Peri-angiography Hemofiltration to Reduce Mortality

8

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8.1 General Principles

One of the most important and well-known complications of contrast agent administration is kidney toxicity and contrast-induced nephropathy (CIN). The incidence of CIN is growing, largely due to the increasing number of cardiac catheterizations and percutaneous coronary interventions (PCI) in elderly patients with associated co-morbidities, such as chronic kidney disease (CKD), diabetes and cardiac failure [1]. The available literature has consistently shown that patients who develop CIN have a greater risk of death, both during hospitalization and for up to one year or more after the contrast-enhanced procedure. Therefore, as CIN is potentially preventable, prophylactic measures are mandatory.

Despite a large number of studies, most of the evaluated prophylactic pharmacologic agents have not proven to be effective, particularly when hard end points are considered. Renal replacement therapies (RRTs) are emerging as useful therapeutic strategies in patients with coexisting cardiovascular and renal pathologies, and they have recently been a matter of deep investigation also in the setting of CIN prevention. This interest lies on the notion that contrast media, due to their relatively small size, lack of protein binding and small volume of distribution, are well suited for removal with RRT [2].

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In this chapter, the potential applications of RRT and, in particular, of hemofiltration, in CIN prevention in patients undergoing PCI, will be discussed on the basis of investigational experiences, with an emphasis on their impact on prognosis.

8.2 Main Evidence

The features and findings of the main studies investigating the prophylactic use of RRT to prevent CIN and to reduce mortality are summarized in Table 8.1.

Hemodialysis was first proposed for CIN prevention after contrast agent administration in patients with CKD, but no clear benefit over hydration, or even potential harm, was demonstrated [3–6]. Indeed, a higher likelihood to have a decline in renal function with additional hemodialysis treatment was reported [4]. Even when hemodialysis was started immediately before contrast agent administration, it did not demonstrate any appreciable protection against CIN [7]. These initial negative results were confirmed in a systematic review [8] and in a more recent meta-analysis [9] that showed no benefit of hemodialysis in CIN incidence as compared to routine preventive care, with, again, a trend toward a greater risk for hemodialysis need [8]. Nevertheless, subgroup analyses found that hemodialysis had a beneficial effect over the standard treatment in reducing the risk of CIN in patients with stage 4 or stage 5 CKD [9]. Consistently, Lee et al. [10] demonstrated the benefit in renal outcome of a 4-h hemodialysis session after coronary angiography in patients with stage 5 CKD. However, hard end points, such as in-hospital and long-term mortality, do not seem to be favourably affected by the use of prophylactic hemodialysis [9, 11].

Continuous hemofiltration, by effectively removing fluid and solute with fluid volume control, is associated with a better hemodynamic stability. Thus, it represents an advantage over high-intensity hemodialysis sessions, especially in the treatment of patients with associated renal and cardiac failure. In 2003, a single-centre randomized controlled trial found that the use of pre-emptive hemofiltration, initiated 4–8 h before contrast exposure and continued for 18–24 h after the procedure, resulted in a significant reduction of CIN incidence (5 % vs. 50 %) and in an improved in-hospital (2 % vs. 18 %) and 1-year (10 % vs. 30 %) mortality in patients with severe CKD undergoing elective PCI [1]. A subsequent randomized study, comparing the use of saline hydration with pre- and post-procedural hemofiltration or the use of post-procedural hemofiltration only in severe CKD patients scheduled for elective procedures, concluded that pre- and post-hemofiltration was superior to the other two strategies, in terms of CIN incidence, in-hospital clinical complications, and mortality [12]. In line with these findings, it has been recently demonstrated, in 46 CKD patients undergoing PCI, that hemofiltration (if serum creatinine <3 mg/dL) or hemodiafiltration (if serum creatinine >3 mg/dL) performed before and after contrast medium administration was more effective in preventing a further worsening of renal function as compared to post-procedural treatment only. Moreover, at 18 months, a significantly lower overall mortality was observed in patients treated with RRT pre-post vs. RRT post (16 % vs. 57 %) [13]. However, in

