Review

Bench-to-bedside review: Preventive measures for contrast-induced nephropathy in critically ill patients

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Published online: 7 January 2005
This article is online at http://ccforum.com/content/9/4/361

Critical Care 2005, **9**:361-370 (DOI 10.1186/cc3028)

Abstract

An increasing number of diagnostic imaging procedures requires the use of intravenous radiographic contrast agents, which has led to a parallel increase in the incidence of contrast-induced nephropathy. Risk factors for development of contrast-induced nephropathy include pre-existing renal dysfunction (especially diabetic nephropathy and multiple myeloma-associated nephropathy), dehydration, congestive heart failure and use of concurrent nephrotoxic medication (including aminoglycosides and amphotericin B). Because contrast-induced nephropathy accounts for a significant increase in hospital-acquired renal failure, several strategies to prevent contrast-induced nephropathy are currently advocated, including use of alternative imaging techniques (for which contrast media are not needed), use of (the lowest possible amount of) iso-osmolar or low-osmolar contrast agents (instead of high-osmolar contrast agents), hyperhydration and forced diuresis. Administration of *N*-acetylcysteine, theophylline, or fenoldopam, sodium bicarbonate infusion, and periprocedural haemofiltration/haemodialysis have been investigated as preventive measures in recent years. This review addresses the literature on these newer strategies. Since only one (nonrandomized) study has been performed in intensive care unit patients, at present it is difficult to draw firm conclusions about preventive measures for contrast-induced nephropathy in the critically ill. Further studies are needed to determine the true role of these preventive measures in this group of patients who are at risk for contrast-induced nephropathy. Based on the available evidence, we advise administration of *N*-acetylcysteine, preferentially orally, or theophylline intravenously, next to hydration with bicarbonate solutions.

Introduction

Contrast-induced nephropathy, defined as an increase in serum creatinine by more than 25% or 44 μmol/l from baseline within 3 days after administration of contrast agents in the absence of an alternative aetiology [1,2], is a major cause of hospital-acquired acute renal failure [3,4]. Indeed, the incidence of contrast-induced nephropathy is as high as 10–30% in high-risk patient groups [5–8]. Contrast-induced nephropathy increases morbidity, mortality and costs of medical care, and length of hospital stay, and not just for those patients who need renal replacement therapy because of this complication [3,5,7–9]. Risk factors for contrast-induced nephropathy include pre-existing renal failure (especially diabetic nephropathy and multiple myeloma), hypovolaemia, administration of (cumulative) high doses of (hyperosmolar) contrast media, and concomitant use of drugs that interfere with the regulation of renal perfusion [3,8, 10–13].

The Contrast Media Safety Committee of the European Society of Urogenital Radiology [14] has produced simple guidelines to prevent contrast-induced nephropathy. These guidelines emphasize the importance of patient selection (avoid the use of contrast media in high risk groups; i.e. use another imaging technique) and advises avoidance of the use (of large doses) of (hyperosmolar) contrast agents. Furthermore, the guidelines recommend ensuring that patients are well hydrated; cessation of diuretics (particularly loop-diuretics); and cessation of concurrent nephrotoxic drugs, such as non-steroidal anti-inflammatory drugs, aminoglycosides, amfotericine B, and antiviral drugs like acyclovir and foscarnet.

Critically ill patients are a group at high risk for the development of contrast-induced nephropathy because they frequently suffer from renal failure as a part of multiple organ failure, and they may have pre-existing diabetic nephropathy. Moreover, they are repeatedly administered contrast media intravenously, sometimes in large dosages. Unfortunately, the preventive measures described in the guidelines cited above

CI = confidence interval; NAC = *N*-acetylcysteine; RR = relative risk.

are frequently not applicable to this high-risk group; for instance, avoidance of use of contrast media is almost never an option in this group, and in most instances nephrotoxic drugs cannot be stopped.

Several additional measures to prevent contrast-induced nephropathy have been tested in randomized controlled trials in recent years. These measures include administration of the free radical scavenger *N*-acetylcysteine (NAC), the adenosine antagonist theophylline, sodium bicarbonate, the dopamine type 1 receptor agonist fenoldopam, and haemofiltration/haemodialysis. In this report, following a brief discussion of the pathogenesis of contrast-induced nephropathy, we review the published clinical trials examining these additional preventive measures. Thereafter, we focus on contrast-induced nephropathy in critically ill patients and attempt to provide clear recommendations regarding whether/when these new preventive measures may be applied in critically ill patients.

