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Commentary

Should Reno-Protective Protocols Be Routine in Extracorporeal Shockwave Lithotripsy?

Nooralhuda Al-Ani[1*], Ahmad Saadi Ahmad Al Sameraaii[2]

[1] Northwest Health. Tasmania. Australia
[2] Australian National University, Canberra, Australian Capital Territory, Australia
* Corresponding author's email: noorulhuda.alani@ths.tas.gov.au

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ABSTRACT

For decades, extracorporeal shockwave lithotripsy (ESWL) has been considered a first-line and non-invasive treatment for kidney stones, especially small and medium-sized stones located in the upper pole and renal pelvis. However, this procedure is not without collateral damage to kidney tissue, with both acute and chronic side effects. Shear stress and cavitation forces generated by shockwaves to fragment stones do not discriminate between stones and renal parenchyma. When they release their energy into the renal parenchyma, shockwaves cause microvascular damage, vasospasm, ischemia-reperfusion injury, oxidative stress, and an inflammatory cascade that might end with fibrosis and nephron loss. These detrimental side effects would be more evident in patients requiring multiple treatment sessions and those with solitary or pre-damaged kidneys.

Although population-level data on long-term systemic effects like hypertension and diabetes are equivocal, imaging, biomarkers, and histopathology consistently demonstrate ESWL-related subclinical renal injury, questioning the traditional "treat and assess" trend.

Given the clear pathophysiological rationale and growing supportive evidence, reno-protective protocols should be an integral component of modern ESWL practice, at least for high-risk groups such as patients with solitary kidneys, pre-existing renal damage, children, and patients with recurrent stones requiring repeated treatment sessions.

Introduction

Since its first introduction by Chausssy and his team as early as 1981, shockwave lithotripsy has revolutionized renal stone management [1]. It has replaced the highly invasive open surgery (pyelolithotomy) and the relatively less invasive, but still invasive, percutaneous nephrolithotomy (PCNL) in the treatment of small and medium-sized kidney stones, and has quickly become the standard of care [2,3]. However, the initial excitement about the non-invasiveness of ESWL has faded over time when growing evidence showed both short- and long-term injury to the kidney [4]. This has created a critical clinical dilemma: a lot of effort has been made to improve stone fragmentation over decades, but little has been done to protect the kidney tissue from possible collateral damage. A central question remains unanswered: Should reno-protective protocols be a routine component of ESWL therapy of renal stones?

This commentary argues that the current practice of "treat and assess" is unacceptable, and a proactive, reno-protective approach is necessary, especially for high-risk patients.

The Physics of Trauma: Mechanisms of ESWL-Induced Renal Injury

Understanding the mechanism of shockwave-induced tissue injury is pivotal in establishing any reno-protective protocol. Shockwaves deliver high energy to tissue and consist of two phases. A compressive phase, where there is a short, rapid, steep pressure rise, followed by a tensile phase, which is longer and shallower with negative pressure. These two phases cause stone fragmentation through different mechanisms: the shear stress of the compressive phase and the cavitation effect of the tensile phase [5].

Unfortunately, these forces do not discriminate between the stone and the surrounding renal tissue. When it hits the soft tissue of the kidney, the compressive phase induces direct mechanical shear stress on the microvasculature, leading to endothelial damage. The negative pressure phase, on the other hand, causes dissolved gases in the blood and interstitial fluid to expand into microscopic bubbles, which later collapse, generating microjets of fluid that tear through capillaries, venules, and renal tubules [3].

Pathophysiology of the Renal Insult

A complex series of ischemia, reperfusion, and inflammatory responses follows the ESWL-induced mechanical damage. In addition, a localized area of ischemia will result from the vascular compromise made by interstitial edema, intrarenal hemorrhage, and vasospasm [6].

