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UPDATE / *MISE AU POINT*

Induction of Diuresis and Natriuresis for Renal Protection: Update on the RenalGuard System™

Emploi de la diurèse et de la natriurèse dans la protection de la fonction rénale : mise à jour sur le RenalGuard System™

R. Solomon · A. Segal

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Abstract "Forced diuresis" is a technique that involves inducing a high urine flow rate. In most circumstances, diuretics and intravenous fluid replacement are necessary. Forced diuresis is recommended in a number of circumstances to improve or protect kidney function. The technique can be difficult to manage in clinical practice, often leading to net volume loss or excess. In this article, we review the data on the use of the RenalGuard system™. RenalGuard® accurately matches urine output and intravenous fluid input in real time and prevents any net volume changes. To date, RenalGuard® has been studied for prevention of acute kidney injury in patients undergoing cardiac angiography, percutaneous coronary intervention, and transcatheter aortic valve implantation. The possible mechanisms involved in producing a benefit are discussed.

Keywords Forced diuresis · RenalGuard® · Contrast media · Contrast induced nephropathy

Résumé La « diurèse forcée » est une méthode qui vise à générer un débit urinaire élevé. Dans de nombreuses situations, le recours aux diurétiques associé à une compensation volémique est nécessaire. La diurèse forcée est recommandée dans de nombreuses situations afin d'améliorer la fonction rénale ou de prévenir sa dégradation. Cette méthode est cependant souvent difficile à mettre en œuvre aboutissant à une balance hydrosodée positive ou négative. Dans cette revue, nous réalisons une mise au point sur les données de la littérature concernant l'utilisation du dispositif RenalGuard®. Ce dispositif permet le contrôle des sorties urinaires et des apports liquidiens en temps réel, prévenant ainsi toute modification volémique. À ce jour, RenalGuard® a été évalué pour la prévention de l'insuffisance rénale aiguë liée à l'injection de produits de contraste iodés (angiographie, TAVI). L'ensemble des études montre un bénéfice à l'utilisation de cette méthode. Les mécanismes expliquant le bénéfice constaté n'ont cependant pas été étudiés laissant entrevoir un champ de recherche intéressant pour apprécier les mécanismes à l'origine des insuffisances rénales répondant à un traitement fondé sur l'augmentation du débit urinaire.

Mots clés Diurèse forcée · RenalGuard® · Néphropathie aux produits de contraste iodés

R. Solomon (✉) · A. Segal
University of Vermont College of Medicine,
Division of Nephrology, University of Vermont Medical Center,
2308 1 South Prospect St. Burlington, VT 05401 USA
e-mail : richard.solomon@uvmhealth.org

Benefits of inducing a large urine output

There are circumstances in which passage of a large urine volume (diuresis) may be expected to be beneficial to kidney health. Prevention of nephrolithiasis is one such example. Both observational studies [1] and randomized trials [2] support the benefit of large urine volumes (>2.5–3.0 L/day) in reducing the incidence of new or recurrent stone formation. In a similar fashion, prevention of acute kidney injury (AKI) from myoglobin generated during rhabdomyolysis and certain drugs that can precipitate to form obstructing urinary crystals are other examples (Table 1). This benefit depends not only on reducing the absolute amount of crystal forming

Table 1 Substances that crystalize in the urine and can cause AKI

Methotrexate	Acyclovir
Sulfonamides	Ciprofloxacin
Sodium phosphate purgatives	Indinavir
Oxalate	Atazanavir
Myoglobin	Amoxicillin

precursors in the urine but also on reducing their concentration in the final urine to below the crystallization threshold.

Diuresis vs. Natriuresis

A special example of the benefit of a large urine output is the enhanced excretion of calcium in patients with hypercalcemia. Based upon an early observational trial [3] urine outputs of >500 ml/h induced by infusion of saline and furosemide were found to successfully lower serum calcium levels. However, this is not an effect of high urine flow rate per se but the effects of natriuresis. Calcium excretion increases in parallel with sodium excretion, particularly if induced by a loop diuretic that also inhibits calcium reabsorption. Such a natriuresis will lead to increases in calcium excretion sufficient to lower serum calcium levels. Guidelines for management of hypercalcemia have given primacy to bis-phosphonate usage based upon efficacy [4] and in part because achieving the targeted high urine flows without causing volume shifts or electrolyte abnormalities is quite difficult.