Search results

A search of the PubMed database (National Library of Medicine, USA; www.pubmed.org) from 1966 to July 2004 for unlimited citations using the MeSH terms 'nephropathy' AND 'media, contrast' yielded a total of 317 publications. A search using the terms 'prevention and control' (as a subheading in the MeSH database) OR 'prevention' found a total of 662,665 papers. Combining these searches and limiting the new search to 'human' and 'clinical trial' resulted in a list of 64 papers, 59 of which were in English language. After carefully reading the abstracts, only those papers reporting on clinical trials in humans were selected for further reading. The reference lists of these publications and several reviews on preventive measures [15–21] were used to find additional papers. This search resulted in identification of a total of 16 papers on NAC [13,22–36], one paper on sodium bicarbonate [37], nine papers on theophylline [38–46], five papers on fenoldopam [23,36,47–49] and four papers on haemofiltration/haemodialysis [50–53]. Only one published study dealt with critically ill patients [43].

Pathogenesis of contrast-induced nephropathy: rationale for additional preventive measures

Although the pathogenesis of contrast-induced nephropathy has not completely been elucidated, it is suggested that nephropathy following contrast administration is caused by a combination of renal ischaemia and direct tubular epithelial cell toxicity. (The reader is referred to several excellent reviews [21,54–56].)

A direct toxic effect of contrast on renal epithelial cells is suggested by histopathological changes, including epithelial cell vacuolization, interstitial inflammation and cellular necrosis, as well as by increased excretion of enzymes in the urine after contrast administration [57,58]. Because contrast-induced nephropathy is less frequent with iso-osmolar or low-osmolar contrast agents than with high-osmolar contrast agents, it is believed that osmolality *per se* may play a role in its pathogenesis. Reactive oxygen metabolites play a role in the pathogenesis of a variety of renal diseases [59]. Generation of reactive oxygen species may play a role in the pathogenesis of contrast-induced nephropathy too [60,61]. Based on this theory regarding the pathogenesis of contrast-induced nephropathy, measures that are aimed at scavenging free reactive oxygen species (such as with NAC – a free radical scavenger) or at limiting the production of free reactive oxygen species (using sodium bicarbonate infusion, which prevents an acidic environment in tubular urine) have been advocated as adjuncts to hyperhydration and use of iso-osmolar contrast media.

Investigations into the pathogenesis of contrast-induced nephropathy [62,63] have demonstrated that following intravenous administration of contrast, after a transient increase, renal blood flow decreases for a prolonged period under normal conditions. The renal medulla normally has an extremely low oxygen tension, which makes the renal medulla susceptible to ischaemic injury. The contrast-induced decrease in renal blood flow further diminishes medullary oxygen tension, resulting in epithelial cell necrosis. Based on preclinical studies, endogenous intrarenal adenosine has been implicated as a causative factor in contrast-induced nephropathy. Adenosine causes afferent arteriolar vasoconstriction and efferent arteriolar vasodilatation, thereby reducing the glomerular filtration rate. This theory on the pathogenesis of contrast-induced nephropathy resulted in the introduction of measures aimed at increasing renal blood flow, for example administration of theophylline (a selective renal adenosine antagonist) or of fenoldopam mesylate (a selective dopamine-1 receptor agonist that increases effective renal plasma flow without concomitant changes in glomerular filtration rate). Previous studies on vasodilators such as calcium antagonists, dopamine, atrial natriuretic peptide and endothelin antagonists either demonstrated no effect or found that these agents had an adverse effect on contrast-induced nephropathy. These vasodilators predominantly increase cortical blood flow, giving rise to an intrarenal steal phenomenon and subsequent increased medullary ischaemia.

Another potential approach to preventing contrast-induced nephropathy is the use of haemodialysis or haemofiltration. The half-lives of contrast media are increased several fold in patients with impaired renal function because most contrast media are excreted in the urine [64]. Haemodialysis removes contrast media effectively, and therefore it may prevent contrast-induced nephropathy [65–67]. Haemofiltration is also able to remove contrast from the circulation [68]. In addition, haemofiltration results in dilution of contrast agents via infusion of the replacement fluid, which decreases the concentration of the contrast agent in the blood, possibly reducing exposure of the kidneys to the nephrotoxic effects of contrast media.

