ROLE OF N ACETYLCYSTEINE IN PREVENTING RENAL INJURY POST ESWL IN PEDIATRICS

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ABSTRACT

Background: N-acetylcysteine (NAC) has been widely used as a prophylactic therapy for contrast-induced nephropathy (CIN). There are several mechanisms underlying the association between NAC administration and CIN risk. NAC has the potential to prevent CIN risk due to its potent antioxidant and vasodilating actions secondary to increased expression of nitric oxide. Management of kidney stones: Extracorporeal shock wave lithotripsy (ESWL) is currently a first-line procedure of most renal stones ≤ 2 cm of size because of established success rates, its minimal invasiveness and long-term safety with minimal complications. N-Acetylcysteine (NAC) has been reported to protect the kidney from injury induced by contrast media, ischemia, and toxins. In all these studies, glomerular filtration rate (GFR) is the surrogate marker of kidney injury and serum creatinine changes are the measured metric of GFR.

Key words: N-Acetyl cysteine, Urolithiasis, Extracorporeal shock wave lithotripsy (ESWL).

I. KIDNEY STONES IN CHILDREN:

Because children with nephrolithiasis constitute a patient population who are at increased risk of stone recurrence during their life-times, prompt evaluation and management is important. However, because pediatric nephrolithiasis is an uncommon condition, not much is known about it. (1).

Pathophysiology

The pathophysiology of nephrolithiasis can be divided into three broad conceptual categories. The formation of stones requires (1) solutes exceeding in concentration relative to their solubility in the urine; (2) crystallization due to an imbalanced presence of promoters and inhibitors; and (3) the attachment and growth of crystals into nephroliths due to epithelial abnormalities.

Examples of common stone-forming solutes include calcium, oxalate, phosphate, citrate, uric acid, and cysteine. In addition, common stone inhibitors include citrate, magnesium, macromolecules, and pyrophosphate (2).

II. MANAGEMENT OF KIDNEY STONES IN CHILDREN

The incidence of pediatric stone disease has increased to approximately 2% in industrialized countries over the past 30 yr. This in itself makes the selection of an appropriate management modality important in this population. The ultimate goal for pediatric stone management has been, and should continue to be, the achievement of a stone-free state because residual stone fragments, regardless of size, can grow and lead to adverse consequences. Most importantly, the emergence of kidney stones as a pediatric disease necessitates that specialist who care for children with nephrolithiasis understand the optimal strategies to evaluate children with kidney stones and the effectiveness of nonsurgical interventions to decrease the risk of recurrence (3).

Extracorporeal shockwave lithotripsy (ESWL):

Extracorporeal shock wave lithotripsy (ESWL) is currently a first-line procedure of most upper urinary tract stones <2 cm of size because of established success rates, its minimal invasiveness and long-term safety with minimal complications. Extracorporeal shockwave lithotripsy is used with stones in various locations but is limited with larger lower pole stones, staghorn stones, and with the anatomically abnormal urinary tract. Extracorporeal
shockwave lithotripsy is now used frequently in children and is considered by many as the first-line interventional therapy (4).

**ESWL in children**

For urolithiasis in children ESWL shows excellent results and has therefore traditionally been the first-line treatment even for large stone burdens. This is because the paediatric ureter is shorter and more elastic, and therefore has a higher stone-transporting capacity and in most cases stenting is unnecessary. (5).

ESWL may be performed at various frequencies ranging from 30 to 120 shockwaves/min. On the basis of clinical and experimental studies, the recommended shockwave frequency for children is 60/min (1Hz) (6).

ESWL is the preferred treatment in pediatric urinary stone patients with uncomplicated upper urinary tract calculi ≤ 15 mm. Although stone free rates after ESWL in children range between 68% and 92%, recent stone free rates are difficult to interpret from the current literature due to discrepancies among trials with regard to the lithotripter model used, number of shocks administered and re-treatment rates. In children, ureteral stenting before ESWL is not needed as often as in adults and it is not clear if ureteral stent placement improves stone free outcomes. ESWL can cause minor complications, including hematuria, perirenal hematoma, bruising (7).

**III. TECHNIQUE OF ESWL**

The efficacy of lithotripters is a compromise among different parameters. Lithotripters have four essential parts, which differ significantly among machines:

- Shockwave generator.
- Localization system.
- Shockwave coupling device.
- Auxiliary equipment.