In all of these clinical examples, the ability to induce a vigorous natriuresis and/or diuresis is often limited by the potential adverse effects of extracellular volume shifts. Ideally, fluid infusion rates should match urine output rates such that net volume changes do not occur. Similarly, net infusion of sodium (and chloride) should match the renal excretion of these same solutes to prevent either hypo- or hypernatremia. In clinical practice, this matching of volume and solute are difficult to achieve. Inducing a natriuresis with infusion of saline alone will result in some extracellular volume expansion as the kidney's excretion of the increased sodium load requires intra- and extra-renal signaling mechanisms that take time to become activated [5]. Likewise, infusion of saline to match urine output usually results in some net volume depletion particularly when natriuresis is initiated with a dose of a diuretic. This is because adjustments in the infusion rate usually lag behind the measurement of urine output. In patients with abnormal kidney function at baseline or comorbidities like congestive heart failure, the difficulties in exactly matching input and output will be more challenging.

Rationale

We have already suggested two mechanisms that might underlie the benefit of a forced diuresis (dilution of a toxic substance within the urinary space and enhanced excretion related to overall enhanced solute excretion). Additional mechanisms can also be considered.

One possibility is that high flow rates and urinary sodium excretion alter renal hemodynamics in such a way as to protect against ischemia induced cell damage. Volume expansion with intravenous (IV) saline used to induce the natriuresis can be expected to reduce the activity of renal vasoconstrictive factors (the renin–angiotensin–aldosterone system and the sympathetic nervous system) and enhance renal vasodilatory factors (cardiac natriuretic peptides and intrarenal prostaglandins). These effects would be expected to enhance oxygen delivery to the medullary portion of the kidney, a site that is particularly vulnerable to ischemia. The medulla has a unique vascular anatomy making it prone to ischemic injury. The vessels ("vasa recti") follow the descending and ascending loops of Henle in very close proximity. Oxygen diffuses from the oxygen rich descending vasa recta to the oxygen depleted ascending vasa recta reducing the oxygen that actually reaches the medulla where cells of the ascending loop of Henle consume oxygen for sodium reabsorption [6].

Finally, it might be argued that the furosemide used to initiate the natriuresis may be important. Furosemide inhibits sodium reabsorption in the loop of Henle, decreasing oxygen consumption in the medulla [7]. Additionally, it is known that both a water diuresis [8] and furosemide [9] stimulate prostaglandin (PGE2) production within the kidney resulting in vasodilation and improved oxygenation in the medulla [10]. Results of trials using furosemide are discussed later in this review.

Contrast media

Iodinated contrast mediums (CMs) are a nephrotoxin. Induction of diuresis and natriuresis has been reported to have benefit in preventing AKI. To understand how a forced diuresis may be protective against CMs injury, it is first necessary to understand how contrast medium causes injury. Although our understanding is incomplete, it is generally agreed that two processes contribute directly to kidney tissue injury. First CMs adversely affect the balance between oxygen delivery and consumption in the medulla. CMs reduced medullary blood flow by promoting vasa recti vasoconstriction [11] while increasing oxygen consumption through an osmotic diuretic effect that delivers more sodium to the loop of Henle. The net result is a decrease in ambient oxygen tension in the medulla leading to generation of reactive oxygen species [12]. Second, CMs are directly nephrotoxic to renal tubule cells as demonstrated in a number of in vitro models [13]. The longer the CMs stay in contact with renal tubule cells, the greater the expected toxicity.