Clinical trials on prevention of contrast-induced nephropathy

N-acetylcysteine

Sixteen randomized controlled trials investigated the efficacy of NAC in preventing contrast-induced nephropathy, both in patients with pre-existing renal insufficiency and in patients with normal renal function (Table 1) [13,22–36]. One of these trials compared NAC with fenoldopam [36]. In another study, two different doses of NAC were compared directly [33]. In the majority of studies, 600 mg NAC twice daily was administered on the day before and on the day of intravenous administration of contrast media. Cumulative dosages varied from 1500 mg to 4800 mg. In all but two studies [28,31], NAC was administered orally.

Of the 16 clinical trials, 14 compared NAC plus hydration with hydration alone [13,22–32,34,35]. Although five trials found a significant protective effect of NAC compared with standard treatment [22,25,27,30,32], eight found no beneficial effect of administration of NAC [13,23,24,26,28, 29,31,35]. Possible explanations for these contrasting results are differences in applied hydration regimens, in the patient populations studied and in the volumes of contrast media administered, and variations in the timing and dosing of NAC. In one study [33], double dose of oral NAC appeared to be more effective than the standard dose in preventing contrast-induced nephropathy. Side-effects of NAC are few. Oral administration of NAC caused gastrointestinal side effects in one study [13]; temporary flushing, itching and rash, as well as congestive heart failure, were observed with intravenous administration [28].

Three meta-analyses [16–18] on the protective effect of NAC against contrast-induced nephropathy were conducted. Birck and coworkers [16] and Isenbarger and colleagues [17] included only seven of the above-mentioned trials in their meta-analyses, and Alonso and coworkers [18] included eight of them. All three meta-analyses concluded that prophylactic use of NAC reduced the relative risk (RR) for contrast-induced nephropathy. In their meta-analysis, Birck and coworkers found a RR reduction of 56% (RR 0.43, 95% confidence interval [CI] 0.21–0.88). The other meta-analyses found RR reductions of 63% (RR 0.37, 95% CI 0.16–0.84) [17] and 59% (RR 0.41, 95% CI 0.22–0.79) [18]. Unfortunately, several studies showing negative results were published after the three meta-analyses.

It is questionable whether NAC truly influences the extent of contrast-induced nephropathy. It may be that NAC has a direct effect on creatinine concentration [69,70]. A recent study, conducted in volunteers with normal renal function, found an effect of NAC on plasma creatinine values and estimated glomerular filtration rate without any effect on cystatin C levels (another marker of glomerular filtration rate). Regrettably, nearly all investigators only used serum creatinine as a surrogate end-point in their trials. In future trials, glomerular filtration rate should be measured directly, or at least additional markers of renal function (e.g. serum cystatin C) must be assessed.

Nevertheless, because the side-effects of NAC are few, it is now widely recommended that NAC be administered before and on the day of contrast administration.

Theophylline

Eight randomized controlled trials and one nonrandomized study have been performed investigating the protective effect of theophylline on contrast-induced nephropathy (Table 2) [38–46]. In one of these studies, theophylline plus hydration was compared with two other preventive regimens (hydration alone or hydration plus dopamine) [41]. The dosage, timing and route of administration varied between the different studies. In six studies, theophylline was given intravenously and in three studies it was given orally. The timing of administration varied from 2 days to 30 min before and 3 days after contrast administration. Cumulative dosages varied from 165 mg to 4000 mg.

Seven trials [38–41,44–46] concluded that theophylline had a preventive effect, and two trials [42,43] did not find a beneficial effect in preventing contrast-induced nephropathy. It is difficult to draw firm conclusions from the available results, primarily because the studies were performed in small groups of patients. Furthermore, inclusion criteria (such as extent of pre-existing renal dysfunction and comorbidity), the amount and osmolality of the contrast media used, and concomitant medication varied widely.

Although optimal intravenous hydration is an important preventive measure (as described above), only a minority of the studies employed a strict intravenous hydration regimen [38,39,41]. In the other trials the hydration regimen was either not mentioned or the amount of fluid administered varied between patients. Another explanation for conflicting effects of theophylline in individual patients may be the unpredictable bioavailability after oral administration of theophylline.

Because the majority of studies show a favourable effect of theophylline and because side effects of this drug are few (especially at the proposed low dosage), theophylline may be an attractive measure to prevent contrast-induced nephropathy. In the case of acute need to use contrast agents (i.e. when adequate hydration cannot be achieved or if NAC was not given on the day before contrast administration), theophylline has the advantage that it can be given directly before contrast injection.

