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**Diuretics use in patients with Acute Renal Failure
and Septic Shock.**

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Abstract

Loop diuretics should be administered in the "de-resuscitative" phase of sepsis, this occurs after the initial resuscitative period during sepsis. The dose of diuretic should be monitored and a continuous infusion of furosemide, which is the most prescribed diuretic, should be no greater than 4mg/min.

There needs to be caution with co-administered nephrotoxic agents such as aminoglycosides, other diuretics, NSAIDS as these increase the toxicity profile. Despite the popular use of loop diuretics in critical care, loop diuretic use in sepsis has not been shown to decrease patients' mortality.

This manuscript aims to discuss the use of diuretics in patients with septic shock exploring the evidence and consensus about the use of this therapy in critically unwell patients.

Introduction

Loop diuretics can be used in critical care to manipulate urine output in patients with hypoperfusion. Loop diuretics benefit the renal medulla during hypoxia by decreasing the tubular energy requirements(1, 2), which makes it a very attractive addition for patients with septic hypoperfusion. A Meta-analysis by K M Ho et al 2006 did not find in reduction in in-hospital mortality, requirement for dialysis, length of stay or number of patients remaining oliguric(3). A positive diuretic response to furosemide may indicate that the patient is in the 'de-resuscitative' phase of sepsis and that renal impairment is less severe. It is also appreciated that patients with non-oliguric renal failure have a lower mortality than patients with oliguric renal failure(4). The timing, duration, and dosing of diuretic therapy, plays a significant role in the morbidity associated with diuretic therapy in sepsis.

Diuretics in critical care; is used as a prophylactic measure that is, to prevent the onset of renal failure; to alleviate renal impairment in patients with established renal compromise or to convert oliguric to non-oliguric renal failure. There was no evidence in the meta-analysis by Ho et al 2006 that there was any benefit in the above listed uses of diuretics(3). There was great heterogeneity between groups in this analysis and most patients had existing renal impairment so that extrapolation to critical care patients with sepsis is problematic.

The goal of transitioning a septic patient from oligemic to non-oligemic renal failure is associated with a decreased mortality trend and diuretic therapy might aid patients with regard to normalizing positive fluid balances (5) but this intervention has associated risks and complications.

Diuretic therapy should be initiated not based on urine output but when the patient has transitioned from the early resuscitative phase to the "de-resuscitative" phase of septic shock. The transit point is determined clinically as the patient is no longer fluid responsive as per passive leg raises or with static/dynamic cardiac output monitoring, is less academic and inotropic support has stabilized or decreased.

Why does this matter?

There are associated side effects when initiating diuretic therapy in critically unwell patients such as ototoxicity, hypernatremia, hypotension and worsening renal function.

OTOTOXICITY

There is changes in the endolymph ionic concentration and fluid composition secondary to the inhibition of the Na-K-2Cl transporter within the stria vascularis of the inner ear(6). Aminoglycoside antibiotics potentiate furosemide ototoxicity, but noise trauma apparently does not. Methods of avoiding ototoxicity are suggested including slow continuous infusion rather than bolus injection, use of divided oral dose regimens, and the measurement of blood levels to avoid exceeding 50 mcg/ml of furosemide(6).

In heart failure patients as outlined by Salvador et al 2005(7), continuous infusions of furosemide resulted in a lower incidence of ototoxicity and fewer side effects. Continuous infusions resulted more than 30% increase in sodium excretion than bolus administration.

The ototoxicity induced by furosemide can be reversible although permanent deafness has been reported. The complication is related to both the peak serum drug concentration and the accumulated dose from continuous infusion and is aggravated with the concurrent use of aminoglycosides or Non-Steroid Anti-Inflammatory Drugs. The maximum recommended infusion dose is 4 mg/min (8).

HYPERNATREMIA

Hypernatremia as outlined by Hai-bin Ni et al 2016(9) was associated with increased mortality whether or not it was associated with diuretic use, this is a common side-effect with liberal diuretic use within the Intensive Care.

Hypernatremia as an independent predictor of mortality regardless of aetiology, speciality and across patients with different ages and co-morbidities (10-14). Risk factors include advancing age, co-existent renal impairment, associated use of nephrotoxic drugs. The phenomenon is poorly understood but correction is based on balancing renal water loss with overcorrection with isotonic solutions versus hypotonic water correction.

It necessities the use of Nasogastric water, naturetics, 5% Dextrose administration, low sodium enteral feeds and re-constituting drugs with 5% Dextrose rather than saline to correct this electrolyte imbalance. These interventions further complicates the management of the critically unwell patient, prevention is of tantamount importance.

WORSENING RENAL FUNCTION

Numerous studies have indicated that there is no benefit in the use of diuretic therapy to improve outcomes

in patients with established acute renal failure in Intensive Care (15, 16). Maeder et al 2012, indicated a trend toward worsening renal function in elderly patients with chronic renal failure within a medical Intensive Care(17). His definition of chronic renal failure was >0.5 mg/dl increase in baseline creatinine over the 6 months follow up, again the findings not only supported renal failure as an independent predictor of mortality, but it was also aggravated by escalating the loop diuretic dose [17].

HOW DO WE ADMINISTER LOOP DIURETICS?

Meta-analyses support the administration of loop diuretics as continuous infusions versus boluses as there is better diuresis at a lower cumulative dose(18), this will inevitably lead to fewer side effects and more efficient fluid balance.

It has been suggested that the infusion dose be limited to 4mg/min to minimize the side effect profile as the loop diuretic has a ceiling effect around this dose [9]. It is also proposed by this author that the diuretic be administered in the 'de-resuscitative' phase of sepsis to manage the patient's overall fluid balance.

The use of diuretics should be for the shortest time possible as there are considerations for electrolyte abnormalities and ototoxicity with a clear focus on serum sodium to gauge the amount of free water loss. While I am not against the administration of loop diuretics in septic patients with acute renal failure the timing of administration of the drug class with the "de-resuscitative phase of sepsis" is vitally important.

DISCUSSION

There is a paucity of evidence supporting the use of loop diuretics in septic critically unwell patients with acute renal failure leading to improved mortality(19, 20). These studies have highlighted increased risk of complications such as electrolyte disturbance without reducing the need for continuous renal replacement therapy or the duration of renal replacement.

Ototoxicity remains an underreported complication as there can be other contributing factors for altered hearing after the critical care episode. This complication will contribute to a patient's post critical care morbidity affecting patient and patient's family quality of life.

The is wide variation with the timing, dose, and indication for diuretic therapy in critical care. Bolus administration, low-dose continuous infusions (20) or high dose titrated to urine output or daily fluid balance are all methods used to administer diuretics. Liborio et al in his observational study of over 14,000 patients found no decreased mortality in critically ill patients with over 60% of

these patient experiencing sepsis with a dose of furosemide up to 80 mg/day(21)

CONCLUSION

The indication and use of diuretics in septic patients with oliguric acute renal failure is varied and confounded by timing and effective dosage. However, there are significant complications associate with the use of diuretics in the critical care population and need serious considerations prior initiation of this therapy as there is no mortality benefit in septic patients with acute kidney injury.

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