Early randomized prospective trials in patients with chronic kidney disease undergoing coronary or peripheral angiography noted that induction of a high urine flow rate with either furosemide or mannitol in addition of saline was inferior to saline alone in preventing contrast-associated AKI [14–16]. Of note, weight loss occurred over the initial 24 h in the furosemide and mannitol-treated patients suggesting that

efforts to match input and output were unsuccessful. As a result of these trials, volume expansion with IV sodium chloride alone became the standard of care for high-risk patients undergoing any IV contrast administration. In a seminal study (Prospective Randomized Trial of Prevention Measures in Patients at High Risk for Contrast Nephropathy [PRINCE]), investigators randomized patients with estimated glomerular filtration rate (eGFR) < 60 ml/min to a variety of interventions aimed at increasing urine output prior to coronary angiography. They found that urine output was significantly correlated with a reduction in the incidence of AKI regardless of how the urine output was stimulated (furosemide, mannitol, intravenous fluid, dopamine, and combinations thereof). Urine outputs of >150 ml/h during the first 24 h were associated with no AKI and individual achieving outputs >240 ml/h experienced no mean change in serum creatinine over the 48 h following angiography. Weights were not recorded in the study [17].

RenalGuard® (PLC Medical Systems, Inc.)

The RenalGuard system™ is a marriage of two existing widely used tools in clinical medicine. The first is the ability to continuously monitor urine flow rate using a Foley catheter with an attached urine collection bag. The second is automated infusion pumps that allow adjustment of IV infusion rates. In the RenalGuard system™, the urine collection bag is attached to a digital scale and the change in weight of the bag (reflecting urine output) drives the IV infusion pump in real time using proprietary software. Any change in urine flow rate results in a change in the collection bag weight that is converted to a signal that causes a similar rate of change in the infusion rate. This marriage of tools allows infusion of saline at rates that keep extracellular volume unchanged. Some trials have referred to this a "matched hydration," although the fluid administered is a saline solution and not water. In clinical use, the patient has a Foley catheter placed, is "primed" with an initial bolus administration of 250 ml of 0.9% saline (50% in those with low cardiac ejection rate), and natriuresis started with 0.25–0.5 mg/kg of IV furosemide. Nurse supervision is necessary for the initial setup, and replacement of saline solution and emptying of urine collection bag when prompted by an alarm sound.

To date, a number of prospective randomized trials have been performed with the RenalGuard system™ (Table 2). These trials have all had a primary goal of prevention of

Table 2 Prevention trials using the RenalGuard system™

Author, year, reference	Trial type	Group	*N*	Kidney function[a]	Control	CIN definition[b]	RG vs. C	Other
Briguori et al., 2011 [22]	R, P	CA/PCI	292	GFR <30 or Mehran >11	NAC/B protocol	0.3 mg/dl in 48 h	11% vs. 20.5%	30 days cumulative major adverse events similar
Marenzi et al., 2012 [18]	R, P	CA/PCI	170	GFR < 60	0.9% saline 12 h pre/post	0.5 mg/dl or 25% in 72h	4.6% vs. 18%	In hospital events similar
Barbanti et al., 2015 [20]	R, P	TAVR	112	GFR ≈ 63 mean	0.9% saline 12 h pre/6 h post	0.3 mg/dl or 50% in 72 h	5.4% vs. 25%	30 days MACE similar
Visconti et al., 2015 [21]	NR, Co	TAVR	48	GFR < 30 or "high risk"	NAC/B protocol	0.3 or 50% in 7 days	4.5% vs. 38%	–
Usmiani et al., 2016 [19]	R, P	CA/PCI	133	GFR < 60	NAC/M protocol	0.3 mg/dl in 48 h or 50% in 7 days	7% vs. 25%	1 year MACCE reduced by RenalGuard®

[a] Expressed as ml/min; Mehran score [23].

[b] Contrast induced nephropathy (CIN) defined as increase in serum creatinine.

