Ulinastatin : A review

Deepak Jeswani[1]

ABSTRACT

Ulinastatin (UTI), a serine protease inhibitor which inhibits trypsin, chymotrypsin, neutrophil elastase and plasmin. This property of inhibition of multiple proteases has been studies for prevention of organ injury. UTI has been evaluated in various studies for prevention of organ dysfunction and other clinical outcomes in sepsis / septic shock, cardiac surgeries and prevention of acute pancreatitis. In this article, we reviewed the clinical utility of UTI in various conditions in prevention of organ injury and clinical outcomes.

Introduction

Ulinastatin (UTI), a urinary trypsin inhibitor, is a serine protease inhibitor isolated from human urine and blood[1]. UTI inhibits trypsin, chymotrypsin, neutrophil elastase and plasmin[2]. Inhibitory activity exerted by UTI in multiple proteases is the major mechanism for preventing organ injury induced these proteases[3,4]. Additionally, by virtue of inhibition of neutrophil infiltration and release of inflammatory cytokines, UTI exhibits the anti-inflammatory activity[5]. These properties have been explored in multiple conditions. It is being considered as one of the rescue treatment option for endotoxin-related inflammatory disorders such as DIC, acute lung injury and acute liver injury[5,6]. Further, inflammatory response is at the core of the sepsis associated organ injury like renal failure or cardiac dysfunction wherein UTI has shown promise in improving the outcomes[7]. Additionally, utility of UTI has been identified in various surgeries including cardiac surgeries to provide organ protective benefits in post-surgical period[8,9]. As it is being assessed in multitude of conditions, here we reviewed the current evidence on utility of Ulinastatin in various conditions.

Ulinastatin

Mechanism of action

[1]Medical Director,
Criti Care Hospital & Research Institute, Nagpur

Address for Correspondence -
Dr. Deepak Jeswani
E-mail : deepakjeswani2@yahoo.co.in

Received on 7th May 2019 Accepted on 20th May 2019

Chemically, UTI (also known as bikunin, urinastatin) is a glycoprotein and has molecular weight of 30 kDa. It is a multivalent Kunitz-type acid-resistant serine protease inhibitor consisting of 143 amino acid residues. It is found inhuman urine and blood[5]. Neutrophilic elastase mediated degradation of inter- -trypsin inhibitors results in secretion of UTI. Trypsin associated proteolytic action on various organs is inhibited by trypsin inhibitors resulting in local anti-inflammatory effects. UTI inhibits numerous serine proteases including trypsin, chymotrypsin, kallikrein, neutrophilelastase, plasmin, cathepsin, thrombin, and factors IXa, Xa, Xia, and XIIa[10]. This results in diminished pro-inflammatory cytokines (e.g. IL-6 and IL-8) secretion during inflammatory response[11]. It is also found to down regulate stimulated arachidonic acid metabolism (e.g. production of thromboxane B2). This metabolic pathway is critical in pathogenesis of sepsis related systemic syndrome. Thus, UTI by modulating TNF- production (in lieu of inhibition of early growth response factor in monocytes) helps in reducing lipopolysaccharide-induced hypotension which might indirect lycontribute to lower mortality in sepsis[12]. Additionally, anti-metastatic properties have been identified with UTI. By inhibition of protein kinase C, UTI suppresses urokinase-type plasminogen activator expression. It further inhibits cell-bound plasmin and cathepsin B activity which are implicated in tumor cell proliferation and progression contributing to anti-metastatic activity[13]. Further, rise of endogenous nitric oxide, inhibition of TNF expression, and lowering of

oxygen free radicals exerts myocardial protective effects. Thus it can be a potential therapeutic option in ischemic reperfusion injuries[12].

