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CLINICAL STUDY

Renoprevention: A New Concept for Reengineering Nephrology Care—An Economic Impact and Patient Outcome Analysis of Two Hypothetical Patient Management Paradigms in the CCU

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Abstract

Background: The impact of acute kidney injury (AKI) on chronic kidney disease (CKD) progression remains uncertain; the common belief is that AKI in CKD is short-lived with subsequent full recovery. However 25.2% of end-stage renal disease (ESRD) Medicare patients all experienced antecedent AKI. We recently described a new syndrome of ESRD following AKI, the syndrome of rapid-onset end-stage renal disease (SORO-ESRD). Renoprevention, which we described in 2009, is the application of preventative measures to reduce AKI incidence. *Methods*: This is a descriptive study based on real clinical experience. Two hypothetical 69-year-old Caucasian male patients, A and B, with symptomatic coronary artery disease (CAD) presented for elective cardiac catheterization and subsequent coronary artery bypass graft procedures; renoprevention was applied in patient A but not in B. *Results*: Aggressive fluid repletion, withholding Lisinopril 40 mg once daily (QD) 1 week before hospitalization (hydralazine substituted) in A—earlier discharge after 6 days, transient minimal change in serum creatinine. Patient B continued on Lisinopril 40 mg QD, experienced prolonged hypotension needing pressors—severe oliguric AKI, volume overload, daily RRT for 6 days, recovered kidney function, was discharged after 20 days. Hospital charges were $68,580 (A) versus $154,650 (B). If patient B had developed ESRD (SORO-ESRD), the savings would be humongous. *Conclusion*: A more forceful and pragmatic application of renoprevention strategies in the coronary care unit (CCU)—preemptive withholding of nephrotoxics including renin angiotensin aldosterone system (RAAS) blockers, aggressive prevention of perioperative hypotension, avoiding nephrotoxic exposure as contrast, and antibiotics–leads to less AKI, potentially less SORO-ESRD, better patient outcomes, and massive dollar savings. Such paradigm shifts would constitute major rethinking in current nephrology practice, a form of nephrology practice reengineering.

Keywords: renoprevention, acute kidney injury, end-stage renal disease, syndrome of rapid-onset end-stage renal disease, economic analysis

INTRODUCTION

AKI and the Impact on CKD–ESRD Progression Revisited

The impact of acute kidney injury (AKI) on chronic kidney disease (CKD) progression remains uncertain; the common belief among most physicians, including nephrologists, is that AKI in CKD is usually short-lived with often subsequent full recovery, hence the leading adjective "acute." This notion needs to be revised especially as it applies to the elderly. Ishani et al., in 2009, in an analysis of 233,803 patients aged $\geq$67 years following hospital discharge in a Medicare database demonstrated that AKI increased the risk of progression to end-stage renal disease (ESRD) in elderly patients with CKD.[1] In this large Medicare study, 25.2% of the patients who received renal replacement therapy for ESRD had all experienced prior AKI.[1] Indeed, Okusa et al., writing on behalf of the Acute Kidney Injury Advisory Group of the American Society of Nephrology, inferred that AKI terminating in permanent ESRD "has an important and growing impact on the global epidemiology of chronic kidney disease (CKD) and end-stage renal disease (ESRD)."[2]

Furthermore, we recently described a new syndrome of irreversible ESRD following AKI, the syndrome of rapid-onset end-stage renal disease (SORO-ESRD).[3–7] We subsequently have examined 15 publications between 1975 and 2010 which have similarly shown the

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real-time translation from AKI to irreversible ESRD in CKD patients.[8] In fact, an accompanying editorial to one of the studies reviewed in this abstract, in 1996, had referred to these observations of ESRD rapidly following AKI in patients as "acute irreversible renal failure."[9] Also, several recent clinical studies based on epidemiological and outcome analysis data in CKD patients have highlighted the important role played by AKI in the pathogenesis and progression of CKD to ESRD.[10–17] For instance, Thakar et al., after investigating 110 patients with AKI requiring dialysis in long-term care hospitals in Cincinnati, Ohio, USA, demonstrated that 33 patients (30%) discontinued dialysis therapy, whereas 70% were deemed to have ESRD on discharge.[15]