Shockwaves can be generated by electrohydraulic, electromagnetic, or piezoelectric sources. In the electrohydraulic generator, an underwater electrode is discharged, inducing evaporation of water and causing a high-pressure wave. This is focused by an ellipsoidal reflector (which contains the first focal point) to generate a shockwave at focal point F2 (the stone). This principle of shockwave generation produces high disintegrative capacity, but also causes considerable pain. Deep analgosedation or anesthesia is necessary. Electromagnetic generators work in a way similar to loudspeakers. High-energy acoustic waves are focused by an acoustic lens or a paraboloid reflector. The resulting shockwave is constant. The energy is focused to a smaller focal point with higher peak energy. Piezoelectric generators consist of multiple spherically aligned piezoelements, inducing a high peak pressure at a small focal point. The resulting shockwave induces little pain, so these machines can be used without any analgosedation (8).

The disadvantage is the large diameter of the source and the limited total energy in the focus because of the low energy, the re-treatment rate is high. The effectiveness of a lithotripter depends on the power expressed at the focal point, which is a function of the peak pressure at the focal point and the size (volume) of the focal point. For example, the actual energy delivered by a lithotripter to a stone generally is greater for the electrohydraulic lithotripters, because they combine moderately high peak pressure and large focal points, than for piezoelectric energy sources, which produce some of the highest peak pressures of any device but deliver it to an extremely small focal volume. Closely correlated with the power, and therefore the effectiveness of the generator, is the pain produced by the shockwaves. There is a direct relation between pain and the diameter of the cutaneous area through which the shockwave enters, the dimensions of the focus, and the power at the focus. By reducing the dimension of the focus, it becomes possible to treat the patient without anesthesia or analgesia, but excessive reduction of the dimensions of the focus increase the re-treatment rate. Concerning the extent of pain, which has been a problem for many first-generation lithotripters, the greater width of the reflector and the modification of the generator have partially resolved the problem without lowering the power expressed at the focal point or the treatment effectiveness. On the other hand, the smaller focal zone of the newer lithotripsy models, although it should provide more precise stone fragmentation, requires more fluoroscopy time to ensure accurate focusing, and ventilatory
movement may reduce the number of direct shockwave strikes on the stone. It thus is evident that the efficacy of lithotripters is a compromise among different parameters. This is why, although currently the electromagnetic lithotripter seems to be the device that best reconciles effectiveness with morbidity, many authors underline the fact that the larger focal area of the original Dornier HM3 machine may provide a larger pulse width and reduced positive pressure, which can result in better stone cleavage and a larger compression zone within the stone (8).

N-acetylcysteine (NAC)

N-acetylcysteine (NAC) is a potent oxygen free radicals scavenger and a metal chelator. N-acetylcysteine (NAC) is a well-known synthetic thiol-containing antioxidant, that acts by raising the intracellular concentration of cysteine, and hence of glutathione (GSH), and/or acts by scavenging of ROS. Also, NAC has a protective effect on Pb-induced cytotoxicity in primary cultures of rat proximal tubular cells. In addition, NAC is a potent chelator of heavy metals, which binds to toxic heavy metals and removes them from the body (9).

Using microalbuminuria as a marker, Levin et al. (10) demonstrated that N-acetylcysteine may attenuate contrast-induced glomerular and tubular injury. Microalbuminuria, however, may also be caused by vigorous exercise, hematuria, urinary tract infection, and dehydration. Additional studies are necessary to further characterize microalbuminuria in the setting of acute kidney injury (AKI), especially with respect to its sensitivity and specificity.

N-acetyl cysteine (NAC) is an antioxidant which can regenerate glutathione and is primarily used for acetaminophen overdose. However, it has also been tested in prevention of acute kidney injury (AKI) in different settings, such as postoperative AKI and contrast induced AKI (CI-AKI) with mixed results, mainly using change in serum creatinine levels before and after NAC treatment as the outcome. Nevertheless, given the low cost and lack of side effects, NAC has been recommended for use by the Kidney Disease Improving Global Outcomes (KDIGO) guidelines in the context of CI-AKI. (11)

Additionally, although NAC is generally recommended for patients with chronic kidney disease (CKD), with an eGFR <60 ml/min/1.73 m2 in clinical practice, the supporting evidence has been inadequate. A recent systematic review from the Agency for Healthcare Research and Quality (AHRQ) also supports its use for CI-AKI prophylaxis. (12)

At present, there are over 20 ongoing trials testing the efficacy of NAC for prevention of acute kidney injury (AKI) in various settings (contrast AKI, perioperative AKI, drug-induced AKI) as well as in CKD for slowing progression or preserving residual kidney function. Therefore, a significant body of research is in progress and the outcome of these large and expensive trials may quantitatively resolve the effectiveness of NAC for preventing CI-AKI. Notably, a biological mechanism or rationale for a protective effect of NAC has never been satisfactorily reported (13).