Studies on fenoldopam

Five trials have been performed evaluating fenoldopam infusion as a preventive measure for contrast-induced nephropathy [23,36,47–49], four of which were randomized

Table 1

Randomized controlled trials with *N*-acetylcysteine as a prophylactic measure to prevent contrast-induced nephouropathy

Reference	Year	Number of patients	Reason for contrast administration	Study design	Dose/timing/route of administration of NAC	Hydration regimen	Main outcome[a]
[22]	2000	83	CT	NAC + hydration versus hydration	600 mg po, twice daily, day before and on day of contrast	1 ml/kg per hour 0.45% saline 12 hours before–12 hours after contrast	RR 0.11 (95% CI 0.02–0.86)
[23]	2002	123	Various	NAC + hydration versus hydration	600 mg po, twice daily, day before and on day of contrast	1 ml/kg per hour 0.45% saline 12 hours before–12 hours after contrast	RR 1.18 (95% CI 0.45–3.12)
[24]	2002	183	Various	NAC + hydration versus hydration	600 mg po, twice daily, day before and on day of contrast	1 ml/kg per hour 0.45% saline 12 hours before–12 hours after contrast	RR 0.59 (95% CI 0.22–1.57)
[25]	2002	54	CAG	NAC + hydration versus hydration	600 mg po, twice daily, day before and on day of contrast	1 ml/kg per hour 0.45% saline 12 hours before–12 hours after contrast	RR 0.18 (95% CI 0.04–0.72)
[26]	2002	79	CAG	NAC + hydration versus hydration	1200 mg po, 1 hour before and 3 hours after contrast	1 ml/kg per hour 0.45% saline 12 hours before–12 hours after contrast	RR 1.2 (95% CI 0.55–2.63)
[27]	2002	121	CAG	NAC + hydration versus hydration	400 mg po, twice daily, day before and on day of contrast	1 ml/kg per hour 0.45% saline 12 hours before–12 hours after contrast	RR 0.14 (95% CI 0.03–0.57)
[28]	2003	80	CAG	NAC + hydration versus hydration	150 mg/kg iv, immediately before contrast	NAC group: 500 ml 0.9% saline before and 500 ml 0.9% saline 4 hours after contrast Control group: 1 ml/kg per hour 0.9% saline 12 hours before–12 hours after	RR 1.20 (95% CI 0.55–2.63)
[29]	2003	179	Elective CAG	NAC + hydration versus hydration	600 mg po, twice daily day before and on day of contrast	75 ml/hour 0.45% saline 12 hours before–12 hours after contrast	13% versus 12%; NS
[30]	2003	200	Elective CAG	NAC + hydration versus hydration	600 mg po, twice daily, day before and on day of contrast	1 ml/kg per hour 0.9% saline 12 hours before–6 hours after contrast	RR 0.32 (95% CI 0.11–0.96)
[31]	2003	108	CAG	NAC + hydration versus hydration	1200 mg iv, 12 hours before and immediately after contrast	20 ml/hour 5% dextrose 12 hours before–12 hours after contrast	3.8% versus 5.9%; NS
[32]	2003	43	Elective CAG	NAC + hydration versus hydration	600 mg po, twice daily, day before contrast; and 600 mg po three times daily, day of contrast	1–2 ml/kg per hour 0.45% saline for 4–12 hours before–75 ml/hour 0.45% saline for 12 hours after contrast	4.8% versus 31.8%; $P = 0.046$
[13]	2003	96	Elective CAG	NAC + hydration versus hydration	375 mg po, twice daily, day before and on day of contrast	1 ml/kg per hour 0.45% saline 12 hours before–12 hours after contrast	RR 1.28 (95% CI 0.30–5.41)
[33]	2004	223	Various	Low-dose versus high-dose NAC	600 mg po twice daily versus 1200 mg po twice daily, day before and on day of contrast	1 ml/kg per hour 0.45% saline 12 hours before–12 hours after contrast	11% versus 3.5%; $P = 0.038$
[34]	2004	91	Cardiovascular procedures	NAC + hydration versus hydration	400 mg po, three times daily, day before and on day of contrast	100 ml/hour 0.9% saline 12 hours before–12 hours after contrast	17.4% versus 13.3%; NS
[35]	2004	80	CAG	NAC + hydration versus hydration	600 mg po, three times daily, day before and on day of contrast	1 ml/kg per hour 0.45% saline 12 hours before–12 hours after contrast	10% versus 8%; NS

[a]Incidences of contrast-induced nephouropathy. CAG, coronary angiography; CI, confidence interval; CT, computed tomography, iv, intravenously; NAC, *N*-acetylcysteine; NS, not significant; po, by mouth; RR, relative risk.