Pharmacokinetics / pharmacodynamics

A pharmacokinetic (PK) study in healthy male volunteers, a linear increment in blood concentration over 3 hours was reported after intravenous injection of 300,000 I.U. / 10 mL of UTI. During this period, half-life of observed for UTI was about 33 min during the first 0-3 h and the same was 2 hours during the following 4 hours[13,14]. Distribution of UTI throughout the body was seen in PK evaluation in animals and was observed to be retained over long duration in the joint tissues. After 6-hours, 24% of UTI was recovered in urine[13,15]. In severe acute diseases like septic shock and circulatory failure, the dose of UTI required to achieve therapeutic concentrations are much higher. To determine the safety of high-dose, a PK study enrolled 51 healthy Chinese subjects. In total 9 dose cohorts (3×10^5 U, 6×10^5 U, 12×10^5 U, 20×10^5 U, 30×10^5 U, 45×10^5 U,60×10^5 U, 70×10^5 U, or 80×10^5 U) of UTI, and randomized to UTI or matching placebo (n = 1). In 10 subjects, total 11 and 2 adverse events (AEs) were reported in the UTI and placebo groups respectively. Dizziness, pain at injection site, and a decrease in white blood cell count were common AEs reported which were mild in severity. Study observation concluded that 2 hours of intravenous infusion of UTI over wide dose range from 3×10^5 to 80×10^5 U was well tolerated[16].

Clinical evidence in various indications

Sepsis

A hyperinflammatory state commonly known as systemic inflammatory response syndrome (SIRS) develops in patients with sepsis which is characterised by enhanced expression of adhesion molecules on monocytes and neutrophilsand endothelial cells. This culminates into accumulation of neutrophils and monocytes in various organs. With release of inflammatory mediators from these cells and accompanied complement activation result in organ damage and further the multi-organ dysfunction in severe sepsis[17,18]. Thus, by targeting reduction of pro-inflammatory mediators or by restoring the disordered immune responses (adaptive & innate), sepsis associated complications may be diminished[19]. Multiple studies have evaluated ulinastatin in patients with sepsis and septic shock. A multicentre randomized study from India reported that ulinastatin (200,000 IU, twice daily for 5 days) was associated with significantly lower mortality (7.3 vs. 20.3%, P = 0.042) than placebo. Among the non-survivors, 25% of the deaths in the ulinastatin group compared to 42 % in the placebo group were judged related to ARDS. Further, a lower frequency of new organ dysfunction and shorter durations of mechanical ventilation and hospital stay compared to placebo was reported[20]. A systematic review of RCTs of ulinastatin in sepsis identified 7 studies and reported that UTI is associated with benefits of significant improvement in inflammatory markers and, toa lesser extent, in organ dysfunction. All 7 studies were associated with lower 28-day mortality with UTI. However, the majority of patients form these RCTs received thymosin- 1in combination. Thus, the conclusions drawn were considered elusive raising questions about the independent the rapeuticpotency of UTI[21]. A recent study from Xu et al. suggest lower 28-day mortality rate with UTI than control (31% vs. 55%; p < 0.001). In multivariable model, the adjusted odds ratio for UTI was 0.304 (95% CI: 0.152 to 0.592; p = 0.001). Further, mediation analysis performed in this study showed that the use of UTI was able to reduce the probability of death by 23.5%. It was also observed that 35% of the total effect of UTI was to be explained with the reduction in C-reactive protein but keeping question unanswered about the direct 65% of the anti-inflammatory effect of UTI[22]. In lieu conflicting results from previous studies with UTI alone or in combination with thymosin 1, findings of a recent meta-analysis of 12 RCTs suggest that the combination of both drugs is associated with lower 28-day (risk ratio (RR) 0.67; 95% confidence interval [CI], 0.570.80; p < 0.00001) and 90-day mortality (RR, 0.75; 95% CI, 0.610.93; p = 0.009) mortality. But, no significant difference in the 28-day mortality (RR, 0.60; 95% CI, 0.301.20; p = 0.15) was found with UTI alone whereas thymosin 1

alone reduced the 28-day mortality (RR, 0.72; 95% CI, 0.550.93; p = 0.01). Metanalysis further identified that intensive care unit stay, mechanical ventilation, antibiotics and vasopressor use, and 28-day APACHE II scores with UTI / thymosin 1 alone or in combination are unclear[23]. Therefore, there is a need of large scale RCT to accept or refute the potential use of UTI alone in sepsis.