Renal glomerular and tubular cells damage results in appearance or increased urinary levels of certain substances e.g. albumin, β2-microglobulin, and cellular enzymes such as N-acetyl-β-d-glucosaminidase (NAG), β-galactosidase, L-glutamyl transaminase, heart fatty acid binding protein, cystatin C, and neutrophil gelatinase-associated lipocalin (NGAL). Urologists spend great effort aiming for improving ESWL results and minimizing the complications either by adding renal protective substances or modifying the technique of shockwave delivery to the kidney. Stepwise voltage ramping can significantly reduce the extent of renal parenchymal hemorrhagic lesions and may even provide a protective effect compared to fixed voltage treatment. N-acetylcysteine (NAC) is a thiol containing cell membrane permeable antioxidant that eliminates a large spectrum of reactive oxygen species (ROS) (14).

Desoky et al., (15) evaluated the protective effect of NAC and stepwise voltage ramping for ESWL-induced renal injury. These reactive oxygen species (ROS) increase the tissue damage by enhancing lipid peroxidation, opposing the antioxidants and promoting DNA damage, leukocyte activation and cytokine production. NAC also increases the level of glutathione, a potent vasodilator, preventing regional vasoconstriction. So, NAC has an important role in nephron-protection from ischemic and toxic acute renal failure.
Protection Against Kidney Injury from Radiological Contrast Agents

Contrast-induced nephropathy (CIN), defined as an acute decline in renal function after the administration of intravenous contrast in the absence of other causes, is the third leading cause of acute renal failure in hospitalized patients behind hypotension and surgery complications. Radiological contrast is used in many settings and NAC is provided through several routes (oral, intravenous, combined) and at various doses (16).

Effectiveness of N-Acetylcysteine for the Prevention of contrast-Induced Nephropathy.

There are several possible mechanisms underlying the association between NAC administration and CIN risk. NAC has the potential to prevent CIN risk due to its potent antioxidant and vasodilating actions secondary to increased expression of nitric oxide synthase. On the cellular level, studies have shown that NAC administration inhibits renal cell apoptosis in a dose-dependent manner, meaning that the larger the dose, the more is the benefit derived (17).

The Efficacy of N-acetylcysteine Against Renal Oxidative Stress after Extracorporeal Shock Wave Treatment:

Extracorporeal shock wave lithotripsy (SWL) remains the initial treatment modality for the majority of patients with renal stones. Moreover, current guidelines suggest that SWL remains the least-invasive procedure for stone management in children (18). Therefore, long-term tissue effects of SWL are needed to be investigated despite its long-term proven efficacy. There have been several reports proposing that SWL causes oxidative stress due to renal ischemia-reperfusion injury.

Furthermore, some agents have been tested to prevent SWL-induced renal oxidative stress (18). N-acetylcysteine (NAC) is a potent oxygen free radicals scavenger and a metal chelator. N-acetylcysteine (NAC) is a well-known synthetic thiol-containing antioxidant, that acts by raising the intracellular concentration of cysteine, and hence of glutathione (GSH), and/or acts by scavenging of ROS. Also, NAC has a protective effect on Pb-induced cytotoxicity in primary cultures of rat proximal tubular cells. In addition, NAC is a potent chelator of heavy metals, which binds to toxic heavy metals and removes them from the body (9).

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IV. PROTECTION AGAINST KIDNEY INJURY FROM RADIOLOGICAL CONTRAST AGENTS

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NAC, a potent antioxidant, was tested to prevent oxidative damage in renal tissues. In a rat model, carbon dioxide pneumoperitoneum was used to induce oxidative stress. It was reported that administration of NAC provided a complete protection against decline in glomerular filtration rate following pneumoperitoneum. In a randomized, double-blind, controlled clinical trial on chronic hemodialysis patients, administration of NAC suggested to reduce oxidative stress without major side-effects. In another experimental study, it was shown that NAC could protect rat kidney against aspartame-induced oxidative stress (19).

Similarly, it has been concluded that NAC showed effective restoration of oxidative stress biomarkers including Malondialdehyde (MDA), Superoxide dismutase (SOD), and glutathione peroxidase. In Ribeiro et al., (20) experimental model, rats that received intraperitoneal NAC at a dose of 300 mg/kg/day for 14 or 28 days showed a significant improvement of Total oxidant status (TOS) as much as two times than the rats without NAC. Similarly, median Total antioxidant status (TAS) value was remarkably increased by NAC injection. Consequently, oxidative stress index (OSI) was lower in the NAC group. Almost two times higher OSI values were measured in rats that underwent ESWL without NAC. Therefore, the study showed that NAC has a protective role against oxidative stress associated with ESWL. Moreover, tubular damage and interstitial inflammation as acute damage parameters were found to be less prominent in rats receiving NAC. The current trial suggests that NAC administration during ESWL can prevent renal oxidative stress, and then, some subsequent morphological alterations may also be improved by NAC.

Conflict of Interest: No conflict of interest.
REFERENCES