The Effect of Administration of Ascorbic Acid in Preventing Contrast-Mediated Nephropathy in Patients with Renal Dysfunction Undergoing PCI

Thesis

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INTRODUCTION

Contrast-induced nephropathy is a leading cause of morbidity and mortality in high-risk patients undergoing any procedure involving the use of radiographic contrast media ***(Cavusoglu et al., 2004)***.

Approximately twenty five percent of all those selected for such procedures are at high-risk of developing contrast-induced nephropathy ***(Cavusoglu et al., 2004).***

Subjects who develop this complication have higher rates of mortality, longer hospital stays and worse long-term outcomes ***(Cavusoglu et al., 2004).***

The occurrence of contrast-induced nephropathy is related to the number of the patients' co-existing clinical risk factors. Among the many risk factors, pre-existing renal impairment, advancing age, the presence of diabetes mellitus as well as the volume and type of contrast agent administered are the most important ***(Cavusoglu et al., 2004).***

The precise pathophysiologic mechanisms responsible for the development of contrast-induced nephropathy are complex and incompletely understood. At present, the only available tool for reducing the risk of developing contrast-induced nephropathy is prevention.

This can be achieved by means of adequate peri-procedural hydration, using N-acetylcyteine as well as the selection of low osmolar or iso-osmolar contrast agents in the least amount possible. Other agents are still being tested for this purpose as well ***(Cavusoglu et al., 2004).***

The action of other antioxidant agents has not been investigated.

The conventional hydration protocols involve the use of ascorbic acid as a peri-procedural hydration protocol ***(Konstantions et al., 2004).***

AIM OF THE WORK

To examine the efficacy of ascorbic acid for preventive hydration, before and after coronary angiography, from the development of contrast-induced nephropathy in the cardiac catheterization laboratory.

This will be evaluated by:

Measurement of serial serum creatinine levels before, the following two to five days after and the procedure.

Contrast-induced Nephropathy

Historical background

Nearly seventy years ago, Osborne et al first reported the imaging of the urinary tract using iodinated contrast material ***(Osborne et al., 1983).***

Over the past 30 years, there has been a marked increase in diagnostic and interventional procedures in which iodinated contrast is used ***(Gleeson and Bulugahapitiya, 2004)***.

The structure of radiocontrast agents has been modified over the last several decades, yielding compounds with significantly less chemotoxicity. Unfortunately, the administration of even the newest radiocontrast agents may cause nephrotoxicity ***(Gleeson and Bulugahapitiya, 2004).***

Contrast-induced nephropathy has become a significant source of hospital morbidity and mortality with the ever-increasing use of iodinated contrast media in diagnostic imaging and interventional procedures such as coronary angiography. It ranks third amongst the causes of hospital-acquired acute renal failure, after surgery and hypotension. Unfortunately, it is frequently the high risk patients; particularly those with preexisting renal insufficiency and diabetes mellitus; which are encountered

by the cardiovascular and interventional radiologist ***(Gleeson and Bulugahapitiya, 2004).***

Definitions

Defining contrast-induced nephropathy has proven to be quite challenging and many studies have put forward various suggestions ***(Barrett, 1994).***

Lautin et al. used six separate definitions with criteria ranging from an increase in serum creatinine level of more than 0.3 mg/dL to an increase of 2.0 mg/dL or more and found that the more restrictive higher cut-off point to be less sensitive for predicting incidences of contrast-related renal dysfunction. Although it has been argued that a low increment of change of serum creatinine levels may not be clinically important, this low increment allows studies of reasonable sample size.

Levy et al. put forward a large cohort study that has shown that even apparently small decreases in renal function can lead to excessive mortality rates independent of other risk factors, and given that small rises in serum creatinine levels actually represent a significant drop in GFR, a definition set at the lower end of the accepted range has become the most commonly quoted.

Hayman has suggested that changes of 0.3 mg/dL are not statistically significant in many laboratories.

Hence contrast-induced nephropathy has become most commonly defined as "impairment of renal function occurring within 48 hours after administration of radiographic contrast media which is maintained for 2 to 5 days. It is manifested by an absolute increase in the serum creatinine level of at least 0.5mg/dL (44.2 µmol/L), or by a relative increase of at least 25% over the baseline value in the absence of another cause" ***(Kolonka et al., 1998).***

This definition may in part account for the large number of cases reported showing only transient elevations of serum creatinine levels or at least elevations that do not require dialysis. Although this large number has led to questioning of the clinical relevance of such rises, these subtle changes have been shown to be associated with significant morbidity rates and, in addition, may help to identify those with borderline renal function who may be at risk of developing fulminant renal failure in the future ***(Levy et al., 1996).***

Ideally, the impairment of renal function should be measured by serial creatinine clearance, but because this step may be neither practical nor cost-effective in many centers, most of the literature describes the use of isolated

measurements of serum creatinine levels, even though this parameter may be less sensitive at reflecting subtle early changes in renal function and may be slower to reach maximal sensitivity than creatinine clearance. Serum creatinine levels may prove to be more sensitive, however, in cases of pre-existing renal impairment, in which tubular secretion of creatinine can lead to overestimation of the glomerular filtration rate (GFR) ***(Gleeson and Bulugahapitiya, 2004).***