Table 8.1 Summary of studies on the prophylactic use of renal replacement therapy to prevent contrast-induced nephropathy and to reduce mortality

Source	Type of study	Number of patients	Type of procedure	RRT modality	Protocol			CIN prevention	Mortality reduction
					Before CE	After CE	Qr/Qd		
Lehnert (1998) [5]	Prospective randomized	30	Angiography	HD	–	3 h	Qd 500 mL/min	No	–
Sterner (2000) [3]	Prospective randomized	32	Angiography	HD	–	4 h	NA	No	–
Vogt (2001) [4]	Prospective randomized	113	Renal PTA Peripheral PTA CT scan CA	HD	–	3 h	Qd 500 mL/min	No	–
Frank (2003) [7]	Prospective randomized	17	CA	HD	–	4 h	Qd 500 mL/h	No	–
Marenzi (2003) [1]	Prospective randomized	114	Elective CA and PCI	HF	4–6 h	18–24 h	Qr 1,000 mL/h	Yes	Yes
Marenzi (2006) [12]	Prospective randomized	92	Coronary angiography + PCI	HF HF	6 h	18–24 h 18–24 h	Qr 1,000 mL/h	Yes Yes	Yes Yes
Lee (2007) [10]	Prospective randomized	82	CA Elective PCI Urgent PCI	HD	–	4 h	Qd 500 mL/min	Yes	–
Reinecke (2007) [11]	Prospective randomized	424	Elective CA	HD	–	2 h	Qd 500 mL/min	No	No
Ghani (2011) [15]	Prospective Observational	98	CA PCI	HF		18–24 h	Qr 2,000 mL/h	Yes	–

(continued)

Table 8.1 (continued)

Source	Type of study	Number of patients	Type of procedure	RRT modality	Protocol			CIN prevention	Mortality reduction
					Before CE	After CE	Qr/Qd		
Spini (2013) [13]	Prospective Observational	46	Elective PCI Urgent PCI Emergent PCI	HD/HDF	6 h	18–24 h 18–24 h	Qr 1,000 mL/h Qd 1,000 mL/h	Yes Pre-post vs. post	Yes Pre-post vs. post
Choi (2014) [16]	Prospective randomized	68	CA Elective and urgent PCI	HF	During CA		Qr 2,000 mL/h	Yes	–
Guastoni (2014) [17]	Prospective Observational	53	CA Elective PCI Urgent PCI	HF		6 h	Qr 25 mL/min	Yes	–
Marenzi (2015) [18]	Prospective Observational	60	Urgent and emergent PCI	HDF		3 h	Qr 2,000 mL/h Qd 30 L/h	Yes	Yes

CA coronary angiography, *CE* contrast exposure, *CIN* contrast-induced nephropathy, *HD* hemodialysis, *HF* hemofiltration, *HDF* hemodiafiltration, *NA* not available, *PCI* percutaneous coronary intervention, *PTA* percutaneous transluminal angioplasty, *Qd* dialysate pump rate, *Qr* replacement rate, *RRT* renal replacement therapy

a recent meta-analysis including 11 trials (9 randomized and 2 nonrandomized), although hemofiltration and haemodiafiltration were found to significantly reduce the risk of acute temporary RRT, their use did not affect CIN occurrence and did not improve mortality [9].

