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The Renal Guard System for the Prevention of Contrast-Induced Acute Kidney Injury

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Abstract

Contrast-induced acute kidney injury (CI-AKI) accounts for approximately 10% of all causes of hospital-acquired renal failure, causes a prolonged in-hospital stay and represents a strong predictor of poor early and late outcome. A general consensus exists on the beneficial prophylactic effect of hydration The Renal Guard system (PLC Medical System, Inc. Franklin, MA, USA) has been developed to facilitate optimal hydration therapy. This device allows to achieve high urine flow rate (≥ 300 ml/h) while simultaneously balancing urine output and venous fluid infusion to prevent hypovolemia. Some studies have shown that the Renal Guard system is more effective than the conventional hydration regimen in preventing CI-AKI. A recent study suggests that the best threshold for CI-AKI prevention is a mean intraprocedural urine flow rate ≥ 450 ml/h.

Keywords: Iodinated contrast media; Nephrotoxicity; Prevention; Antioxidant

Introduction

In the last decades percutaneous coronary, peripheral and valvular procedures have substantially increased. The administration of iodinated contrast media (CM) is essential for all these procedures. Although usually well tolerated; CM may induce acute kidney injury (AKI). CM-induced AKI (CI-AKI) has become the third cause for hospital-acquired renal failure with a prolongation of the hospital stay and consequently an increase of health costs1. Beyond that, patients developing CI-AKI are at higher risk of both a further deterioration of kidney function and an unfavorable clinical outcome [1]. The most common clinical definitions of CI-AKI are based on the increase in serum creatinine levels ≥ 25% and ≥ 0.5 mg/dl from the baseline value at 48 hours after CM administration or the need for dialysis [2]. Different strategies have been proposed to prevent this complication [3]. In this review we discuss on the potential advantages of the Renal Guard system to prevent CI-AKI.

The Renal Guard® System

A general consensus exists on the beneficial effect of hydration in preventing CI-AKI [3]. Hydration induces an increase of urine flow rate (UFR), reduces the concentration of CM in the tubule and expedites CM excretion thus reducing the exposure time of tubular cells to the toxic effects of CM [4-6]. The most recommended hydration regimen is normal saline infusion at 1 ml/kg/h 12 hours before and 12 hours after CM exposure [3]. Limitations of this hydration regimen include 1) preclusion in urgent/emergent settings, and 2) suboptimal efficacy in high risk patients.

One approach for CI-AKI prophylaxis implies the induction and maintenance of a high UFR. The Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation (PRINCE) study indicates that increasing the UFR to ≥ 150 ml/h reduces the toxic effect of CM [7]. However, this UFR was reached in <30% of patients. In particular, in patients treated with ipotonic infusion alone UFR was 122 ± 54 ml, whereas in those treated with ipotonic infusion plus furosemide, dopamine and mannitol UFR was 167 ± 58 ml [7]. The high UFR should be reached by maintaining a constant intravascular volume in order to prevent hypovolemia [7].

Theoretically, furosemide should protect the kidney by reducing the outer medullary hypoxia caused by CM by blocking the Na-K-2Cl transporter in the medullary thick ascending limb [8]. However, compelling data support that neither mannitol nor furosemide offer additional protection against (but may actually exacerbate) CI-AKI as compared with saline hydration alone [9,10]. Significant weight loss was observed in the patients treated with furosemide, suggesting that the potentially deleterious effect of furosemide was the result of a negative fluid balance.

The Renal Guard system (PLC Medical System, Inc. Franklin, MA, USA) has been developed to facilitate optimal hydration therapy. This device allows to achieve high urine output while simultaneously balancing urine output and venous fluid infusion to prevent hypovolemia [11]. The Renal Guard system includes a) a closed loop fluid management system; b) a high volume fluid pump, c) a high accuracy dual weight measuring system; d) motion detection artifact reduction; e) a single use intravenous set and urine collection system that interfaces with a standard Foley catheter; f) real-time display of urine and replacement fluid volume; g) a timely alerts to drain the urine bag or to replace the hydration fluid bag; f) and safety features such as automatic air and occlusion detection [11] (Figure 1).

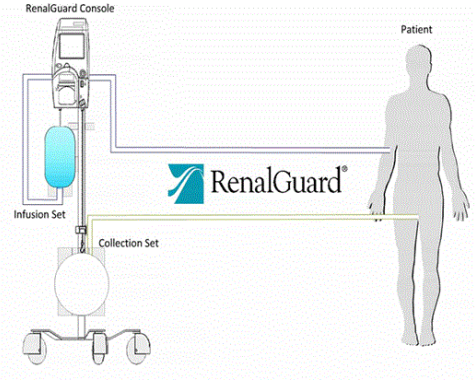

Figure 1: The Renal Guard system.

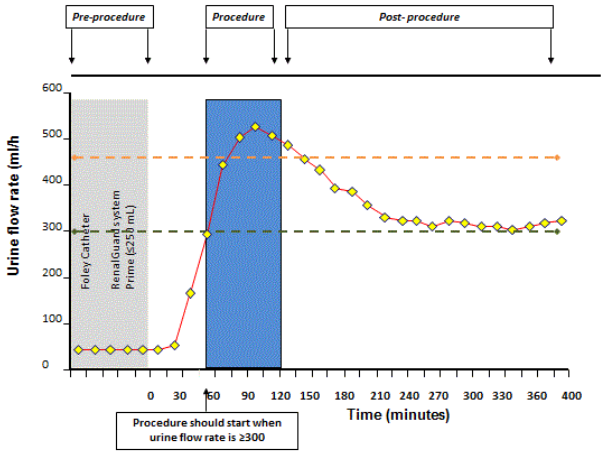

Figure 2: Diagram showing each stage of the Renal Guard therapy. The dotter-green line represents the suggested mean urine flow rate cutoff of 300 ml/h. The dotter-orange line represents the suggested intraprocedural urine flow rate cutoff of 450 ml/h.