Other suggested definitions include: a rise in serum creatinine levels of more than 100%, a rise in serum creatinine levels of more than 1 mg/dL, a post-procedural serum creatinine level greater than 5 mg/dL, or acute renal failure requiring dialysis ***(McCullough et al., 1997).***

Epidemiology

The rate of incidence of contrast-induced nephropathy as a complication of radiographic diagnostic and interventional studies varies markedly depending on the definition used and on other variables such as the type of radiology procedure performed, the dose and type of contrast agent administered, the differing patient populations in regard to number and type of risk factors, and the length of patient follow-up ***(Gleeson, 2004).***

An overall incidence of 14.5% was recently quoted in a large epidemiologic study ***(McCullough et al., 1997).***

(Defined as more than 25% increase in serum creatinine levels over baseline in the first 5 days), but rates may vary from 0% to 90%, depending on the presence of risk factors, most notably chronic renal insufficiency, diabetes mellitus, and high contrast volume administered ***(Parfrey et al., 1989).***

Incidence among patients with diabetes mellitus has been reported to be 5 to 30% in patients with normal renal functions, 9 to 40% in patients with mild-to-moderate chronic renal insufficiency and 50 to 90% in those with severe chronic renal insufficiency. ***(Manske et al., 1990) (Harkonen and Kjellstrand, 1977).*** In contrast, the incidence in the general population is much lower and has been calculated to be less than 2% ***(Berg, 2000).***

Despite a lack of consensus as to exact rates and definitions, contrast-induced nephropathy remains a significant source of morbidity and mortality ***(Gleeson and Bulugahapitiya, 2004).***

McCullough et al. quoted an in-hospital mortality rate of 35.7% for patients undergoing coronary angiography and an 18.8% 2-year-survival rate.

Levy et al. had similar findings in a study of more than 16,000 patients undergoing contrast-enhanced examinations (CT of the head and body, cardiac angiography, and peripheral angiography). They showed that in the 1% of patients who developed contrast-induced nephropathy (defined as an increase of serum creatinine levels of more than or equal to 25% above baseline), there was a significantly higher mortality rate than in the patient group from the same population matched for age and baseline creatinine levels who underwent similar contrast-enhanced procedures but did not develop renal failure (34% versus 7%). The overall mortality rate for the cohort was 0.4%, with 0.1% requiring renal replacement therapy. Contrast-induced nephropathy was thus found to result in excessive mortality rates, independent of other risk factors. The authors also found that not only does the condition increase the risk of death from preexisting non-renal conditions, but it is also associated with major non-renal morbidity rates from acquired sepsis, bleeding, coma, or respiratory failure ***(Levy et al., 1996).***

Clinical Features and Management

Contrast-induced nephropathy most commonly manifests as a non-oliguric and asymptomatic transient decline in renal function ***(Anderson et al., 1977)*** the serum creatinine level begins to rise within 24 hours of contrast

administration in 80% of patients in whom contrast-induced nephropathy develops. It usually peaks within 3 to 5 days, and returns to baseline within 10 to 14 days **(*Fang et al., 1980).***

Oliguric acute renal failure requiring hemodialysis can also occur. This condition presents with oliguria (defined as twenty-four hour urine volume less than 400 mL) within 24 hours of contrast administration and typically persists for 2 to 5 days. Serum creatinine levels peak within 5 to 10 days and return to baseline within 14 to 21 days ***(Katzberg, 1997)*** Morbidity and mortality rates are significantly higher in this group of patients when compared with those who have non-oliguric renal failure. ***(Anderson et al., 1977)***

Urinary epithelial cell casts, debris, along with urate and calcium oxalate crystals are non-specific findings in contrast-induced nephropathy ***(Rudnick et al., 1994).*** Low urinary sodium and fractional excretion of sodium (less than 1%) have been reported as being distinctive characteristics of this condition, ***(Fang et al., 1980) (Katzberg, 1997)*** but these findings have not consistently been shown to be specific for contrast-induced nephropathy ***(Anto et al., 1981).*** A persistent nephrogram on radiography or CT 24 hours after contrast administration is also said to be suggestive of a diagnosis of contrast-induced

nephropathy ***(Lang et al., 1981)*** but is not a consistent or a specific finding ***(Love et al., 1994).***

Treatment of established contrast-induced nephropathy should start with the recognition of renal impairment after the study. In patients at higher risk, renal function should be carefully monitored by measuring serum creatinine levels before and once daily for 5 days after the radiographic procedure ***(Brady and Singer, 1995).***

After contrast-induced nephropathy is identified, the subsequent management of this condition is the same as that for acute renal failure due to other causes. Admission to the hospital and subsequent judicious monitoring of serum electrolyte levels are required to prevent hyperkalemia, hyponatremia, hyperphosphatemia, hypocalcemia, hyper-magnesemia and metabolic acidosis associated with acute renal failure ***(Brady and Singer, 1995).***

Appropriate nutritional support is essential and strict recording of patient weight and fluid input-output is required until creatinine levels return to baseline. High phosphate levels can be treated using phosphate binders such as calcium carbonate. Hyperkalemia is treated by dietary restriction and potassium-binding resins or insulin-dextrose infusion when the potassium level is greater than (6.5 mmol/L). Correction of acidosis may require oral

sodium bicarbonate. More severe cases may require temporary hemodialysis, but a minority of patients who do not respond to conservative treatment will require permanent dialysis or kidney transplantation ***(Brady and Singer, 1995).***

The rates of patients who required hemodialysis or who died after occurrence of contrast-induced nephropathy reported in the different clinical trials are listed in table 1.

