenisn inhibition withdrawal study, there was a clear association of renal failure exacerbation with the concurrent use of NSAIDs and angiotensin inhibition in 10 (10%) patients.[16] Given that the only current therapy that is available for AKI is supportive therapy, or renal replacement therapy when indicated,[23] the importance of preventative nephrology (renoprevention) to mitigate AKI incidence must be the overarching goal of every physician, not just every nephrologist.[10,14,17]

Finally, as was recently emphasized by Fournier *et al.*, physicians, especially nephrologists, must remain increasingly aware of the potential impact of 'triple whammy' medications on renal function in (hospitalized) CKD patients.[11-13] The importance of such enhanced pharmacovigilance to reduce iatrogenic renal failure from prescription and over-the-counter medications cannot be overemphasized.[11-13,22,24,25] Monitoring of serum creatinine and potassium of patients treated with ACEIs, ARBs or diuretics and receiving a first NSAID dispensing is insufficiently performed and needs to be reinforced through specific interventions.[10] Doctors around the world must be aware of the potential for several agents, including angiotensin inhibitors, singly or in combination with other agents especially the 'triple whammy' combination, to initiate or exacerbate AKI in CKD patients. We must make every effort to limit the use of drugs to reduce harm to our patients. Indefinite monitoring of kidney function, especially in older CKD patients, must remain the norm, and doctors must be ready to discontinue potentially nephrotoxic drugs when unexplained AKI is diagnosed. "Quadruple whammy", the

syndrome of accelerated post-operative AKI in CKD patients concurrently on 'triple whammy' medications is preventable if 'triple whammy' combinations are pre-emptively discontinued 4-7 days prior to elective surgical procedures, and if peri-operative hypotension is aggressively prevented or rapidly corrected if and when it develops.[25]

The fact that both the patients reported herein were morbidly obese raised the significant question of a plausible role of obesity in the causation and/or exacerbation of peri-operative AKI in both the patients.[26-29] An analysis of determinants of peri-operative outcomes among patients with the modified metabolic syndrome who were undergoing noncardiac surgery studied 310,208 patients in the American College of Surgeons National Surgical Quality Improvement Program database.[26] This investigation demonstrated that in patients with the modified metabolic syndrome, the risk of AKI was 3- to 7-fold higher in these patients: obese (AOR 3.30; 95% CI 2.75-3.94), morbidly obese (AOR 5.01; 95% CI 3.87-6.49), and super obese (AOR 7.29; 95% CI 5.27-10.1).[26] Furthermore, more recent data support the observation that obesity and oxidative stress predict AKI after cardiac surgery.[27-29] A recent matched case-control study of patients enrolled in the Obesity and Surgical Outcomes Study, using data of Medicare claims enriched with detailed chart review identified 514 AKI cases and 694 control patients.[29] Of the cases, 180 (35%) followed orthopedic procedures and 334 (65%) followed colon or thoracic surgery. After matching, obese patients undergoing a surgical procedure demonstrated a 65% increase in odds of AKI within 30 days from admission (odds ratio = 1.65, $P < 0.005$) when compared with the nonobese patients.[29] After adjustment for potential confounders, the odds of postoperative AKI remained elevated in the elderly obese (odds ratio = 1.68, $P = 0.01$.).[29] Kelz *et al*. concluded that obesity is an independent risk factor for postoperative AKI in patients older than 65 years. Therefore, efforts to optimize kidney function pre-operatively should be employed in this at-risk population along with keen monitoring and maintenance of intraoperative hemodynamics.[29] The conclusion from another study was that obesity independently predicted AKI after cardiac surgery, and that oxidative stress may partially mediate this association.[27] From the foregoing, the observation that our case reports were both significantly and morbidly obese is a further anecdotal confirmation of the additional risk factor of obesity in the causation of peri-operative AKI. We submit that the quadruple whammy syndrome may indeed be more commonly observed in the more obese patients. Further studies are warranted to study this phenomenon.

Acknowledgments

This work is dedicated in the memory of a very dear friend, Ikechukwu Ojoko (Idejuogwugwu), who passed away when back home in Port Harcourt, Nigeria, some years ago, after a reported brief illness. Idejuogwugwu, you are truly missed. This work is also dedicated in the memories of the 153 Nigerians who died in a fiery plane crash in Lagos, Nigeria, on June 3, 2012. May their souls rest in peace. Finally, we dedicate this work in the memory of late Professor Dimitrios Oreopoulos; he was indeed a great teacher and mentor to the first author.

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