ULINASTATIN: CAN IT BE THE NEW THERAPEUTIC OPTION IN AKI ?

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OBJECTIVE

- In critically ill patients with AKI, unacceptably high mortality rates reaching up to 50-80% in all dialyzed ICU patients are seen despite the availability of intensive renal support. At present there is no specific or targeted therapy for AKI. The exact molecular pathophysiology of AKI is complex and also multifactorial.
- Ulinastatin is a multifunctional Kunitz type serine protease inhibitor; it has been shown to exhibit significant renoprotective effects in various models of mechanical and chemical injury.Our premise regarding the use of molecule in AKI was based on the fact that this molecule acts at multiple levels in the sepsis and can act to stop the cascade and thereby stop the “storm”.
- The aim of our study, done in a semi urban nephrology set up, was to find out if using ulinastatin in patients with AKI has any beneficial result on the outcomes in patients with AKI. Ours is a retrospective comparative study done in patients with AKI who were critically ill.

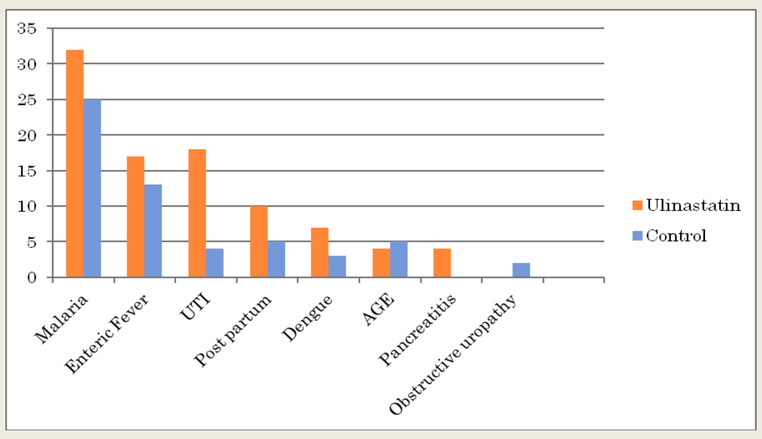
METHODS

- We studied a total of 150 patients with AKI who needed ICU care in our hospital in the period between May 2012- Dec 2014. Out of these, 75 patients received Injection ulinastatin 3 doses a day for 5 days, against a similar number of control patients. We included those patients with AKI who had SOFA scores more than 8.
- We recorded the age of the patients, it varied from 11-94 years (mean age 52 years), > 60 %(92) of the patients being in the age group of 26-40 years. The ratio of males to females 1.8:1 (M: F 98:52).
- The etiologies were as follows:
- Malaria – complicated – P vivax, P falciparum (n= 57) 38%
- Enteric fever (n= 30) 20%
- UTI (n=22) 15%
- Post partum (n=15) 10%
- Dengue (n = 10) 7%
- Acute gastroenteritis/diarrhoeal diseases (n= 9) 6%
- Pancreatitis (n= 4) 2.9%
- Obstructive uropathy (n= 2) 1.3%
- 33 %(n= 50) patients had diabetes as a co morbid condition.
- The renal function tests of all the patients were recorded .The liver function tests, sepsis parameters like d-dimer, serum procalcitonin levels, CRP-hs levels, coagulation tests, complete blood counts, and arterial blood gas analysis were done apart from the routine tests.
- We recorded the length of stay, need and duration of renal replacement therapy, time to stoppage of renal replacement therapy, need for mechanical ventilation, mortality and post AKI recovery and progression to CKD.

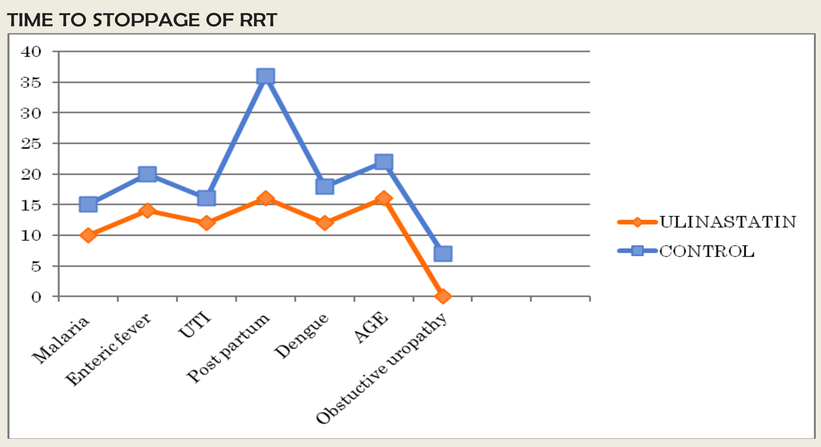
RESULTS:

- We compared the same number of patients who had received ulinastatin with controls.Injection ulinastatin 1,00,000IU was given three times a day for 5 days.All the patients included had received dialytic therapy.
- The patients who received ulinastatin had a shorter stay in the ICU ($p < 0.01$ vs control group); also the time to stoppage of renal replacement therapy was shorter ($p < 0.05$). The recovery to renal function was seen in 84% (n=80). The progression to CKD was seen in 11% (n=17; 10 in control group), of patients .The average number of sittings of dialysis needed were 11 (range3-20), less number of dialysis were needed in the ulinastatin group .The overall mortality was 36 %(n=54).

THE PATIENT POOL



TIME TO STOPPAGE OF RRT



DISCUSSION:

- Ulinastatin is an immunomodulator currently being used for pancreatitis. It has been found to inhibit various serine protease inhibitors and is found in human urine and blood and produced by hepatocytes.
- The molecular pathophysiology of sepsis includes numerous factors such as intrarenal hemodynamic changes, endothelial dysfunction, intraglomerular thrombosis obstruction of tubules with necrotic cells and debris and infiltration of kidneys by inflammatory cells.[4] Ulinastatin inhibits various serine proteases and inhibits inflammation by suppressing the infiltration of neutrophils and release of inflammatory mediators. It also inhibits production of various interleukins.[5] Also it inhibits production of various interleukins. Hence it can be believed to quell the “*cytokine storm*” that is at the centre of pathogenesis and progression of AKI.
- There have been different studies done in various animal models to elucidate the renal protective mechanisms of action of ulinastatin. Ischemia reperfusion injury is a part of the pathogenetic effect in AKI. Chen et al [6] in their study found ulinastatin reduced the renal dysfunction and injury associated with ischemia reperfusion of the kidney .The protective effect might be associated with the upregulation of Bcl-2 expression and the effect on membrane fragility. In another animal study, ulinastatin was found to attenuate renal interstitial inflammation and inhibit fibrosis progression in rats under unilateral ureteral obstruction [7].
- In yet another study of sepsis in CLP rats, ulinastatin improved the survival of rats ,attenuated proinflammatory response and prevented systemic disorder and organ dysfunction .The molecular mechanism investigation showed that ulinastatin’s protection was possibly related to the down regulation of NF-kB activity and inhibition of TNF- α,IL-6 and elastase expression in the tissues[8]
- Ulinastatin has been found to ameliorate AKI following liver transplant. The levels of tumor necrosis factor –α , interleukin -6 ,hydrogen peroxide and reactive oxygen species were reduced in the corresponding animal model ,while level of super oxide dismutase was increased in the ulinastatin group[9] Ulinastatin has been shown to exhibit significant renoprotective effects in other models of mechanical and chemical renal injury as well[10,11,12,13]
- Therefore ulinastatin can be of benefit in patients having AKI/MODS. Ulinastatin inhibits the action of inflammatory mediators and hence can halt the progression of clinical symptoms and signs of sepsis /MODS. The major chunk of our patients had AKI due to infective etiologies. Since all the patients needed ICU care, sepsis/MODS was the common factor in all. In this study, we found that those patients who received ulinastatin did better on almost all the parameters of comparison .Lesser number of patients progressed to CKD and also ulinastatin group needed less dialysis as well .There are hardly any human studies about use of ulinastatin in AKI .Various immunomodulators ,immune factors ,immune stimulators have been proposed as possible agents that can be of use in sepsis, but there is no definite agent that can alter the pathophysiology of AKI especially in septic patients .This is where ulinaststin can be of help. Every single additional day spent in ICU and added sittings of RRT add up to the financial burden of treatment and India being a country where penetration of medical insurance is poor, any treatment that can shorten the stay and improve the outcomes is worth looking at.

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