Acute Pancreatitis

Since past three to four decades, endoscopic retrograde cholangio-pancreatography (ERCP) is in use for evaluation of pancreatic and biliary disorders. However, post-procedural complications like pancreatitis, cholangitis, perforation, and bleeding should not be overlooked. Post-ERCP pancreatitis (PEP) is common and incidence may range from 1 to 10% and to 30% in high-risk cases[24,25]. Preventive strategies are adopted during ERCP to reduce risk of pancreatitis. UTI is used in many studies for prevention of PEP. However, inconsistent results in studies are seen with some having benefits[26] and other showing no benefits with UTI[24]. A metanalysis to address this question from Zhu et al. found that prophylactic administration of UTI before or during the ERCP significantly reduced the PEP risk (RR=0.49; 95% CI: 0.33-0.74; P=0.0006). Interestingly, the risk reduction observed only in patients with low or average risk for PEP and with use of high-dosage ulinastatin (150,000 or 200,000 U). Prophylactic UTI also significantly reduced the post-ERCP hyperamylasaemia risk (RR=0.68; 95% CI: 0.56-0.83; P=0.0001; I2=19) and marginally reduced the incidence of post-ERCP abdominal pain (RR=0.67; 95% CI: 0.45-1.00; P=0.05; I2=67)[27]. This suggests that there is still lacuna of clinical evidence to establish the therapeutic efficacy of UTI in prevention of PEP especially in high-risk patients necessitating future research to be focused on this issue. Further, recent studies indicate that in patients with severe acute pancreatitis in ICU, use of UTI was associated with lower hospital mortality, resolution of existing and prevention of new-onset of organ dysfunction and thus the complications associated with acute pancreatitis[28,29].

Postoperative Outcomes in Cardiac Surgery

Cardiopulmonary bypass during cardiac surgery leads to activation of leukocytes resulting in a systemic inflammatory response[30]. Such response is linked to development of various complications like myocardial dysfunction, acute lung injury and multiorgan dysfunction[31,32]. The property of UTI to inhibit inflammatory response and prevent tissue injury in patients undergoing cardiac surgeries have been evaluated in multiple small studies. Including such 15 RCTs involving 509 patients treated with UTI, He et al. in their meta-analysis observed that UTI had no effect on hospital mortality, postoperative complication rate, or length of stay in ICU. However, it was associated with decreased time for extubation, increased oxygenation index on day 1 post-operatively and decreased the plasma level of cardiac troponin-I. Further, UTI inhibited the increase in the levels ofinflammatory markers like TNF-alpha, polymorphonuclear neutrophil elastase (PMNE), IL-6, and IL-8[33]. Though results on clinical outcomes are not found favourable in this meta-analysis, recent studies have demonstrated that UTI is associated with a lower risk of acute kidney injury (AKI) in patients undergoing cardiopulmonary bypass surgery. A propensity score matched retrospective study involving 409 patients treated with UTI and equal number of controls undergoing cardiac surgery reported higher incidence of AKI (40.83 % vs. 30.32 %, P?=?0.002) and the need for renal replacement therapy (2.44 % vs. 0.49 %, P?=?0.02) in the control than in the UTI group[34]. A multivariate analysis from another study identified that UTI use was associated with a reduced incidence of AKI (OR 0.694, 95% CI 0.557-0.881, p=0.006) in patients undergoing CABG[35]. Another metanalysis of 15 RCTs reported that UTI administration was associated with a significant reduction in TNF- , IL-6, IL-8, and PMNE levels at 6?h and 24?h after UTI treatment and an increase in IL-10 levels.Reduction in respiratory index and an improvement in the oxygenation index was also identified suggesting potential utility of UTI in reducing pulmonary injury and improving pulmonary function after CABG[36]. Thus, there is need of further exploration on beneficial effect of

UTI in prospective, large, RCTs in reducing AKI and other clinical outcomes including mortality in patients undergoing cardiac surgeries like CABG.

Other conditions

Liver transplantation

Studies have reported that administration of UTI in patients with orthotopic liver transplantation is associated with lower incidence of AKI and acute lung injury[37,38].