When reperfusion starts, and the tissue attempts to recover, a classical ischemia-reperfusion injury (IRI) evolves. An ample amount of reactive oxygen species (ROS) would be generated during the reperfusion phase, such as superoxide anion, hydrogen peroxide, and hydroxyl radicals. These ROS devastate the antioxidant defense mechanism of the tissue and cause cell membrane lipid peroxidation, protein denaturation, and DNA damage [6].

To complicate the situation, cytokines release (IL-6 and TNF-α) along with macrophage / neutrophil recruitment will augment the inflammatory response and initiate fibrosis [7,8].

Clinical Manifestations and Long-term Sequelae: The Debate

Acute renal injury following ESWL is well-known. Hematuria, macroscopic or microscopic is reported in almost all patients [3]. Up to 30% of patients develop subcapsular or perinephric hematomas detectable by MRI or CT, a sign of significant renal trauma. However, less than 1% of patients develop clinically significant bleeding necessitating intervention [9,10]. Many urinary biomarkers indicating tubular injury, such as N-acetyl-beta-D-glucosaminidase (NAG) and beta-2-microglobulin, spike after shockwave therapy and may last for several days to weeks [11].

While all urologists agree on the acute detrimental effects of shockwaves on the kidney tissue, the long-term effects remain a subject of intense debate. Early studies conducted in the 1980s and 1990s warned about an increased incidence of new-onset hypertension, decreased renal function, and even the development of diabetes mellitus due to collateral damage to the tail of the pancreas [12], but, subsequent, more rigorously controlled studies have shown conflicting data, and failed to find a definitive causal link between shockwaves and long-term systemic sequelae [13].

However, the absence of systemic, population-level harm does not negate localized and clinically significant renal damage. Recurrent stone formers requiring multiple ESWL treatment session over years may develop a cumulative fibrotic scarring from repeated kidney insults and a significant loss of functioning nephrons and renal reserve. The same concerns are depicted for patients with pre-existing renal impairment or solitary kidneys. Therefore, assuming that ESWL is entirely safe in the long term might be a dangerous fallacy.

Physical Reno-Protective Protocols: Modifying the Delivery

Evan and colleagues of Indiana University have pioneered the research focusing on shockwave modification in an attempt to mitigate the detrimental effect on renal parenchyma, and provided what can be considered a roadmap for (kidney-friendly) lithotripsy [14,15]. Researchers studied modifications in shockwave voltage, rate, and continuity.

- Voltage Ramping (Step-up Protocol): one of the methods used to protect the kidney soft tissue is by initiating ESWL therapy at a low energy setting and gradually increasing it. The theory behind this is that the transient and localized vasoconstriction resulting from the low-energy shockwaves significantly reduces the blood volume in the targeted area, minimizing the magnitude of microvascular tearing and subsequent hemorrhage [15]. In modern ESWL therapy protocols, this method is mandatory.
- Slowing the Shockwave Rate: delivering the shockwaves at a rate of 120 shocks per minute would result in a quicker procedure, but at the expense of tissue safety and stone fragmentation drawbacks. Slowing the rate to 60 or 90 shocks per minute allows time for cavitation bubbles to vanish between shocks. When a subsequent shockwave hits existing cavitation bubbles, the bubbles coalesce and collapse more violently, resulting in more tissue trauma. Studies have proved that slower rates would improve the efficacy of fragmentation and significantly spare the renal parenchyma [16,17].
- Treatment Pauses: pausing the treatment for 3-4 minutes after the first 100-200 low-energy shocks allows the protective vasoconstriction explained above to fully develop before the high-energy mediated renal parenchymal damage commences [16,17].

Pharmacological Reno-Protective Protocols:

While shockwave delivery modifications try to reduce the shockwave induced renal parenchymal trauma, pharmacological interventions aim to mitigate the ischemia reperfusion injury and the associated inflammatory cascade.

