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REVIEW

The place of hydration using intravenous fluid in patients at risk of developing contrast-associated nephropathy

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Abstract

There has been a significant rise in the incidence of contrast-associated nephropathy caused by administration of contrast media during cardiac interventions. This is one of the major complications of percutaneous coronary interventions, which may proceed to acute renal failure. Risk factors, including pre-existing renal dysfunction, older age and use of high osmolar contrast media, predispose patients to the development of contrast-associated nephropathy. Different risk-reduction strategies have been used to prevent contrast-associated nephropathy, including use of low osmolar contrast media, N-acetylcysteine, alkalisation of tubular fluid with intravenous sodium bicarbonate, and oral and intravenous hydration with isotonic solution. Hydration using intravenous saline is one of the main treatments used to prevent the development of nephropathy in patients receiving contrast media during cardiac interventions. Prehydration, before administering contrast media, seems to be crucial. The results of studies of the relative efficacy of sodium bicarbonate and/or N-acetylcysteine in reducing the development of contrast-associated nephropathy are not consistent and any beneficial effects may depend on the pre-existing state of the kidney. This review discusses hydration of patients who are at risk of developing contrast-associated nephropathy using intravenous fluid.

Key words: Intravenous; N-acetylcysteine; Nephropathy; Oral; Saline; Sodium bicarbonate

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Introduction

Owing to the increased use of radiographic contrast media in diagnostic and interventional procedures, there has been a significant rise in the incidence of contrast-associated nephropathy (Soma et al, 2002; Perazella, 2009), making this one of the major complications of percutaneous coronary interventions, and one which may proceed to acute renal failure (Mueller et al, 2005). Contrast-associated nephropathy is defined as an absolute increase in the serum creatinine level of 44.2 µmol/litre or a relative increase of 25% from baseline within 48–72 hours after administration of intravenous iodinated contrast media (Weisbord et al, 2008). Pre-existing renal dysfunction, older age and use of high osmolar contrast media may predispose patients to the development of contrast-associated nephropathy (Rashid et al, 2009; Hafiz et al, 2012).

The mechanisms involved in the development of radiocontrast-induced nephropathy are not clearly understood. However, it is proposed that alterations in renal haemodynamics, development of renal tubular ischaemia and/or direct toxicity to the tubular cells may contribute to the development of nephropathy (Massicotte, 2008). Risk-reduction strategies include the use of low osmolar contrast media or N-acetylcysteine, alkalisation of tubular fluid with intravenous sodium bicarbonate, and oral and/or intravenous hydration with isotonic solution (Massicotte, 2008; Weisbord et al, 2009; Kagan and Sheikh-Hamad, 2010). Among these, intravenous volume expansion with isotonic solution is one of the most widely used strategies to reduce development of nephropathy (Stacul et al, 2006; Weisbord and Palevsky, 2008). This article discusses the hydration of patients who are at risk of the development of contrast-associated nephropathy using intravenous fluid.

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Use of intravenous isotonic saline to prevent contrast-associated nephropathy

Evidence showing a reduction in nephropathy using intravenous fluid

Several clinical studies have shown beneficial effects of hydration in preventing the development of contrast-associated nephropathy in patients undergoing cardiac interventions. An initial study explored the effect of hydration using intravenous fluid (5% dextrose and 0.5% normal saline) over a period of 12 hours before catheterisation and thereafter giving water orally in ciclosporin-treated cardiac transplant patients undergoing cardiac catheterisation using ionic and non-ionic contrast media. There was a significant decline in the blood urea nitrogen and serum creatinine levels following hydration in these patients, and there was no worsening of kidney function, suggesting that intravenous fluid was effective in preventing the deterioration of kidney function (Denys et al, 1991). Jurado-Román et al (2015) found that the incidence of nephropathy was 11% in patients receiving hydration with isotonic saline (1 ml/kg/h) compared to 21% in patients not receiving hydration.