Table 2

Randomized controlled trials with theophylline as a prophylactic measure to prevent contrast-induced nephropathy

Reference	Year	Number of patients	Reason for contrast administration	Study design	Dose/timing/route of administration of theophylline	Hydration regimen	Main outcome[a]
[38]	1994	39	Various reasons	RCT: theophylline versus placebo	5 mg/kg body weight iv, 45 min before contrast	1000 ml/hour saline 0.9% NaCl iv, 4 hours before–12 hours after contrast	GFR and CC↓ in placebo ($P < 0.01$)
[39]	1995	93	Various reasons	RCT: theophylline versus placebo; non-ionic, low-osmolality CM versus ionic, high-osmolality CM	4 × 2.88 mg/kg body weight, po, start 1 hour before contrast	>1.43 ml/kg per hr dextrose 5% iv or po 24 hours before– 48 hours after contrast	Non-ionic, low-osmolar: CC ↓ 18 ± 4% in placebo versus 0% in theophylline group ($P < 0.05$) Ionic, high-osmolar: CC ↓ 42 ± 5% in placebo versus 24 ± 3% in theophylline group ($P < 0.01$)
[40]	1998	58	Various reasons	RCT: theophylline versus placebo	165 mg iv, placebo, 30 min before contrast	Not specified	GFR ↓ in placebo ($P < 0.001$)
[41]	1999	60	Coronary angioplasty	RCT: theophylline versus dopamine versus placebo	4 mg/kg iv, 1 hour, start 2 hours before contrast followed by 0.4 mg/kg per hour for 12 hours	1 ml/kg per hour 0.45% saline iv 12 hours before–12 hours after contrast	35% versus 50% versus 30%; NS
[42]	1999	80	Various reasons	RCT: theophylline versus placebo	810 mg daily po, 2 days before–3 days after contrast	2000–2500 ml 0.45% saline iv or po 24 hours before–24 hours after	6% (2/35) versus 3% (1/29); NS
[44]	2002	100	Various reasons	RCT: theophylline versus placebo	200 mg iv, 30 min before contrast	Variable (>2000 ml was advised)	4% versus 16%; $P = 0.046$
[45]	2002	70	Coronary angiography	RCT: theophylline versus placebo	200 mg po, twice daily, 24 hours before–48 hours after contrast	Not specified	3% versus 31%; $P = 0.004$
[46]	2003	100	Coronary angiography	RCT: theophylline versus placebo	200 mg iv, 30 min before contrast	Variable (>2000 ml was advised)	4% versus 20%; $P = 0.0138$

[a]Incidences of contrast-induced nephropathy, unless stated otherwise. BW, body weight; CC, creatinine clearance; GFR, glomerular filtration rate; iv, intravenously; NS, not significant; po, by mouth; RCT, randomized controlled trial.

controlled trials (Table 3). In two studies fenoldopam was compared with standard therapy [48,49]; in the other studies fenoldopam was compared with NAC [23,36]. Fenoldopam administration varied from 15 min to 4 hours before and from 4 to 12 hours after intravenous administration of contrast media. In all studies, infusion of 0.1 μg/kg per min fenoldopam was prescribed.

None of the randomized controlled studies found any beneficial effect regarding prevention of contrast-induced nephropathy. One study, however, suggested that fenoldopam is as effective as NAC in preventing contrast-induced nephropathy [23].

One important drawback of fenoldopam administration is a potential fall in systemic blood pressure caused by fenoldopam-induced vasodilatation. Based on the negative effects of fenoldopam and the drawback of potential hypotension, use of fenoldopam as a measure to prevent contrast-induced nephropathy cannot be recommended.

Sodium bicarbonate

Only one study [37] evaluated the protective effect of sodium bicarbonate. In that study 154 mEq/l sodium bicarbonate was administered at a dosage of 3 ml/kg per hour for 1 hour, starting 1 hour before the intravenous administration of contrast media followed by 1 ml/kg per hour for 6 hours. That study found a strong beneficial effect of infusion of sodium bicarbonate; whereas contrast-induced nephropathy developed in 13.6% of patients receiving sodium chloride, only 1.7% of patients receiving sodium bicarbonate developed nephropathy.

