IS N-ACETYLCYSTEINE USEFUL IN PREVENTION OF CONTRAST INDUCED NEPHROPATHY?

A REVIEW

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INTRODUCTION

The increasing use of iodinated contrast medium in radiological procedures, especially in coronary angiogram has raised concerns in growing incidence of contrast induced nephropathy (CIN). CIN is the 3rd leading cause (1) of acute renal failure in hospitalised patients which can be prevented if adequate preventive measures are taken. The risk of CIN after primary cardiac intervention (PCI) not only extends to patients with preexisting renal failure but also to those with normal baseline renal function. Although there have been many studies on preventive measures on hydration, Sodium bicarbonate, aminophylline and Ascorbic acid, N-acetylcysteine (NAC) has been of great interest due to its low cost and negligible side effects.

Evidence for renal parenchymal injury by oxygen free radicals led to the evaluation of effectiveness of antioxidants in prevention of CIN, N-acetylcysteine is essential to reduce morbidity and mortality in this clinical setting. NAC attenuates CIN, owing to its ability to scavenge oxygen free radicals, thereby preventing direct oxidative tissue damage and its ability to counteract dye induced renal vasoconstriction.

Use of non-ionic low osmolality contrast media and preprocedural hydration with intravenous fluids both appear to decrease the risk of contrast nephropathy. Recent work suggests that administration of NAC further reduces the likelihood of contrast nephropathy, but other trials have failed to confirm this finding. Hence it has remained controversial till date.

OBJECTIVE

The aim was to review the recent studies and literatures to assess the new developments about the use of NAC in preventing CIN in

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patients undergoing Coronary angiography (CAG) and/or PCI because of the homodynamic instability, the need for a high volume of contrast medium, and the lack of effective prophylaxis for the procedure. This has created great interest in researchers in the recent times.

METHODS AND RESULTS

Analysis of the works regarding the NAC in prevention of CIN was done using the MEDLINE search engine and reviewed important papers & recent analysis on this topic. I have chosen the few important studies to discuss the benefits or uselessness of NAC.

The major report was by Tepel et.al (2) who randomised 83 hydrated patients with chronic renal insufficiency, given a small IV dose (75mL) of non ionic low osmolar radiocontrast agent, to receive placebo vs. NAC orally, 600mg every 12hrs, a day before & a day after the procedure. The incidence of CIN after 48hrs was 2% in NAC treated vs. 21% in control group. This was a significant study which gave rise to further thoughts about benefits of NAC.

Another study is by Carbonell et al (3) using two different strengths of NAC in CAG. First, it is a randomized placebo controlled trial in patients at high risk for developing CIN. Despite the small number of patients in this study, the homogeneous and restricted inclusion criteria of patients with baseline renal insufficiency allowed the investigators to appropriately assess the impact of NAC and placebo on a continuous variable such as serum creatinine elevation after angiography. Second, high-dose intravenous administration of NAC (rather than low-dose oral administration as used in several other studies) might be the optimal regimen to be applied, given its rapid onset of effect, complete bioavailability, and higher peak serum NAC levels. Assuming that oral bioavailability of NAC is up to 20%, an intravenous dose of 600 mg twice a day, as reported by Carbonell et al, ensures that as much as—or higher—NAC levels reached the systemic circulation compared with previously reported studies in which 2400 mg of oral NAC (600 mg twice daily for 4 doses) was used. Accordingly they proved that NAC may prevent CIN with a dose-dependent effect and showed it may improve hospital outcome.

Recently Kinbara et al, (4) studied 45 consecutive patients undergoing CAG / PCI who were randomly assigned to receive hydration and NAC (704mg orally BD; NAC group, n=15), hydration and aminophylline (250mg IV 30min before CAG and/or PCI; aminophylline group, n=15), or hydration alone (control group, n=15). They compared serum creatinine (SCr), creatinine clearance (Ccr), blood beta-2 microglobulin, and urinary beta-2 microglobulin levels at baseline and 48h after CAG / PCI. In the NAC group, SCr decreased from 1.00+/-.36 to 0.67+/-.016mg/dl (p<.01), and Ccr significantly increased from 62.4+/-.15 to 80.4+/-.39ml/min (p<.01). In the aminophylline group, SCr and Ccr were unchanged. In the control group,
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SCr significantly increased from 0.94+/-0.21 to 1.28+/-0.21mg/dl (p<0.01), and Ccr significantly decreased from 63.7+/-16.1 to 46.1+/-10.6ml/min (p<0.01) after CAG and/or PCI. In the NAC group, mean blood beta-2 microglobulin significantly decreased from 2.38+/-0.58 to 1.71+/-0.38mg/dl (p=0.01), and in the aminophylline group, mean urinary beta-2 microglobulin concentration significantly decreased from 337+/-31.0 to 239+/-34mug/ml (p=0.01). From these studies they showed that prophylactic NAC is effective in preventing CIN but not with hydration alone in CAG/PCI group. They inferred probably both worked in different ways against CIN.