Several pharmacological agents have been studied, but only a few have made the way into routine ESWL protocols. Of the commonly studied agents are:

1. Antioxidants: because reactive oxygen species and free radicals released during ESWL play a pivotal role in ESWL induced renal injury, they have been targeted very early. Animal studies have shown a significant reduction in lipid peroxidation biomarkers, tubular damage and long-term fibrosis following pre-treatment with ascorbic acid (Vit C), α-tocopherol (Vit E) or allopurinol [18]. However, the lack of similar human studies and Phase III trials, the routine use of these agents is not part of any modern ESWL protocol.

2. Calcium Channel Blockers: Vasospasm as a core event in ESWL associated renal parenchymal injury have been targeted through the use of calcium channel blockers like verapamil and nifedipine. These agents will at least partially neutralize the vasoconstriction effect of ESWL and maintain a better tissue perfusion, thus limiting both IRI and associated inflammatory response [19].
3. Osmotic Diuretics (Mannitol): intraprocedural infusion of mannitol has a dual protective effect, in one hand it is a potent free radical scavenger, and in the other it reduces cellular edema and improves renal blood flow [20].
4. Statins: the anti-inflammatory and anti-oxidant properties of these lipid-lowering agents made the basis of their use in many non-hyperlipidemia conditions. Recent studies have suggested a significant reduction in tubular injury biomarkers after ESWL therapy in patients who have received a short course of statin therapy before shockwave therapy [21].

Barriers to Routine Implementation

Despite the compelling evidence supporting reno-protective protocols, they are not universally adopted. The barriers are primarily logistical, economic, and cultural.

Reducing the ESWL rate from 120 to 60 shocks per minute will double the treatment time, which in turn will reduce the number of patients treated per day. This reduction is usually resisted by the hospital administration or even the treating clinicians themselves.

Furthermore, implementing pharmacological protocols will add another layer of complexity to the procedure that has been primarily marketed for its non-invasiveness and simplicity.

Lastly, the lack of definitive evidence proving that omitting these protocols leads to long-term clinical harm (hypertension and end-stage renal disease) in the general population provides a justification for maintaining the current status.

Conclusion and Recommendations

As urologists, we are bound by the principle of (first, do no harm). While ESWL remains an essential tool in our armamentarium against urolithiasis, it is not free of side effects. Cavitation and shear stress related mechanical injury, and the following ischemia-reperfusion injury, can result in significant, but often clinically silent, renal parenchymal damage.

Should reno-protective protocols be adopted in routine ESWL protocols? The simple answer (yes). The pathophysiological ground is evident, the preclinical evidence is vigorous, in addition, their efficacy in alleviating ESWL related renal injury has been increasingly supported by clinical studies.

We must shift away from the "one-size-fits-all" approach and implement standardized, evidence-based protective measures. The following minimum standards for modern ESWL can be proposed:

- Mandatory Step-up Protocol: Treatments should commence with low voltage for a minimum of 200-300 shocks to induce protective vasoconstriction, followed by a gradual increase in voltage setting.
- Rate Reduction: The delivery rate of 90 shocks per minute should never be exceed, with 60 shocks per minute being highly advised for a better stone fragmentation and to reduce cavitation trauma.
- Risk Stratification and Pharmacological Adjuvants: Pharmacological agents including intravenous mannitol infusion should be considered for high-risk patients like those with single functioning kidneys, pre-existing renal parenchymal disorders, and children, as well as for patients with recurrent stones that require multiple ESWL treatment sessions.

Urological must prioritize the long-term health of the kidney over the short-term goals and results. Routine adoption of reno-protective protocols is not merely an academic exercise; it is an ethical imperative that aligns the technological capabilities of lithotripsy with the fundamental goals of patient safety.

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Conflict of Interest

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Data availability

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Author Contributions

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The author meets the ICMJE criteria for authorship and agrees to be accountable for all aspects of the work.

ORCID

Noorulhuda Alani	0009-0000-3338-2162
Ahmad Al Sameraaii	0009-0007-5927-4275

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