Ischemia-reperfusion injury

Results from multiple experimental studies suggest that UTI ameliorates the ischemia / reperfusion injury[39,40,41]. Clinical studies are awaited to confirm the results from animal studies.

Orthopaedic surgeries

Use of preoperative UTI was found to reduce the blood loss in early postoperative period in patients undergoing major orthopaedic surgery[42]. Further, in combination with rivaroxaban, continuous infusion of UTI in postoperative period was associated with no increment in levels of thrombomodulin, IL-6, thrombin-antithrombin complex and D-Dimer compared to control or single injection UTI group. This suggests along with rivaroxaban, UTI affects correct blood hypercoagulability in major orthopaedic surgerieswhich may help in prevention of deep vein thrombosis[43].

Multi-organ dysfunction in the ICU

A retrospective observational study in a single center ICU study from Japan reported that in multivariable logistic regression analysis, UTI was not associated with lower 28-day mortality (odds ratio (OR) 1.22; 95% CI, 0.542.79) in elderly patients with multi-organ dysfunction. Similar result was seen in patients with sepsis (OR 1.92; 95% CI, 0.527.13). However, ICU-free days and ventilator-free days was significantly fewer in the ulinastatin compared to control[44].

Conclusion :

Ulinastatin, a serine protease inhibitor, has been evaluated in multitude of indications associated with inflammation induced organ injuries. Its utility in sepsis associated inflammatory response and organ injuries, in prevention acute pancreatitis especially post-ERCP pancreatitis and organ dysfunction after cardiac surgery has been well studies in various RCTs. But, evidence from studies and meta-analyses demand careful evaluation of utility of UTI in each of these indications large, prospective RCTs to confirm the observations form these small studies. Nonetheless, it has potential to reduce inflammatory response and the organ injury associated with SIRS which can translate in to benefits of prevention of organ dysfunction. Thus, use of UTI in patients at high-risk of SIRS can translate in potential benefits of prevention of organ injury or multi-organ failure.

References :

1. 1. Jonsson-Berling BM, Ohlsson K,Rosengren M. Radioimmunologicalquantitation of the urinary trypsin inhibitorin normal blood and urine.Biol Chem Hoppe Seyler. 1989;370:1157-61
2. Nishiyama T, Aibiki M, Hanaoka K. The effect of ulinastatin, a human proteaseinhibitor, on the transfusion induced increase of plasma polymorphonucleargranulocyte elastase. Anesth Analg 1996;82:108-12
3. Ohnishi H, Kosuzume H, Ashida Y, et al. Effects of urinary trypsin inhibitoron pancreatic enzymes and experiment alacute pancreatitis. Dig Dis Sci1984;29:26-32
4. Okabe H, Irita K, Kurosawa K, et al. Increase in the plasma concentration of reduced glutathione observed in rats with liver damage induced by lipopolysaccharide/D-galactosamine: effects of ulinastatin, a urinary trypsin inhibitor. Circ Shock 1993;41:268-72.
5. Inoue K, Takano H. Urinarytrypsin inhibitor as a therapeutic option for endotoxin-related inflammatory disorders. Expert OpinInvestig Drugs 2010; 19:513520.
6. Inoue K, Takano H. Urinary Trypsin Inhibitor, an Alternative Therapeutic Option for Inflammatory Disorders, Inflammatory Diseases - A Modern Perspective, Dr. Amit Nagal (Ed.), ISBN: 978-953-307-444-3, InTech, 2011. Available from : http://www.intechopen.com/books/inflammatory-diseases-a-modernperspective/urinary-trypsin-inhibitor-an-alternative-therapeutic-option-for-inflammatory-disorders
7. Feng Z, Shi Q, Fan Y, Wang Q, Yin W. Ulinastatin and/or thymosin 1 for severe sepsis : A systematic review and meta analysis. J Trauma Acute Care Surg. 2016; 80:335-340.
8. He QL, Zhong F, Ye F, Wei M, Liu WF, Li MN, et al. Does intraoperative ulinastatin improve postoperative clinical outcomes in patients undergoing cardiac surgery: a meta-analysis of randomized controlled trials. BioMed research international. 2014;Article ID 630835.
9. Lv ZT, Huang JM, Zhang JM, Zhang JM, Guo JF, Chen AM. Effect of ulinastatin in the treatment of postperative cognitive dysfunction: review of current literature. BioMed research international. 2016;Article ID 2571080.
10. Pugia MJ, Valdes R Jr, Jortani SA. Bikunin (urinary trypsin inhibitor) : structure, biological relevance and measurement. Adv ClinChem 2007;44:223-45.