Intravenous vs oral hydration

Studies have shown comparable efficacy of intravenous and oral hydration in preventing contrast-associated nephropathy. A prospective, double-blind, placebo-controlled study demonstrated efficacy of hydration therapy (oral or intravenous) started 24 hours before and lasting 24 hours after administration of contrast media in maintaining glomerular filtration rate in patients (n=80) with pre-existing chronic renal insufficiency and receiving contrast media (Erley et al, 1999). A study reported the very low incidence of contrast-associated nephropathy (6/425 patients) in patients undergoing percutaneous coronary intervention who were given comprehensive intravenous and oral hydration therapy (Mueller et al, 2005). A large cohort study explored the role of intravenous and oral volume supplementation in 958 patients with diabetes or chronic renal failure (stage 3) receiving contrast media during percutaneous coronary intervention. The incidence of contrast-associated nephropathy was very low in patients with diabetes (2.7%) and those with stage 3 kidney disease (6.5%) (Mueller-Lenke et al, 2008). Another study on patients with diabetes (n=102) undergoing percutaneous coronary intervention revealed that both oral and intravenous hydration prevented contrast-associated nephropathy (Wróbel et al, 2010). Kong et al (2012) also found equivalent efficacy of oral hydration (5.0%; 2/40) and intravenous saline hydration (7.5%; 3/40) in preventing contrast-associated nephropathy. Moreover, renal function recovered in seven patients who experienced contrast-associated nephropathy within 7 days following hydration therapy.

Need for individualised fluid volume for optimal results

It is suggested that the fluid volume required for hydration should be individualised for better results. In a randomised, parallel, single-blind phase III trial, Brar et al (2014) suggested that the volume of fluid administered should be individualised and one factor that may be used to adjust the fluid volume is the determination of left ventricular end-diastolic pressure. Indeed, the authors advocated the use of haemodynamic-guided fluid administration for the prevention of contrast-associated nephropathy. Patients were allowed to receive intravenous fluid according to left ventricular end-diastolic pressure (n=196) or standard fluid administration (n=200), and the frequency of contrast-associated nephropathy was less in the left ventricular end-diastolic pressure-guided group (6.7%) than in the control group (16.3%). Maioli et al (2018) also emphasised the need to calculate the optimal fluid volume instead of using a standard fluid volume for hydration. The authors reported that bioimpedance-guided hydration yielded better results in terms of decreasing the incidence of nephropathy than giving a fixed fluid volume.

Preprocedural hydration is critical in reducing kidney injury

To explore the timing of hydration, a randomised trial was conducted in 39 patients with normal renal function who were receiving low-osmolality contrast media. Patients were given intravenous fluids either during (n=20) or 12 hours before (n=19) the administration of contrast media. There was a significant preservation of glomerular filtration rate in patients receiving intravenous prehydration and the incidence of contrast-associated nephropathy

was lower in prehydrated patients (5.3%) as compared to another group in which fluids were given during contrast media administration (15%), suggesting that prehydration is effective in preserving renal function (Bader et al, 2004).

Another study reported that both oral (started 2 days before contrast media administration) and intravenous prehydration (started 6 hours before contrast media administration) produced beneficial effects and about 8.7% (27/312 patients) of patients with chronic renal failure developed nephropathy (Dussol et al, 2006). Maioli et al (2011) also compared the relative efficacy of early hydration (pre- and post-procedure) and late hydration (post-procedure) in 450 patients undergoing percutaneous coronary intervention. The incidence of nephropathy was significantly lower in the early hydration group (12%) compared to the late hydration group (22.7%) and a control group with no hydration (27.3%), signifying the importance of pre-procedure hydration in reducing the incidence of nephropathy. The authors also reported that lower hydration volume resulted in a higher incidence of nephropathy and the optimal cut-off point of hydration volume was described as ≤960 ml. Torigoe et al (2013) reported that prehydration 20 hours before contrast media is not superior to prehydration given 5 hours beforehand in preventing an increase in serum creatinine and cystatin C levels. Thus, hydration may be given just 5 hours before contrast media administration without a significant decline in efficacy.