Unfortunately, the positive results of that study have not (yet) been confirmed by other trials. However, because side effects of this regimen are few, in the case of acute need to administer contrast (i.e. when there is not sufficient time to achieve adequate hydration and NAC administration has not yet started) hydration with sodium bicarbonate is an option.

Haemodialysis/haemofiltration

Four studies evaluated the effect of haemodialysis or haemofiltration on contrast-induced nephropathy [50–53]. Three studies were performed in a randomized manner (Table 3) [50,52,53]. In one study, patients were randomly assigned to receive haemodialysis or standard therapy [50]; unfortunately, harmful effects of haemodialysis were found in that study. Two studies compared standard therapy with haemofiltration; while one study did not show any effect of haemofiltration [53], the study by Marenzi and coworkers [52] found haemofiltration to be a very effective preventive measure. Contrast-induced nephropathy developed in only 5% of patients treated with haemofiltration versus 50% of control patients [52]. Regrettably, however, patients were admitted to different wards (patients assigned to receive haemofiltration were admitted to an intensive care unit, whereas control patients were admitted to a step-down facility). This difference might have had an impact on outcome. In addition, the lower plasma creatinine concentration that was found in the haemofiltration group does not imply less renal dysfunction because haemofiltration itself lowers the plasma creatinine concentration. Based on these findings, at present, haemodialysis and/or haemofiltration cannot be recommended as a measure to prevent contrast-induced nephropathy.

Prevention of contrast-induced nephropathy in critically ill patients

It is uncertain whether contrast-induced nephropathy is an important entity in intensive care medicine. Indeed, no data are available on the incidence of contrast-induced nephropathy in the critically ill or on whether it has a profound impact on morbidity and mortality in these patients. However, the critically ill form an important group at risk for development of contrast-induced nephropathy. Renal failure is a common complication of critical illness; the incidence of acute renal failure among intensive care admissions reaches 15–20%, with 4–6% requiring some form of acute renal replacement therapy [71]. Furthermore, the critically ill are often subject to a number of risk factors for the development of contrast-induced nephropathy (e.g. pre-existing renal insufficiency, especially diabetic nephropathy), factors that influence renal perfusion (e.g. hypovolaemia) and administration of concomitant nephrotoxic medication. It has been shown that even modest degrees of acute renal failure without need for haemodialysis increase the risk for death by fivefold [7].

To the best of our knowledge, there are at present no (randomized controlled) studies on use of NAC, bicarbonate hydration and haemofiltration/haemodialysis as measures to prevent contrast nephropathy in critically ill patients.

Only one published report on measures to prevent contrast-induced nephropathy included critically ill patients [43]. Huber and coworkers investigated whether theophylline reduced the incidence of contrast-induced nephropathy in a prospective study in which results were compared with a series of patients at similar risk for contrast-induced nephropathy in a medical intensive care unit. Seventy-eight patients with at least one risk factor for contrast-induced nephropathy underwent 150 consecutive radiocontrast administrations. Patients received theophylline intravenously 30 min before infusion of contrast medium. Concentrations of serum creatinine and blood urea nitrogen, urine volume, fluid balance, and the incidence of contrast-induced nephropathy were monitored for 48 hours. Despite the large number of risk factors (6.8 per patient), including a high dose of contrast agent, impaired renal function, diabetes mellitus, use of aminoglycosides, vancomycin and catecholamines, serum creatinine concentrations were not increased 24 hours after contrast administration. Only three patients (2%) developed contrast-induced nephropathy, which was significantly lower than the 14% (78/565) in the retrospective data obtained in patients at comparable risk for contrast-induced nephropathy.