B: sodium bicarbonate solution; C: consecutive; Co: controlled; CA: coronary angiography; GFR: glomerular filtration rate (expressed as ml/mn, at baseline); CIN: contrast induced nephropathy; NAC: *N*-acetylcysteine; NR: nonrandomized; M: sodium bicarbonate/isotonic saline/*N*-acetylcysteine/vitamin C; P: prospective; PCI: percutaneous coronary intervention; R: randomized; RG: RenalGuard system™; TAVR: transcatheter aortic valve replacement; MACE: major adverse cardiac events; MACCE: major adverse cardiac and cerebrovascular events

AKI following the administration of contrast media in patients at high risk for injury. The procedure (administration of contrast) is started once urine output reaches a rate of 300 ml/h as determined from the infusion pump rate. This usually takes 45–60 min after the initial prime. Urine output continues >300 ml/h for usually ≈6 h, often peaking ≈600–800 ml/h in the first couple of hours. If urine output falls below the 300 ml/h rate, additional doses of furosemide can be administered. At 4 h following the contrast procedure, the RenalGuard® is shut off. The only staffing requirements needed are for replacing the IV infusion bags and the urine collection bag as needed in response to machine alarms.

The first prospective multicenter randomized trial (Renal Insufficiency After Contrast Media Administration Trial II [REMEDIAL II]) from four different centers in southern Italy randomized 292 subjects with eGFR <30 ml/min or Mehran score of >11 (high risk) [23] who were undergoing coronary angiography [24]. In these patients the risk of AKI was greater because of the lower baseline eGFR. Patients in the control group received saline, acetylcysteine, and bicarbonate (per REMEDIAL I protocol), whereas the RenalGuard® group received only acetylcysteine. AKI occurred in 20.5% of the control patients and 11% of the RenalGuard® patients (relative risk [RR] 0.47, confidence interval [CI] 0.24–0.92, $p = 0.025$). Four patients developed pulmonary edema; three in the RenalGuard® group and one in the control. However, all three RenalGuard® patients developed their symptoms following the procedure and all had depressed left ventricular ejection fraction (LVEF) and elevated left ventricular end diastolic pressure at the time of the angiography. Dialysis was required in seven control patients and only one RenalGuard® patient ($p = 0.031$).

A second prospective randomized trial was Induced Diuresis with Matched Hydration Compared to Standard Hydration for Contrast Induced Nephropathy Prevention Trial (MYTHOS), performed at the Centro Cardiologico Monzino in Milan, Italy [18]. One-hundred and seventy patients with eGFR <60 ml/min were randomized to RenalGuard® versus normal saline at 1 ml/kg/h for 12 h before and 12 h after coronary angiography. AKI occurred in 18% of the saline group and 4.6% of the RenalGuard® group (RR = 0.29, CI 0.10–0.85, $p = 0.005$). The benefit was particularly evident in those undergoing urgent angiography where the incidence was 32% in the saline group and 5.0% in the RenalGuard® group (RR = 0.16, CI 0.04–0.58, $p = 0.003$). In-hospital events such as need for dialysis, new myocardial infarction, arrhythmias, pulmonary edema, shock, and death were similar in the RenalGuard® group and the controls. Specifically, there was no difference between the groups in the incidence of congestive heart failure.

A third randomized trial (Acute Kidney Injury GUARDing Device [AKI-GUARD]) of 133 subjects with eGFR <60 ml/min followed patients for 12 months following RenalGuard® use [19]. The incidence of contrast-induced nephropathy (CIN) was reduced to 81% ($p = 0.02$), 12-month major adverse cardiovascular and cerebrovascular event 82% ($p = 0.01$), and days in the hospital at 12 months 82% ($p = 0.02$).

Two trials have been conducted in patients undergoing transcatheter aortic valve implantation (TAVI), a procedure associated with a high risk of AKI. The first trial randomized 112 consecutive patients to either RenalGuard® or treated with *N*-acetylcysteine (NAC) and bicarbonate (per REMEDIAL protocol) [20]. Patients were not selected based upon impaired kidney function and the average eGFR was 63 ml/min. AKI defined per Kidney Disease Improving Global Outcomes (KDIGO) criteria occurred in 25% of the NAC/bicarbonate group but only 5.4% of the RenalGuard® group. A smaller pilot study of 48 patients all with initial eGFR <30 ml/min that did not randomize patients reported an AKI rate of 38% in the control (again NAC/bicarbonate) compared to 4.5% RenalGuard® [21].