Moreover Ochoa et.al.(5) Showed abbreviated high dose NAC regimen (1000mg PO 1hr before and 4 hr after CAG/PCI) helps prevent rise in creatinine 48hrs after CAG/PCI and may prevent CIN after 48hrs of CAG/PCI. The study by Kay J et.al (6) concluded that acetylcysteine protected patients with moderate chronic renal insufficiency from CIN after CAG with minimal adverse effects and low cost. Lastly Giancarlo Marelini et.al (7) showed that N-acetylcysteine reduced the severity of contrast-medium–induced nephropathy in patients with acute myocardial infarction treated with primary angioplasty. The effect appears to be dose-dependent and is accompanied by a significantly improved in-hospital outcome. The mechanisms underlying the improvement in the in-hospital clinical outcome have not been completely elucidated, and studies of potential extra renal effects of N-acetylcysteine are warranted.

In contrary Amini M et.al (8) showed that NAC had no detectable benefit to prevent CIN in patients with Diabetes mellitus & Chronic kidney disease undergoing elective diagnostic CAG over an aggressive hydration protocol, NAC vs. Placebo 11% vs. 14.5% respectively. Moreover Oldmeyer JB et al (9) showed that NAC didn’t reduce the risk of CIN in patients with reduced renal function undergoing coronary angiography. CIN occurred in 8.2% (4/49) of patients taking NAC and 6.4% (3/47) of patients taking placebo.

In another study by Goldenberg I et.al (10) prophylactic administration of NAC in an adjunct to saline hydration for prevention of CIN in chronic renal insufficiency pts undergoing coronary angiography was not supported, 10%vs 8% (NAC vs. Placebo). The study by Vallero et.al (11) analyzing 100 patients undergoing CAG with NAC 600mg BD a day before and after vs. hydration with half normal saline had no potential benefit in preventing CIN in patients with normal or mild renal failure.

In contrast to Carbonell et al, Webb et al (12) did not find any protective effect of NAC in high-risk patients using the same route of administration in a larger population. A single, lower dose of NAC used as well as a shorter, less aggressive hydration protocol may explain their negative results.

Also Coyle LC et al (13) studied diabetic patients undergoing elective CAG using hydration vs. hydration with NAC .The mean Creatinine clearance change in the NAC group was 0.14 +/- 0.47 versus 0.08 +/- 0.11 mg/dL in the hydration only group (P = NS), hence showing no benefit of NAC over an aggressive hydration protocol. A large randomized control study done by
Webb JG et al enrolling high risk group with impaired renal function in cardiac catheterization setting showed NAC was ineffective in preventing CIN 23.3% vs. 20.7%(NAC vs. Placebo). They had to terminate the study early because of a determination of futility by the Data Safety Monitoring Committee after enrolment of 487 patients.

Finally Durham et al, (14) studied 79 pts with chronic renal failure who underwent CAG/or PCI, using oral NAC vs. placebo, who in addition received hydration with 0.45% saline 12hrs before and after procedure. He showed there was no difference in incidence of CIN between two groups 26.3% vs.22 %( NAC vs. Control)

DISCUSSION

Several studies have attempted to evaluate the effectiveness of NAC in preventing CIN. Results have been conflicting and while some studies have shown benefit, others have failed to show reduction in CIN with NAC over hydration alone.

In most of the trials which supported the use, the use of NAC 600mg BD or higher doses in special conditions over placebo in addition to hydration in patients with prior renal insufficiency reported lower incidence of CIN with NAC vs. Hydration alone. In addition renal function improved with NAC in comparison with saline hydration alone 48 hrs after contrast administration. Use of other agents like aminophylline didn’t show any added benefit in the study.

However other studies have failed to show a benefit of NAC vs. hydration alone. In a direct comparative trial of saline hydration and NAC, the most efficient and cost effective preventive measure was saline hydration. While compelling evidence for usefulness of NAC is lacking, NAC has a low incidence of adverse effects and low cost. NAC could be used as a preventive measure for contrast induced Nephropathy in high risk patients undergoing contrast procedures.

Use of safer, non-ionic low molecular weight contrast agents with the appropriate hydration and other preventive medication has been proven beneficial in prevention of CIN.

CONCLUSION

In conclusion the prophylactic use of N-Acetylcysteine in prevention of CIN is still controversial. However there has no disadvantages using the NAC along with other preventive measures. NAC may reduce the incidence of acutely increased serum creatinine after administration of intravenous contrast, but this finding was of borderline statistical significance, and there was significant heterogeneity between trials. Before NAC becomes the standard of care for all patients receiving intravenous contrast, new
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randomized trials evaluating its effect on clinically relevant outcomes are required.

REFERENCES