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Umar Sadat

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N-acetylcysteine in contrast-induced acute kidney injury: clinical use against principles of evidence-based clinical medicine!

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Umar Sadat

Cambridge Vascular Unit, Box 201, Addenbrooke's Hospital, Hills Road, Cambridge University hospitals NHS Foundation Trust, CB2 0QQ, Cambridge, UK
Tel.: +44 122 324 5151
sadat.umar@gmail.com

Contrast-induced acute kidney injury (CI-AKI) is one of the most widely discussed and debated topic in cardiovascular medicine and N-acetylcysteine (NAC) is the most widely used pharmacological agent assessed in clinical trials for offering renal protection against CI-AKI. Results of these clinical trials are though split between those that favor its use and *vice versa*. In this brief communication we discuss the latest research advances regarding the use of NAC against CI-AKI. Recent clinical evidence and overview of in-depth statistical analyses of relevant clinical trials and their meta-analyses do not support the use of NAC in prophylaxis against CI-AKI. Adequate hydration before and after contrast media exposure, along with avoidance of nephrotoxic drugs, remains the recommended prophylaxis against CI-AKI.

Contrast-induced acute kidney injury (CI-AKI) is one of the most widely discussed and debated topic in cardiovascular medicine. Despite continued efforts at understanding its underlying pathophysiology and devising prophylactic strategies, the incidence of CI-AKI is on an increase due to an increasing number of contrast media (CM)-enhanced radiological studies. The 'Contrast Media Safety Committee' (CMSC) of the 'European Society of Urogenital Radiology' (ESUR) only recommends adequate hydration before and after CM exposure along with avoidance of nephrotoxic drugs against CI-AKI [1]. No pharmacological agent has been recommended so far by the CMSC. Recently, a statistically robust systematic review of nine randomized controlled trials (RCTs) reported that ascorbic acid reduces the risk of CI-AKI [2]. Other pharmacological agents have also been used as prophylactic agent against CI-AKI such as statins [3,4] and theophylline [5]. However, N-acetylcysteine (NAC) is the only pharmacological agent which has been most extensively studied in RCTs.

Traditionally, NAC has been used for treating acetaminophen poisoning because of its ability to replenish glutathione reserves. It also increases renal glutathione levels *in vivo* which seems to attenuate renal injury in renal ischemia-reperfusion injury models [6]. These antioxidant properties of NAC have the potential to combat oxidative stress generated during CI-AKI [7]. NAC also acts as a powerful scavenger of reactive oxygen species which have also been implicated in the etiology of CI-AKI [8]. Tepel *et al.* used NAC in the first RCT to demonstrate that it can successfully reduce the incidence of CI-AKI in patients undergoing coronary arteriography [9]. Since then numerous RCTs have been performed, some of them reporting benefits and most of them reporting no benefit. Some 17 meta-analyses have been published on this subject, with evidence split in its favor and *vice versa*. Most of these meta-analyses have reported significant heterogeneity and

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bias, making it difficult to synthesize clinical treatment recommendation based on the available data. These different outcomes are a result of the heterogeneity of patients, different inclusion criteria and measurement methods for renal biomarkers, stage of renal impairment and differences in doses and routes of administration of NAC [10]. To resolve this heterogeneity, a stratified meta-analysis of 22 studies was performed, recently [11]. The included RCTs were grouped into two distinct, significantly different and homogeneous populations. Eighteen studies constituted cluster 1 and four studies were in cluster 2. Cluster 1 did not show any benefit with NAC ($p = 0.28$) but cluster 2 showing significant benefits with NAC ($p = 0.0001$). This benefit was observed to be unexpectedly associated with NAC-induced decreases in serum creatinine (SCr) from baseline. In the view of previous reports that NAC in the absence of CM may decrease SCr levels in normal volunteers [12] and patients [13], this response to NAC may be a drug effect independent of changes in glomerular-filtration-rate. It was also noted that studies in cluster 2 were relatively early, small and of lower quality compared with cluster 1 studies ($p = 0.01$ for the three factors combined).

Significant publication bias was identified in the published trials assessing nephroprotective role of NAC [14]. Published manuscripts presented a treatment-effect estimate that was more optimistic than that found in unpublished abstracts. There was a temporal trend in that the estimate of treatment effect was greatest with early publications, which diminished as additional data became available. Exclusive meta-analyses on oral [15] and intravenous use [16] of NAC also do not support its use. A meta-analysis of RCTs on its use in patients with peripheral arterial disease undergoing conventional peripheral arteriography has also shown no benefit in reducing CI-AKI [17]. Recently the largest RCT (n = 2308) to assess its role against CI-AKI has failed to show any benefit [18].

Very recently, it has been reported that a randomized, double-blind, multicenter trial called the Prevention of Serious Adverse Events following Angiography (PRESERVE) trial will enroll 8680 patients to compare the effectiveness of intravenous isotonic sodium bicarbonate versus intravenous isotonic sodium chloride and oral NAC versus oral placebo for the prevention of serious, adverse outcomes associated with CI-AKI [19]. Investigators state that its design takes into consideration all imperfections of previous RCTs. The published data to date however does not provide convincing evidence regarding the nephroprotective role of NAC. Despite being easily available and being inexpensive, strictly speaking the continued use of NAC in clinical settings seems to be against principles of evidence-based medical practice. Adequate hydration before and after CM exposure along with avoidance of nephrotoxic drugs against CI-AKI is the only recommended prophylactic strategy to date [1].

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