Mild or no beneficial effects of hydration with intravenous saline

In contrast, studies have also shown either a mild or no significant effect of intravenous therapy in preventing contrast-associated nephropathy. In the PRECORD trial, 201 patients without severe chronic renal insufficiency underwent percutaneous coronary intervention using ionic low osmolar radiographic contrast agent. In addition to standard oral hydration using 2000 ml of water within 24 hours after percutaneous coronary intervention, patients received intravenous hydration using normal saline (1000 ml) or no additional hydration. There was a slight improvement in creatinine clearance (1.07 ml/min) in the group receiving saline compared to the control group (0.91 ml/min) (Angoulvant et al, 2009). A randomised trial found no change in serum creatinine levels at 24 or 48 hours following overnight hydration (n=26) or bolus hydration (n=37) in patients (total n=63) with moderate renal insufficiency and receiving contrast media. Indeed, four out of the 37 patients receiving bolus hydration developed contrast-associated nephropathy, suggesting the need for precise evaluation of hydration therapy in patients undergoing angiography who are at risk for contrast nephropathy (Krasuski et al, 2003).

Intravenous sodium chloride vs sodium bicarbonate in preventing contrast nephropathy

Scientists have also attempted to replace hydration using 0.9% sodium chloride (NaCl) solution with sodium bicarbonate ($NaHCO_3$) infusion to compare the relative efficacy of these interventions in preventing contrast-associated nephropathy. A prospective, randomised, single-centre, double-blind trial on 145 patients with elevated baseline serum creatinine levels, receiving contrast medium, was conducted to explore this. Five patients developed contrast-associated nephropathy (3.4%) with no significant difference between the $NaHCO_3$ (4.2%) and NaCl (2.7%) groups, suggesting that hydration with either agent is useful in reducing the toxicity of contrast media (Adolph et al, 2008). In another randomised, double-blind controlled trial, 265 patients undergoing percutaneous coronary intervention were prehydrated with either a combination of $NaHCO_3$ and saline (n=135) or isotonic saline alone (n=130) 1 hour before contrast injection, followed by infusion for 6 hours after the procedure. There was no significant difference between the $NaHCO_3$ and saline groups in terms of alteration in serum creatinine level, glomerular filtration rate and urine pH. Nine patients (7.4%) in the group receiving $NaHCO_3$ developed nephropathy, which was not statistically different from the saline group in which seven patients (5.9%) developed nephropathy (Vasheghani-Farahani et al, 2009).

Vasheghani-Farahani et al (2010) conducted a single-centre, double-blind, randomised, controlled trial on 72 patients with high serum creatinine levels who were receiving contrast media for elective percutaneous coronary intervention. The patients were given either an

infusion of $NaHCO_3$ plus saline (n=36) or saline alone (n=36). There was no significant difference between these two groups in terms of the development of contrast-associated nephropathy: the incidence of nephropathy was 6.1% in patients receiving $NaHCO_3$ plus saline and 6.3% in patients receiving saline alone.

However, a study on patients (n=144) with mild renal insufficiency undergoing percutaneous coronary intervention showed that a single-bolus intravenous injection of $NaHCO_3$ (20 mEq) in addition to hydration with NaCl effectively prevented contrast-associated nephropathy. The incidence of development of nephropathy was significantly lower in those who received an injection of $NaHCO_3$ (1.4%) than in patients who received saline alone (12.5%) (Tamura et al, 2009). In an open-label multicentre randomised trial involving 570 patients with chronic kidney disease, Kooiman et al (2014) demonstrated that the protective effects of hydration were comparable in patients receiving 250 ml of 1.4% $NaHCO_3$ hydration or 1000 ml of 0.9% saline pre- and post-contrast administration. They suggested that large volume intravenous saline may be replaced by smaller volume $NaHCO_3$ without any loss of efficacy.