A currently active Phase III prospective randomized trial in the United States (NCT01456013) has enrolled over 200 patients. Inclusion criteria include a eGFR <60 ml/min with two other risk factors (diabetes, congestive heart failure, proteinuria, or age >75) or eGFR <45 ml/min. Patients are randomized to RenalGuard® (per the protocol noted above) or saline (3 ml/kg × 1 h preangiography, and 1.5 ml/kg during and for 4 h postangiography). Site-specific protocols for the use of NAC are permitted. To date, the Data Safety Monitoring Board has kept the trial open and no safety concerns have been raised.

Finally, a registry of 400 patients who underwent RenalGuard system™ (many included in some of the above trials) looked at independent predictors of AKI as well as adverse events [22]. The RenalGuard® was very accurate in replacing only what was lost, both in patients with and without impaired ejection fractions. Over 90% of patients achieved the target rate of ≥300 ml/h. A correlation was observed between mean urine flow rate and eGFR with patients with the lowest eGFR having the least urine flow rates. The average furosemide dose was 14 mg with 17% achieving the target urine flow rate without any furosemide. AKI was more frequent in patients with the lower urine flow rates. A urine flow rate of ≥450 ml/h at the time of the procedure was associated with the lowest rate of AKI. One percent of patients ($n = 4$) developed pulmonary edema following the procedure and RenalGuard® was prematurely discontinued to allow negative fluid balance. Asymptomatic hypokalemia ($K^+ < 3.5$ mEq/l) occurred in 7.5% and K^+ replacement was given to approximately half of these patients. Hypomagnesemia ($Mg^{++} < 1.7$ mg/dl) was noted in 11%. As expected, 1-month mortality and need for dialysis were significantly higher in those who developed AKI.

Table 3 Trials using furosemide for prevention of CIAKI

Author, date, reference	Dose (mg) of furosemide	Weight change control (kg)	Weight change furosemide (kg)	Incidence of CIAKI reduced?
Weinstein et al., 1992 [16]	110	+1.30	−0.70	No
Solomon et al., 1994 [15]	80	−0.49	−0.78	No
Dussol et al., 2006 [25]	100	+0.13	−0.46	No
Majumdar et al., 2009 [14]	100	Control gained 266 ml more than furosemide		No

Use of furosemide

Prior prevention trials that used furosemide found that it was associated with a higher incidence of contrast induced acute kidney injury (CIAKI) (Table 3). In the trials by Solomon, Weinstein, and Dussol, no attempt was made to replace urine losses and patients all lost weight [15,16,25]. In the Majumdar et al. study, urine was replaced hourly but the control group still ended up with more IV fluid than the intervention group (no weights were reported) [14]. This suggests that the use of furosemide in these trials was associated with volume depletion and activation of renal vasoconstrictive mechanism that would exacerbate the vasoconstriction caused by iodinated contrast. Second, the doses of furosemide used in these trials were in the order of 1.0 mg/kg or more. Such doses may have direct effects on the distribution of renal blood flow [26]. The RenalGuard system™ as used in the clinical trials uses 0.25–0.35 mg/kg of furosemide, a dose that may have less direct vascular effect. Finally, mannitol was administered simultaneously in the Majumdar et al. study [14]. This osmotic diuretic would be expected to deliver more sodium to the loop of Henle resulting in an increase in oxygen consumption offsetting the potential benefits of furosemide (see above).

Unanswered Questions

Although the above cited data are very encouraging, the total number of patients treated with RenalGuard® remains relatively small and further experience is clearly needed.

All patients thus far studied were stable and in steady state. The use of RenalGuard® in nonsteady-state patients (hypotension, volume depletion, intensive care unit has not been studied. Potential adverse effects may be more common in such patients.

Conflict of interest: None.

Summary

Induced natriuresis and diuresis without extracellular volume shifts as achieved with the RenalGuard device™ may have beneficial effects on prevention of AKI from a number of insults, including contrast media. The RenalGuard device™ enables large urine volumes to be generated safely with minimal side effects. Studies on the mechanisms by which such large urine volumes and natriuretic effects protect against AKI are greatly needed. This may open new approaches to the prevention and/or treatment of AKI in other situations.

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