Table 3

Randomized controlled trials with fenoldopam, sodium bicarbonate, and haemodialysis/haemofiltration as prophylactic measures to prevent contrast-induced nephropathy

Reference	Year	Number of patients	Reason for contrast administration	Study design	Dose/timing/route of drug administration	Hydration regimen	Main outcome[a]
Clinical trials with fenoldopam							
[23]	2002	123	Cardiovascular procedures	RCT: hydration plus NAC po versus hydration alone versus hydration plus fenoldopam	Fenoldopam: 0.1 μg/kg per min, 4 hours before– 4 hours after contrast NAC 2 × 600 mg	1 ml/kg per hour 0.45% NaCl iv 12 hours before–12 hours after contrast	18% in the NAC group versus 15% in the NaCl group (P = NS; RR 1.18, 95% CI 0.45–3.12)
[48]	2002	45	Cardiovascular procedures	RCT: hydration versus hydration plus fenoldopam	Fenoldopam at 0.1 μg/kg per min, >1 hour before contrast	100 ml/hour 0.45% NaCl iv, 3 hours before–4 hours after contrast	41% in the saline group versus 21% in the fenoldopam group (P = 0.148); diabetes patients 64% versus 33% (P = 0.14)
[49]	2003	315	Angiography	RCT: fenoldopam	Fenoldopam 0.05 μg/kg per min titrated to 0.10 μg/kg per min, 30 min before–12 hours after contrast	1.5 ml/kg per hour 0.45% NaCl iv 2–12 hours before–12 hours after contrast	34% in fenoldopam group versus 30% in the placebo group (P = 0.61; RR 1.11, 95% CI 0.79–1.57)
Clinical trials with sodium bicarbonate							
[37]	2004	119	Various reasons	RCT: saline versus sodium bicarbonate before and after contrast administration	3 ml/kg per hour 154 mEq/l sodium bicarbonate 1 hour pre-procedure + 1 ml/kg per hour 154 mEq/l sodium bicarbonate 6 hours post-procedure	The control group received a similar infusion, but with 154 mEq/l NaCl	14% in saline patients versus 2% in patients receiving sodium bicarbonate (P = 0.02; 95% CI 0.03–0.21)
Clinical trials with haemodialysis/haemofiltration							
[50]	2001	113	Various reasons	RCT: haemodialysis versus nonhaemodialysis treatment after injection of contrast	Directly after contrast exposure	1 ml/kg per hour 0.45% NaCl iv 12 hours before–12 hours after contrast	No significant differences
[52]	2003	114	Coronary angioplasty	RCT: haemofiltration (in an intensive care unit) versus hydration (in a step-down unit)	4–8 hours before to 18–24 hours after procedure	1 ml/kg per hour 0.45% NaCl iv 12 hours before–12 hours after contrast	5% versus 50% (P < 0.001)
[53]	2003	17	Angiography	RCT: 4-hour online dialysis during contrast injection versus standard therapy	Haemodialysis simultaneously with contrast administration	2000 ml 0.9% NaCl 6 hours before–6 hours after contrast	No significant differences

[a]Incidences of contrast-induced nephropathy. CI, confidence interval; iv, intravenously; NAC, *N*-acetylcysteine; po, by mouth; RCT, randomized controlled trial; RR, relative risk.

Side effects such as tachyarrhythmias were not described. Unfortunately, there was no control group.

Nevertheless, because NAC has few side effects, based on studies conducted in non-critically-ill patients this preventive measure may be applied in critically ill patients. Where there is an urgent need for imaging studies that require administration of contrast media, theophylline and bicarbonate hydration are options. However, future studies are needed to determine whether such preventive measures really work. In future trials, the glomerular filtration rate should preferably be measured directly, or at least additional markers of renal function (such as serum cystatin C) should be assessed to determine the effect of the studied strategy. In addition, other 'hard' end-points, such as hospital morbidity and mortality and dialysis dependency, should be considered in the study design [69].

Conclusion

Given the scarce data on preventive measures to reduce contrast-induced nephropathy in intensive care unit patients, no clear recommendations can yet be given. New studies are needed to determine whether such preventive measures are effective in critically ill patients. In addition to plasma creatinine concentrations and glomerular filtration rate, additional markers of renal function (such as serum cystatin C) must be assessed, and other end-points such as hospital morbidity and mortality and dialysis dependency should be considered in the study design.

Simple preventive measures such as avoidance of contrast agents (if possible), adequate hydration and use of low-osmolar contrast agents at the lowest possible volume should be applied. Concomitant use of nephrotoxic medication should be avoided. Despite the absence of studies on preventive measures for contrast-induced nephropathy in critically ill patients, we recommend use of preventive measures that have a demonstrated potential effect in patents who are not critically ill, specifically oral NAC on the day before and on the day of contrast administration, as well as hydration with bicarbonate. If administration of NAC is not possible, then theophylline administration is an alternative preventive measure.

Competing interests

The author(s) declare that they have no competing interests.

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