Conflicting results of using both N-acetylcysteine and hydration therapy to prevent nephropathy

Non-beneficial effects of N-acetylcysteine

A study explored the role of N-acetylcysteine in preventing renal dysfunction in 20 men undergoing endovascular abdominal aortic aneurysm repair. The patients were administered either intravenous fluid or intravenous fluid and N-acetylcysteine (600 mg twice daily orally, four doses). The addition of N-acetylcysteine to intravenous fluid did not prevent the rise in urinary retinol-binding protein and albumin/creatinine ratio, suggesting no positive impact of N-acetylcysteine in improving renal function (Moore et al, 2006). A prospective, double-blind, randomised, placebo, controlled trial on 40 patients undergoing percutaneous coronary intervention revealed no significant difference in groups receiving intravenous fluid (n=20) or intravenous fluid plus N-acetylcysteine (n=20), suggesting no significant effect of N-acetylcysteine (Seyon et al, 2007). Similarly, a study on patients with moderate-to-severe chronic kidney disease (n=414) receiving contrast media reported no significant benefit of combining isotonic $NaHCO_3$ and N-acetylcysteine in comparison to the hydration-only group (Staniloae et al, 2009).

Beneficial effects of N-acetylcysteine

There has been a randomised clinical trial on 111 patients undergoing emergency percutaneous coronary intervention (Recio-Mayoral et al, 2007). In one group (56 patients), an infusion of $NaHCO_3$ and N-acetylcysteine was given along with intravenous hydration before contrast injection and continued for 12 hours after percutaneous coronary intervention, while those in the other group (55 patients) were only given intravenous fluid. The results showed a positive impact of $NaHCO_3$ and N-acetylcysteine in preventing contrast-associated nephropathy. There was a rise in serum creatinine concentration (>0.5 mg/dl from baseline) in one patient in the first group (1.8%), while there was a rise in serum creatinine level in 12 patients in the second group (21.8%). Similarly, acute anuric renal failure was observed in one patient (1.8%) in the first group, while this was seen in seven patients in the second group (12.7%) (Recio-Mayoral et al, 2007). A clinical trial on 220 patients revealed the higher efficacy of N-acetylcysteine and hydration with normal saline in comparison to the hydration alone group (Koc et al, 2012). Another study showed that a combination of N-acetylcysteine and hydration with normal saline is more efficacious than hydration alone. Six patients (12%) in the hydration alone group and no patients in the N-acetylcysteine combination group developed nephropathy (Awal et al, 2011). A prospective, randomised clinical trial on 320 patients demonstrated the efficacy of N-acetylcysteine with or without $NaHCO_3$ in preventing contrast-associated nephropathy. There was no significant difference in the incidence of nephropathy in normal saline and N-acetylcysteine (11.8%) compared to $NaHCO_3$ and N-acetylcysteine (8.8%) (Hafiz et al, 2012).

Alessandri et al (2013) analysed the comparative efficacy of pre- and post-contrast hydration with 0.9% saline or N-acetylcysteine plus $NaHCO_3$. The efficacy of these

Key points

- Contrast-induced nephropathy is a major complication of percutaneous coronary interventions; hydration using intravenous saline or sodium bicarbonate prevents the development of nephropathy.
- There is a clear benefit of prehydration, that is hydration before contrast media is administered to patients.
- Any additional benefit of administering N-acetylcysteine depends on the pre-existing state of the kidney.

interventions was dependent on the patients' renal function. In patients with normal serum creatinine levels and creatinine clearance, both interventions produced a comparable decrease in the incidence of nephropathy. However, in patients with normal serum creatinine levels and reduced creatinine clearance, N-acetylcysteine was more effective than hydration alone (0% vs 18%). In patients with moderately reduced serum creatinine levels and creatinine clearance, hydration with saline solution was more effective than N-acetylcysteine plus $NaHCO_3$ (8.6% vs 17.6%). In contrast, in patients with severe renal dysfunction, the combination of N-acetylcysteine plus $NaHCO_3$ was very effective in preventing nephropathy in comparison to hydration alone (0% vs 50%). It suggests that the efficacy or non-efficacy of these interventions is dependent on the state of renal function.

Conclusions

Hydration using intravenous saline is one of the cornerstones of preventing development of nephropathy in patients receiving contrast media. Prehydration before administering contrast media seems to be crucial. Studies of the relative efficacy of sodium bicarbonate and/or N-acetylcysteine in preventing the development of contrast-associated nephropathy are not consistent and any additional benefit seen may depend on the pre-existing state of the kidney.

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Conflicts of interest

The authors declare no conflicts of interest.

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