Contrast-induced nephropathy (CIN) is usually defined by a fixed (0.5 mg/dL or 44 µmol/L) or a proportionate (25%) rise in serum creatinine (SCr) levels after contrast exposure. Prospective studies of patients admitted with acute renal failure (ARF) demonstrated that contrast medium was responsible in 14.5% of cases. The mechanism through which nephropathy is induced by contrast is not completely known. Some studies showed evidence of ischaemic acute tubular necrosis. Major theories are renal vasoconstriction resulting in medullary hypoxaemia, possibly mediated by alterations in nitric oxide, endothelin and/or adenosine, and direct cytotoxic effects of the contrast agents. Free radical-induced renal ischaemia may also be involved in the process. Once identified, treatment of CIN is mainly supportive, consisting mainly of careful fluid and electrolyte management.

Risk Assessment

Risk factors for CIN include hypotension (systolic blood pressure < 80 mmHg for at least 1 hour requiring inotropic support or intra-aortic balloon pump (IABP) within 24 hours periprocedural), use of IABP, chronic heart failure (NYHA class III/IV and/or history of pulmonary oedema), age > 75 years, anaemia (haematocrit < 39% for men or < 36% for women, diabetes mellitus, contrast volume, and kidney disease. Other risk factors for CIN include nephrotoxic drugs, liver cirrhosis, hypoalbuminaemia, and multiple myeloma.

General Measures

Potentially nephrotoxic drugs, including but not limited to: ACE inhibitors, angiotensin receptor antagonists, diuretics, NSAIDs/COX-2 inhibitors and metformin should be discontinued 1 day before and 1 day after contrast. Some advocate that metformin should be withheld for 48 hours before the administration of contrast medium and until it is certain that CIN has not occurred, due to the risk of developing lactic acidosis under possible ARF. Patients should be pre-hydrated with normal saline 1ml/kg/hour (0.5ml/kg/hour for patients with left ventricular ejection fraction < 40%) for at least 12 hours before imaging, till up to 12-25 hours post procedure.

The volume of contrast should be minimised to reduce the chance of CIN. Non-ionic low-osmolar contrast (e.g. iohexol) may cause fewer ARF than ionic high-osmolar contrast (e.g. diatrizoate), but is more expensive. Pharmacoeconomic data have shown that a high risk for development of CIN may be considered as one of the indications for the use of low-osmolar or iso-osmolar contrast as it may be more cost effective, whereas in patients with normal renal function and no risk factors present, no advantage over the traditional ionic high-osmolar contrast has been shown.

N-acetylcysteine

N-acetylcysteine (NAC) is a scavenger of oxygen free radicals and a glutathione precursor capable of replenishing depleted intracellular glutathione, and in theory augments antioxidant defences. Intravenous and oral NAC prevented CIN in patients with normal baseline renal function undergoing primary angioplasty secondary to acute myocardial infarction with a dose-dependent effect in patients treated with primary angioplasty and improved hospital outcome in a study. Another randomised, 2-centre, double-blind study in patients with chronic kidney diseases, volume supplementation by sodium bicarbonate plus NAC was superior to the combination of normal saline with NAC alone or with the addition of ascorbic acid in CIN in patients at medium to high risk. Nevertheless, a meta-analysis of 13 randomised, placebo-controlled clinical trials did not find convincing evidence that NAC protects against CIN in patients with baseline renal insufficiency. In summary, as a strategy to prevent CIN, NAC is well tolerated with very limited side effects. It is inexpensive and easy to administer in oral form, and has been advocated to reduce the incidence of CIN. However not all studies have uniformly shown a benefit, and there are variations in NAC dosing. Its use may be considered in high risk patients but is not considered mandatory.

Ascorbic Acid

A randomised, placebo-controlled trial of ascorbic acid in 231 patients with SCr ≥1.2mg/dL who underwent coronary angiography and/or intervention showed that ascorbic acid reduced the risk of CIN compared with placebo (OR, 0.38; 95% CI, 0.17 to 0.85; P=0.02). However, another trial failed to detect a significant risk reduction in CIN when ascorbic acid was used as an adjunct to hydration. The benefit of ascorbic acid in the prevention of CIN is inconclusive.
Sodium Bicarbonate

It has been proposed that free radical formation is promoted by an acidic pH typical of tubular urine but is inhibited by the higher pH of normal extracellular fluid. Therefore alkalinising the renal tubular fluid with bicarbonate may reduce CIN.

In a study, 119 patients with stable SCr levels of at least 1.1 mg/dL (97.2 μmol/L) were randomised to receive a 154-mEq/L infusion of either sodium chloride (n=59) or sodium bicarbonate (n=60) before and after iopamidol administration found that sodium bicarbonate was more effective than sodium chloride infusion as prophylaxis of CIN. A systematic review and meta-analysis (12 trials, 1,854 participants) showed that sodium bicarbonate significantly decreased the risk of CIN but without a significant difference in need for renal replacement therapy, in-hospital mortality, or congestive heart failure compared with normal saline with or without NAC. Risk reduction for CIN was seen when sodium bicarbonate was compared with normal saline alone, but not when sodium bicarbonate/NAC combination was compared with NAC/normal saline combination.

Effectiveness of sodium bicarbonate to prevent CIN in high-risk patients remained uncertain in another systematic review (23 published and unpublished trials, 3563 patients, 396 CIN events). The pooled relative risk was 0.62 (95% CI, 0.45 to 0.86), with evidence of significant heterogeneity across studies. No clear effects of treatment on the risk for dialysis, heart failure, and total mortality were identified. Earlier reports probably overestimated the magnitude of any benefit, whereas larger, more recent trials have had neutral results. Overall, these results suggest that sodium bicarbonate infusion may be superior to normal saline. However all of these studies are limited by small sample sizes. True benefit remains to be proven in larger, prospective multicentre trials.

Theophylline

Theophylline, a xanthine derivative, might reduce the risks of contrast-induced nephropathy. Theophylline 810 mg/day, starting 2 days before contrast and continuing until 3 days after contrast appeared to have prevented renal tubular damage for patients (n=80) undergoing contrast administration with preexisting renal insufficiency in a prospective, double-blind placebo-controlled study. A marker of tubular damage increased in both groups but significantly more in the placebo group. A systematic review and meta-analysis of 6 randomised trials of theophylline for the prevention of contrast-induced nephropathy showed that theophylline (oral or IV) was associated with a tendency for risk reduction but was statistically non-significant. (RR 0.49, 95% CI 0.23-1.06)

Conclusion

Conclusive, evidence-based recommendations for the prevention of CIN are difficult to be established from available evidence. This is due to: variations in the definition of CIN; different criteria for identification of high-risk patients; inconsistency in the administration of cotherapies, e.g., hydration; and small sample sizes with suboptimal study designs.

Pre- and post-hydration is the single most important protective measure for the prevention of CIN. Nephrotoxic drugs should be discontinued prior to contrast. The use of low-osmolar contrast media may be associated with lower risks of CIN, but its high cost militates against routine use in all patients, and many recommend that it should be continued to be reserved for those patients with multiple risk factors for CIN. Other strategies that are worth considering due to at least some evidence backing the efficacy are NAC and sodium bicarbonate. They are inexpensive, well tolerated and more worthwhile in “high-risk” patients but should not be considered mandatory.

References