Late-Onset Renal Failure from Angiotensin Blockade

We first described the syndrome of late-onset renal failure from angiotensin blockade (LORFFAB) in 2005.[18] Since then, we have reported severally on this syndrome.[6,7,19–24] LORFFAB is the observation of late-onset acutely worsening renal failure occurring in CKD patients, with normal renal arteries as demonstrated by conventional angiography, who had been on the same dose of an angiotensin converting enzyme inhibitor (ACEI), an angiotensin receptor blocker (ARB), or a combination of both, for more than 3 months, and in the absence of identifiable known so-called traditional precipitating risk factors.[6,7,18–24] The so-called traditional risk factors that have previously been associated with worsening azotemia in patients on concurrent angiotensin blockade include hypovolemia, dehydration, contrast exposure, increased dose of angiotensin blockade, perioperative periods, use of non-steroidal anti-inflammatory drugs (NSAIDs), renal artery stenosis involving single or bilateral functional kidneys, overdiuresis and new onset acute illness.[6,7,18–24] In addition to our first description of the syndrome of LORFFAB, first in 2005, and several subsequent reports on this syndrome, we have also demonstrated the clear association of angiotensin blockade (ACEIs and/or ARBs) with acutely worsening renal failure under various other clinical scenarios such as contrast-induced nephropathy, perioperative, and during critical illness.[6,7,18–31]

Furthermore, recently, we published the results of a literature review which recognized, apart from our own published reports, an increasing number of reports over the last decade that have identified concurrent use of ACEI/ARB as a de facto risk factor for AKI exacerbations under very different clinical scenarios.[30–38] These clinical scenarios are contrast-induced nephropathy, after cardiac surgery, and following the use of oral phosphate sodium preparations for lower bowel preparations.[32–38] Correspondingly, Komenda et al. had demonstrated improved renal outcomes when ACEIs were temporarily withheld from patients, 2 days before undergoing coronary angiography, when compared to historical controls.[36] Moreover, the perioperative use of ACEIs/ARBs was shown to be significantly associated with an increased risk for AKI after cardiac surgery in two tertiary medical centers in Buffalo, NY.[38] Anecdotally, in our suburban four-physician nephrology practice, at the Mayo Clinic Health System, in Northwestern Wisconsin, USA, we have, in the past decade, noticed an increasing number and severity of cases of AKI among hospitalized patients, sometimes associated with life-threatening hyperkalemia and metabolic acidosis, often requiring renal replacement therapy, in older CKD patients concurrently on an ACEI, an ARB, or a combination of both.[29]

Most pertinently, in a 2008 report from Barcelona, Spain, 41 patients who presented with AKI in the absence of any immunologic, septic, or toxic-related causes, mean age 71 years (46–94), there was an association with RAS inhibitors in 20 (49%) of 41 of the patients.[39] Preadmission serum creatinine had increased from 153+/−104 mmol/L (84–293) to 658+/−330 mmol/L (300–1700) on admission, associated with hyperkalemia in 14 (70%) of 20 patients with mean admission potassium level of 5.8+/−1.5 mEq/L (3.4–8.6).[39] Of the 20 patients with AKI treated in this center, 13 (65%) needed hemodialysis treatment. One patient died and discharge serum creatinine in this cohort was nearly double of the preadmission levels at 262+/−23 mmol/L (98–700).[39] The authors of this Spanish report, Navarro et al, concluded that advanced age, vascular disease, previous renal failure, and asymmetry of renal sizes appear to constitute main risk factors and that angiotensin blockade therapy in this subset of patients must be carefully balanced in terms of risk/benefit implications.[39] It must be acknowledged that these observations from Barcelona, Spain, very strongly support our previous reports of LORFFAB.[6,7,18–31]