11. Han JI. Urinary trypsin inhibitor : miraculous medicine in manysurgical situations? Korean J Anesthesiol2010;58:325-7.
12. Xu CE, Zhang MY, Zou CW, Guo L. Evaluation of the pharmacological function of ulinastatin in experimental animals. Molecules. 2012;17:9070-80.
13. Ulinastatin for injection. U-TrypTM. Available at: https://www.bharatserums.com/product/critical/U-Tryp %20 (Liquid) %20 Common %20 Pack %20 Insert %20 for %20 Domestic.pdf Accessed: 04 April 2019.
14. Jonsson-Berling BM, Ohisson K. Distribution and elimination ofintravenously injected urinary trypsin inhibitor. Scan J Clin LabInvest 1991;51:549-57.
15. Yanez JA, Remsberg CM, Sayre CL, Forrest ML, Davies NM. Flip-flop pharmacokinetics : delivering a reversal of disposition : challenges and opportunities during drug development. Ther Deliv 2011;2:643-72.
16. Chen Q, Hu C, Liu Y, Liu Y, Wang W, Zheng H, et al. (2017) Safety and tolerability ofhigh-dose ulinastatin after 2-hour intravenousinfusion in adult healthy Chinese volunteers: Arandomized, double-blind, placebo-controlled,ascending-dose study. PLoS ONE 12(5):e0177425.
17. Ward PA. The harmful role of C5a on innate immunity in sepsis. J Innate Immun. 2010; 2:439-445.
18. Andrades M, et al. Bench-to-bedside review : Sepsis - from the redox point of view. Critical Care.2011; 15:230.
19. Bosmann M, Ward PA. The inflammatory response in sepsis. Trends Immunol. 2013;34:129-36.
20. Karnad DR, Bhadade R, Verma PK, et al. Intravenous administration of ulinastatin (human urinary trypsin inhibitor) in severe sepsis: a multicenter randomized controlled study. Intensive Care Med. 2014;40(6):830-838.
21. Linder A, Russel JA. An exciting candidate therapy for sepsis : ulinastatin, a urinary protease inhibitor. Intensive Care Med. 2014; 40:1164-1167.
22. Xu Q, Yan Q, Chen S. Ulinastatin is effective in reducing mortality for critically ill patients with sepsis : a causal mediation analysis.Scientific Reports. 2018; 8:14360.
23. FenZ, Shi Q, Fan Y, Wang Q. Ulinastatin and/or thymosin > 1 for severe sepsis: A systematic review and meta-analysis. J Trauma Acute Care Surg. 2016; 80:335-40.
24. Yuhara H, Ogawa M, Kawaguchi Y, Igarashi M, Shimosegawa T and Mine T. Pharmacologic prophylaxis of post-endoscopic retrograde cholangiopancreatography pancreatitis : Protease inhibitors and NSAIDs in a meta-analysis. J Gastroenterol 2014; 49: 388-399.
25. Yu G, Li S, Wan R, Wang X and Hu G .Nafamostatmesilate for prevention of post-ERCP pancreatitis: A meta-analysis of prospective, randomized, controlled trials. Pancreas2015 44:561-569.
26. 3. Chen S, Shi H, Zou X and Luo H. Role of ulinastatin in preventing post-endoscopic retrograde cholangiopancreatography pancreatitis: The emperor's new clothes or aladdin's magic lamp? Pancreas 2010; 39:1231-1237.
27. Zhu K, Wang J-P, Su J-G. Prophylactic ulinastatin administration for preventing post-endoscopic retrograde cholangiopancreatography pancreatitis: A meta-analysis. Experimental and Therapeutic Medicine 2017; 14:3036-3056.
28. Lagoo JY, D'Souza MC, Kartha A, Kutappa AM. Role of Ulinastatin, a trypsininhibitor, in severe acute pancreatitis in critical care setting: A retrospective analysis. J Crit Care. 2018;45:27-32.