Table (1): Rates of hemodialysis and death after contrast-induced nephropathy reported in the different clinical trials. ***(Goldenberg and Matetzky, 2005)***

Study	No. of patients	Diagnostic procedure	Dialysis rate	Mortality after dialysis
McCullough et al.	3,695	Coronary angiography	0.5%	37%
Gruberg et al.	12,054	Coronary angiography	0.4%	17%
Levy et al.	16,248	Radiocontrast procedure	1.1%	12%

Pathogenesis

The underlying mechanism for the development of contrast-induced nephropathy involves the interplay of several pathogenic factors (figure 1):

I. **Intrinsic causes**, which all culminate in renal medullary ischemia, include the following: ***(Prasad PV et al, 2001) (Weisberg LS, Kurnik PB, Kurnik BR, 1992) (Bakris GL et al, 1990)***
    1. Increased vasoconstrictive forces.
    2. Decreased local prostaglandin- and nitric oxide (NO)-mediated vasodilatation.
    3. A direct toxic effect on renal tubular cells with damage caused by oxygen free radicals.
    4. Increased oxygen consumption.
    5. Increased intra-tubular pressure secondary to contrast-induced diuresis.
    6. Increased urinary viscosity.
    7. Tubular obstruction.

II. **Extrinsic (pre-renal) causes**, which act in conjunction with the intrinsic ones, include the following: ***(Prasad et al., 2001).***
    1. Dehydration.
    2. Decreased effective intra-vascular volume.
    3. It has to be noted that laboratory animals have not been shown to have renal failure when given radiographic contrast agents unless the systemic and renal circulation is compromised in some way. ***(Prasad et al., 2001).***

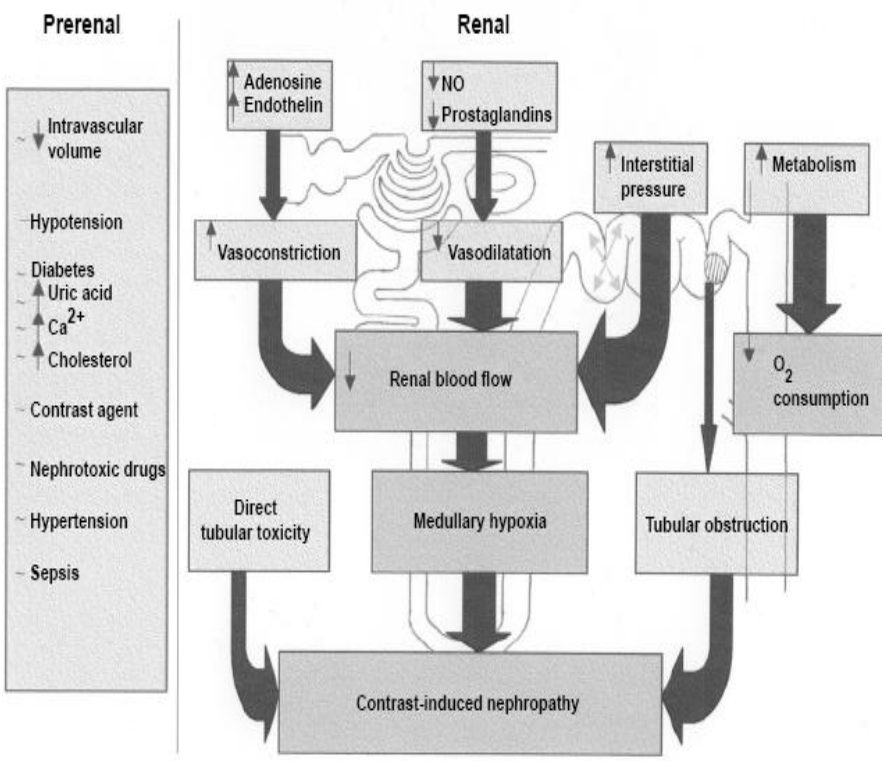

Figure (1): Diagram showing proposed pathophysiologic mechanisms for the development of contrast-induced nephropathy (NO = nitric oxide) ***(Gleeson and Bulugahapitiya, 2004)***

Brezis and Rosen have speculated that such renal failure occurs because of vulnerability of the renal medullary circulation to stimuli that disrupt the balance between the high metabolic needs of the tubular segments of the renal medulla and their hypoxic environment. This balance is normally maintained by the interplay between vasodilator and vasoconstrictor influences, mediated by the activity of NO, prostaglandin, and endothelin systems within the medulla ***(Brezis and Rosen, 1995).***