Some studies have shown that the approach of controlled, forced diuresis using the Renal Guard therapy is more effective than the conventional therapy in preventing CI-AKI in patients undergoing percutaneous coronary interventions [12-14] or transcatheter aortic valve implantation [15,16]. An initial bolus (priming) of 250 ml is infused over 30 minutes.

Following the priming, furosemide (0.25 mg/kg) is administered intravenously in order to achieve high (≥ 300 ml/h) UFR. Controlled hydration by the Renal Guard system continued during the procedure and for 4 hours following the procedure. Urine flow should be monitored and maintained at the target value throughout the procedure and during the following 4 hours (Figure 2).

Additional furosemide doses are allowed in instances where there is a decrease in UFR below the target value. Briguori, et al. [12] reported a 53% relative risk reduction CI-AKI rate in patients treated by the Renal Guard system compared to the standard therapy. The beneficial effect was also documented by a lower severity of kidney damage, a lower rate of in-hospital dialysis and a smaller increase in serum cystatin C in the Renal Guard group than in the Control group. In the same way, Marenzi, et al. observed a 60% reduction in the incidence of CI-AKI in elective angiography patients who were treated with Renal Guard system [13].

Concerns have been raised for the high UFR obtained with the Renal Guard system due to the potential hazards of impairment in electrolyte balance and the risk of acute pulmonary edema. However, no significant changes in electrolyte balance were documented and the highly accurate, temporally matched fluid replacement observed reduced the risk of hypovolemia. Furthermore, the rate of pulmonary edema was very low [12].

In order to clarify the relationship between UFR and CI-AKI, we conducted a study assessing what should be the ideal UFR for an optimal CI-AKI prevention. We observed that the best threshold for CI-AKI prevention is a mean intraprocedural UFR ≥ 450 ml/h [17]. In high risk patients, this intraprocedural UFR target (≥ 450 ml/h) was reached in less than 50% of patients, and in 92% of those patients who did not developed CI-AKI, whereas an UFR ≤ 450 ml/h was observed in 68% of patients who developed CI-AKI.

On the contrary, the proposed UFR threshold ≥ 300 ml/h showed lower performance. In high risk patients, this proposed UFR target (≥ 300 ml/h) was reached in the 91.5% of patients, whereas in the remaining 8.5% patients it was constantly below the target. This cutoff has been adopted from the PRINCE study, which suggests that increasing the UFR ≥ 150 ml/h reduces the toxic effect of CM, but was never directly confirmed in the clinical practice [7]. The observed prevalent importance of the mean intraprocedural UFR emphasizes its crucial role in the CI-AKI prevention. A strong time-dependence of contrast-induced renal cell cytotoxicity has been reported [6].

Additional trials are ongoing in order to confirm these preliminary positive findings on Renal Guard system in preventing CI-AKI (Table 1). In particular, only one study compared this strategy with continuous veno-venous hemofiltration (CVVH), which has been reported to be effective in very-high risk population [18]. Bertelli et al., indeed, compared the impact on major events of Renal Guard system (n=33), continuous veno-venous hemofiltration (CVVH; n=35) and conventional hydration (Hy; n=32) in 100 patients with severe CKD scheduled for an elective percutaneous coronary and/or peripheral interventions. In-hospital dialysis occurred in none of Renal Guard patients, 7 (20%) of CVVH patients vs 2 (6.3%) of Hy group.

Futhermore, one of Renal Guard patients died at 6 month, versus 9 (25.7%) CVVH patients and 2 (6.3%) hydration protocol patients (p=0.002). Albeit not significant, CI-AKI occurred less frequently in the Renal Guard patients (15.2%) than CVVH (31.4%) and hydration protocol (25.0%) (p=0.288) [19]. Finally, it should be clarified why UFR did not reach the proposed cutoff in approximately 9% of patients [12,17]. One hypothesis is that the effect of furosemide may be attenuated in the presence of renal artery stenosis.

Trial	Design	Registration Number
Evaluation of Renal Guard® System to Reduce the Incidence of Contrast Induced Nephropathy in At-Risk Patients (CIN-RG)	Standard therapy versus Renal Guard system	NCT01456013
Renal Insufficiency Following Contrast Media Administration Trial III (REMEDIAL III)	LVEDP-guided hydration versus Renal Guard system	NCT02489669
The Use of Renal Guard System in Patients Undergoing CRT Implantation	Standard therapy versus Renal Guard system	NCT01936142
The Effect of the Forced Diuresis With Matched Hydration in Reducing Acute Kidney Injury During TAVI	Standard therapy versus Renal Guard system	NCT01866800
Renal Guard System for Prevention of Contrast Induced Nephropathy (REPRECIN)	Standard therapy versus Renal Guard system	NCT02029820

Table 1: Ongoing studies on the RenalGuard® system in CI-AKI prevention. LVEDP: Left Ventricular End Diastolic Pressure; CRT: Cardiac Resynchronization Therapy.

Contrast-enhanced ultrasound, based on the injection of an intravascular biocompatible tracer (that is, galactose microparticle suspension containing microbubbles [Levovist]), allows the quantification of renal tissue perfusion [20]. This promising non-invasive method seems to be ideal for screening patients with suspected renal artery stenosis. Future studies using contrast-enhanced ultrasound should clarify the role of renal artery stenosis on the efficacy of the Renal Guard therapy.

Conclusion

AKI may complicate CM exposure. The Renal Guard system seems to be helpful in preventing CIAKI by allowing a high UFR and maintaining an optimal fluid balance.

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