Although the notion that a pre-procedural RRT session is required in order to obtain a full clinical benefit, its use before coronary angiography and PCI is unsuitable for many patients with acute coronary syndrome (ACS), who often need an emergency or urgent intervention. In addition, ACS patients represent a population at high risk of CIN, given the large amount of contrast that may be required, the frequently associated hemodynamic instability and the preclusion from adequate CIN prophylaxis measures before contrast exposure [14]. In 2011, Saudi et al. [15] demonstrated that a 24-h hemofiltration session, performed as soon as possible after contrast injection in 98 CKD patients undergoing coronary angiography, resulted in a very low CIN incidence (1 %). However, since a clinical follow-up was not available, the potential prognostic implications of hemofiltration could not be determined. In a subsequent study, hemofiltration performed only during coronary intervention in CKD patients, with stable and unstable (about 40 %) coronary artery disease, provided a similar protection against CIN occurrence and a better 30-day renal outcome using significantly less medical resources as compared to periprocedural hemofiltration, suggesting that simultaneous hemofiltration can be immediately performed in patients undergoing emergency coronary intervention [16]. In agreement with these preliminary data, Guastoni et al. [17] demonstrated that hemofiltration performed for 6 h after a diagnostic or interventional coronary procedure in patients with severe CKD, also including those with ACS, was able to remove more than half of the administered contrast medium. Again, this was associated with a low incidence of CIN. A recent study evaluated such a strategy in high-risk ACS patients with associated severe renal and cardiac dysfunction, undergoing urgent or primary PCI and found that a 3-h treatment with haemodiafiltration, initiated immediately after PCI, significantly impacted on in-hospital (3 % vs. 23 %) and 1-year mortality (10 % vs. 53 %) [18]. Of note, the incidence of stage 2–3 acute kidney injury (10 % vs. 40 %) and the need for rescue RRT (7 % vs. 27 %) during hospitalization were significantly lower among haemodiafiltration-treated patients, suggesting that the possible clinical benefit associated with haemodiafiltration could have been driven by the marked reduction in the occurrence rate of severe acute kidney injury.

8.3 Pathophysiological Principles

A possible explanation for the lack of a beneficial effect associated with the use of hemodialysis is that, by inducing hypovolemia, it may worsen renal ischemic injury, delay recovery of renal function and result in a need for prolonged treatment. On the other hand, continuous hemofiltration is associated with hemodynamic stability and, by preserving the volume of circulating blood, it safeguards against renal hypoperfusion. This effect is particularly useful when coronary procedures are

performed in patients with critical conditions. In addition to hemodynamic stability, hemofiltration provides controlled high-volume hydration and removal of contrast agent from the circulation, with a resultant reduction in the kidneys' exposure to the agent. It can also be speculated that, in addition to high-volume controlled hydration, the removal by convective filtration and by adsorption to the filter membrane of mediators of contrast-induced toxicity, such as endothelin, angiotensin, prostaglandins and adenosine, as well as of uremic toxins, may play an additional protective role during the hemofiltration session preceding contrast exposure. Finally, a renal protective effect may also derive from the alkalinizing bicarbonate-based solution, used in the replacement fluid during hemofiltration.

8.4 Therapeutic Use

Taken together, these data indicate that hemofiltration represents an important advance for CIN prevention, because it allows us to extend the range of patients with advanced CKD who were previously excluded from cardiac catheterization, despite their high coronary atherosclerotic burden, and who may currently undergo invasive cardiovascular procedures safely. However, although a growing amount of data seems to support its use, there is still insufficient evidence to confirm a routine employment of hemofiltration for both CIN prevention and outcome improvement in clinical practice in high-risk patients [19]. Accordingly, the most recent guidelines on myocardial revascularization of the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery have recommended (Class IIa recommendation, level of evidence B) the use of prophylactic hemofiltration for prevention of CIN only in patients with severe CKD undergoing complex PCI [20].

In conclusion, the role of these therapies in the highest risk patients, namely, those with associated cardio-renal dysfunction, where adequate intravenous hydration may be difficult and fraught with complications, seems to be promising. As only patients with very low residual renal function seem to benefit from these therapies, they should be the focus of studies that wish to test the potential clinical

Clinical Summary

Strategy	Indications	Side effects	Dose
Peri-angiography hemofiltration	Complex PCI in severe CKD patients	*Related to vascular access* (haemorrhage, infection, insertion complication) *Related to heparinization* (haemorrhage, thrombocytopenia)	Prophylactic 6 h before PCI continued for 24 h after the procedure Fluid replacement rate 1,000 mL/h without negative loss and saline hydration

advantage of RRT. Therefore, future studies are warranted to better define the specific role of these approaches, with particular emphasis on hard clinical end points, optimally customized prophylactic protocols and their most cost-effective application.

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