Finally, in 2009, we defined renoprevention as the practice of preventing renal dysfunction by avoiding potential nephrotoxic exposure (NSAIDs, contrast, etc.), early and aggressive correction of volume depletion, appropriate choice and frugal dosing of pharmaceuticals, especially antibiotics, and in our opinion, and based on our experience at the Midelfort Clinic (now called Mayo Clinic Health System), and most importantly, the withholding of ACEIs and/or ARBs before parenteral contrast exposure, perioperatively, during severe illness and in any setting associated with cardiovascular compromise.[25] In subsequent years, we have demonstrated in several publications that this concept of renoprevention, although simple, life-saving, cost-saving and would lead to significant renal salvage, is not commonly practiced.[6–8,23–25] Eddy and Nelson, writing in the Journal of the American Society of Nephrology, in 2006, acknowledged that "Whether we like it or not, nephrologists around the world have been called to action. Our mission is to attenuate the growth of chronic kidney disease (CKD)."[40]

Based on real life clinical experiences in our coronary care unit (CCU) at the Mayo Clinic Health System, Eau Claire, in Northwestern Wisconsin, we have constructed

a hypothetical model of the renal outcomes in two clinical scenarios in our CCU, where in one instance the cardinal principles of renoprevention were aggressively pursued, but not in the other. The objective is to show the advantages of such a paradigm shift in the way we work as critical care nephrologists.

METHODS

This is a descriptive study based on real CCU clinical experience. Two hypothetical 69-year-old Caucasian male patients, A and B, both hypertensive stage III CKD, with baseline serum creatinine of 1.6 mg/dL, equivalent to an modification of diet in renal disease estimated glomerular filtration rate (MDRD eGFR) of 46 mL/min/1.73 sq. m BSA, with symptomatic coronary artery disease (CAD) presented for elective cardiac catheterizations and subsequent coronary artery bypass graft (CABG) procedures, respectively. The concepts of renoprevention were rigorously and meticulously applied in the management of patient A, but not for patient B.

RESULTS

Aggressive fluid repletion, withholding Lisinopril 40 mg once daily (QD) 1 week before hospitalization (hydralazine was substituted in place of Lisinopril as antihypertensive agent) in patient A. Patient A outcome was as following:earlier discharge after 6 days, with no significant change in serum creatinine (Table 1). Patient B was continued on Lisinopril 40 mg QD before and during the elective cardiac catheterization and subsequent CABG procedure. Patient B experienced prolonged intraoperative and postoperative hypotension requiring the use of intravenous pressors. Patient B outcomes were as following: severe oliguric AKI, volume overload, required more days of mechanical ventilation, daily renal replacement therapy with ultrafiltration for 6 days starting on postoperative day 5, with only partially recovered kidney function, and discharged after 20 hospitalization days with new baseline serum creatinine of 2.5 mg/dL (Table 1). Total hospital charges were $68,580 (Patient A) versus $154,650 (Patient B) (Table 1). If patient B had developed ESRD (SORO-ESRD), which was indeed a likely outcome, the dollar savings would have been only better imagined.

DISCUSSION

We have demonstrated in this hypothetical comparison model, the differing patient and renal outcomes, as well as the associated healthcare dollar savings that can result from the rigorous and meticulous application of the concepts of renoprevention in critically ill CCU CKD patients undergoing elective cardiac catheterization and subsequent CABG procedure.

At the minimum, physicians and nephrologists alike must acknowledge the potential propensity of AKI events to result in potentially irreversible renal damage, and even more importantly, in the temerity of AKI to in fact terminate in irreversible ESRD, under certain conditions.[1–15,41–55] We could not agree more with Okusa et al that AKI terminating in permanent ESRD "has an important and growing impact on the global epidemiology of chronic kidney disease (CKD) and end-stage renal disease (ESRD)."[2] More research is mandated in this field of nephrology, and this most urgently.[6–8,23–31]