29. Guo H, Chen J, Suo D. [Clinical efficacy and safety of ulinastatin plusoctreotide for patients with severe acute pancreatitis]. Zhonghua Yi Xue Za Zhi. 2015;95:1471-4.
30. Paparella D, Yau TM, Young E. Cardiopulmonary bypass induced inflammation: pathophysiology and treatment. An update. European Journal of Cardio-Thoracic Surgery, 2002; 21:232-44.
31. Munger MA, Johnson B, Amber IJ, Callahan KS, Gilbert EM. Circulating concentrations of proinflammatory cytokines in mild or moderate heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. The American journal of cardiology. 1996;77:723-7.
32. Holmes Iv JH, Connolly NC, Paull DL, Hill ME, Guyton SW, Ziegler SF, et al. Magnitude of the inflammatory response to cardiopulmonary bypass and its relation to adverse clinical outcomes. Inflammation Research. 2002;51:579-86.
33. He QL, Zhong F, Ye F, Wei M, Liu WF, Li MN, et al. Does intraoperative ulinastatin improve postoperative clinical outcomes in patients undergoing cardiac surgery: a meta-analysis of randomized controlled trials. BioMed research international. 2014;Article ID 630835.
34. Wan X, Xie X, Gendoo Y, Chen X, Ji X, Cao C. Ulinastatin administration is associated with a lower incidence of acute kidney injury after cardiac surgery: a propensity score matched study. Critical Care. 2016;20:42.
35. Xie X, Wan X, Ji X, Chen X, Liu J, Chen W, et al. Reassessment of acute kidney injury after cardiac surgery: a retrospective study. Internal Medicine. 2017;56:275-82.
36. He G, Li Q, Li W, Ruan Y, Xiong X, Song X, et al. Effect of ulinastatin on interleukins and pulmonary function in bypass patients: a meta-analysis of randomized controlled trials.Herz. 2018:1-2.
37. Li X, Li X, Chi X, Luo G, Yuan D, Sun G, et al. Ulinastatin ameliorates acute kidney injury following liver transplantation in rats and humans. Experimental and therapeutic medicine. 2015;9:411-6.
38. Luo GJ, Yao WF, He Y, Luo CF, Li XY, Hei ZQ. Ulinastatin prevents acute lung injury led by liver transplantation. journal of surgical research. 2015;193:841-8.
39. Okuhama Y, Shiraishi M, Higa T, Tomori H, Taira K, Mamadi T, et al. Protective effects of ulinastatin against ischemiareperfusion injury. Journal of Surgical Research. 1999;82:34-
40. Cao ZL, Okazaki Y, Naito K, Ueno T, Natsuaki M, Itoh T. Ulinastatin attenuates reperfusion injury in the isolated blood-perfused rabbit heart. The Annals of thoracic surgery. 2000;69:1121-6.
41. Ren B, Wu H, Zhu J, Li D, Shen Y, Ying R, et al. Ulinastatin attenuates lung ischemia-reperfusion injury in rats by inhibiting tumor necrosis factor alpha. Transplantation Proceedings2006 38:2777-9.
42. Lee JY, Lee JY, Chon JY, Moon HS, Hong SJ. The effect of ulinastatin on hemostasis in major orthopedic surgery. Korean J Anesthesiol. 2010;58:25-30.
43. Yu X, Tian Y, Wang K, Wang YL, Lv GY, Tian GG. Effect of ulinastatin combined rivaroxaban on deep vein thrombosis in major orthopedic surgery. Asian Pacific journal of tropical medicine. 2014 Nov 1;7(11):918-21.
44. Uchida M, Abe T, Ono K, Tamiya N. Ulinastatin did not reduce mortality in elderly multiple organ failure patients: a retrospective observational study in a single center ICU. Acute Med Surg. 2017;5:90-97.