We must not fail to acknowledge the recent report by El Nahas and his group, from Sheffield Kidney Institute, Northern General Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK, who demonstrated significant and yet sustained improvements in eGFR following the discontinuation of angiotensin blockade in patients with advanced CKD.[56] The Sheffield group demonstrated that 12 months following the discontinuation of ACE inhibitors and/or ARBs in 52 patients with advanced stage of CKD, mean age 73.3 years, the mean eGFR increased significantly from 16.38 ± 1 mL/min/1.73 sq.m BSA to 26.6 ± 2.2 mL/min/1.73 sq.m BSA ($p = 0.0001$).[56] In this study, 61.5% of patients experienced >25% increase in eGFR with follow up after the ACEI or ARB was discontinued.[56] Furthermore, 19 (36.5%) patients experienced increased eGFR following drug discontinuation exceeding 50%.[56] Moreover, there was a significant reversal in the eGFR slope from -0.39 ± 0.07 in the 12 months preceding discontinuation of the renin angiotensin aldosterone system (RAAS) blocking agents, a negative eGFR slope, to $+0.48 \pm 0.1$ ($p = 0.0001$), now a positive eGFR slope.[56] Besides, overall, proteinuria was not affected [protein creatinine ratio (PCR) (before) $= 77 \pm 20$ and PCR (after) $= 121.6 \pm 33.6$ mg/mmoL].[56] These findings from El Nahas et al., to date, remain the most audacious and vivid evidence in the literature to support our previous findings from the Midelfort Clinic, Eau Claire, Wisconsin, USA (now called Mayo Clinic Health System,

Table 1. Economic impact of prolonged hospital stay for Patient B versus Patient A.

Patient	Admission serum creatinine (mg/dL)	CVVHD with UF	Hospital LOS (days)	PRBC needED	Discharge serum creatinine (mg/dL)	Days on the vent	Cost of CVVHD Rx ($)	Cost of vent days ($)	Total hospital charges
A	1.6	0	6	1	1.7	2	0	25,000	$68,580
B	1.6	6	20	3	2.5	8	11,070	100,000	$154,650

Eau Claire, Wisconsin, USA) of the syndrome of LORFFAB.[6,7,31,56]

Escalating Unsustainable Cost of US Healthcare—Time to Bend the Healthcare Cost Curve

In conclusion, economic analysis demonstrates that the US healthcare system is troubled by run-away escalating healthcare costs which have outstripped inflation, consuming an increasing percentage of the gross domestic product (GDP) at an unsustainable rate.[57] Indeed, over the last 15 years, the United States has far surpassed most countries in the developed world for total healthcare expenditures per capita.[58,59] In 2009, the United States spent 17.4% of GDP on healthcare, translating to $7960 per capita, whereas Japan spent only 8.5% of its GDP, averaging $2878 per.[59] At current rates, the US Healthcare bill will increase from $2.5 trillion in 2009 to over $4.6 trillion in 2020.[60]

We must begin to reengineer the way we deliver care here in the United States to begin to bend the Healthcare cost curve or the US Healthcare system is doomed to a catastrophic implosion, sooner than later.[61] In management sciences, reengineering is defined as the fundamental rethinking and radical redesign of business processes to achieve dramatic improvements in critical, contemporary measures of performance, such as cost, quality, service, and speed.[62] Quite often, again as evident from the management sciences, reengineering frequently requires a great deal of process orientation changes as well as some "rule-breaking" in order to achieve organizational goals.[62] We submit that it is time for such rethinking in nephrology practice. As noted in an April 2012 Lancet comment, the most entrenched conflict of interest in medicine is a disinclination to reverse a previous opinion.[63] Renoprevention can only enhance renoprotection as we know it.[6–8,23–25] We posit that contrary to some widely held opinion, renoprevention is not meant to trump renoprotection. The ACEI and/or ARB can always be restarted after the CKD patient has survived the surgery, the critical illness or the cardiac catheterization and coronary artery stenting procedures. By so doing, we would have succeeded in the following—"Do no harm," saved more lives, salvaged more kidneys, and yes, saved healthcare dollars as we strive to a more sustainable US Healthcare delivery system.[57–62] Let's do it. Yes, we can. Yes, we must.

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