Editorial

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Urinary trypsin inhibitor: miraculous medicine in many surgical situations?

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Recently, we encounter several articles regarding urinary trypsin inhibitor (UTI) published nationally [1,2]. When we take a glance at these articles, it feels like UTI acts as a miraculous medicine on patients under general anesthesia because of its protection effect against surgical stress. Yet, even after the first report on antitryptic action of urine by Bauer and Reich III in 1909 [3]; the start of use of the term UTI by Astrup and Sterndorff in 1955 [4]; and numerous animal experiments and clinical research done about UTI (803 articles about UTI and 982 articles about ulinastatin in SCOPUS), UTI is not yet to be used commonly. Therefore, it is important to understand the reason behind this situation. According to the webpage of Nextbio, it records that "currently, the drug is being used for research purpose only."

UTI is a glycoprotein stable in both heat and acids derived from human urine, and is a serine protease inhibitor found in human urine or blood. UTI is secreted when inter-α-trypsin inhibitors are degraded by neutrophilic elastase [5]. UTI is found to have many physiologic effects, including the inhibition of neutrophilic elastase, trypsin, α-chymotrypsin, plasmin, and cathepsin G. It has been known for a long time [3] and called ulinastatin, mingin, human inhibitor 30, serpin, miraclid, urinastatin (in japanese literature) and bikunin [6]. It has been reported that, in human, the plasma half-life of UTI is 33 min [7]. Currenlty, there are three pharmaceutical companies in Korea that produce UTI: Ulistin®, Han Lim Pharmaceutical, Ustatin®, Kolon Pharmaceutical, Statin®, Yu Young Pharmaceutical. These three companies produce two types of UTI, which is 50,000 IU (9,962−14,650 won) and 100,000 IU (14,926−21,950 won).

Trypsin inhibitors act to suppress the proteolytic action of trypsin on a variety of tissues and exert a localized anti-inflammatory effect [8]. Therefore UTI is indicated for acute inflammatory disorders, including acute pancreatitis, systemic inflammatory reaction syndrome, circulatory insufficiency, Stevens-Johnson syndrome, Toxic epidermal necrolysis (TEN), disseminated intravascular coagulation (DIC) and multiple organ failure [9]. Previous studies of UTI have focused mainly on modulating inflammatory reaction. UTI attenuates the elevation of neutrophil elastase release, thereby blunting the rise of pro-inflammatory cytokine level; however, the actual mechanism in vivo is not clear [10]. In twenty years, lately, there has been an increase in the number of reports that UTI inhibits secretion of cytokines (IL-6 and IL-8) regarding inflammation. Regardless of such fact, there was an additional report in this issue on how UTI influences cytokine reactions during gastrectomy [1]. This addition of one more report maybe because of the fact that UTI's clinical usage is yet limited and the usage has not been standardized for the real practice. In this issue of KJA, Park and co-workers [1] reported that 100,000 U of UTI infusion during gastrectomy inhibited the secretion of IL-6, which is an inflammatory cytokine produced after operation. They showed that UTI could decrease the inflammatory reaction caused by surgical stress.

In addition to UTI's effect on inflammation, there has been a lot of studies of influence of UTI on shock. In 1985, Ohnishi et al. [11] proved that UTI lowers the elevated enzyme activities in the serum during shock so that UTI has protective effect against shock in his animal experiment. There also has been

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a study that UTI is effective in maintaining microcirculation during hemodilution and hypothermia [12]. UTI's anti-shock effect was as effective as that of methyl prednisolone (MPS); both substances showed similar effects in endotoxin-induced shock animal experiments [13]. MPS showed effect when after the shock occurred, whereas UTI showed effect when injected prophylactically [14]. Recently, there was a clinical research that the combined usage of UTI and Thymosin alpha1 (Talph1) increased the survival rate of sever sepsis patients [15-17], which proves UTI's usefulness as a potential medicine.

A study about the hemostatic effects of ulinastatin in clinical practice was demonstrated in our journal three months ago [2]. Lee et al. [2] concluded that a single infusion of ulinastatin during major orthopedic surgery reduces blood loss in the early postoperative period. UTI inhibit proinflammatory cytokine release, reduce reperfusion lung injury and preserve pulmonary function but it failed to inhibit platelet activation and to prevent blood loss during CPB [18].

There were studies about UTI's effect on liver, lung, heart, small intestine, pancreas, uterine muscle etc. UTI is important in liver regeneration [19], can protect against sever liver injury [20], and decreases reperfusion injury after hepatic ischemia [21]. High dose of UTI inhibits pulmonary fibrosis by decreasing inflammatory response in lungs [22] and also has protective effect against ischemia/reperfusion injury in lungs. Also, the cardioprotective effect decreases the infarct size in patients with the regional myocardial I/R injury [23]. When UTI is used preventively, pancreatitis occurring frequencies decrease and, through the regulation of intracellular calcium, UTI suppresses the uterine muscle contraction. It furthermore suppresses activity of plasminogen activator, which leads to improvements in joint pain and range of motion in osteoarthritis patients [24].

Saitoh reported contents regarding anesthetic drugs in UTI studies; in neuromuscular junctions, protease inhibitor homologs release acetylcholine which results in delay of onset of neuromuscular block by vecuronium and accelerates the recovery [25]. Mastumoto explained that UTI increases the blood flow in liver [26], so it promotes hepatic elimination of vecuronium and increases urine volume [27]. Because UTI may increase hepatic and/or renal clearance of vecuronium, recovery of vecuronium-induced neuromuscular block would be quickened.

As shown above, UTI will be useful if its various effects are proven clinically and its dose and ways usage are standardized accurately. When used in case of general anesthesia in high-risk patients, UTI can better the microcirculation during circulatory insufficiency which can potentially occur during the operation; therefore, UTI can better the perfusion for main organs and decrease the inflammatory response so that post-surgical progress can be improved, pain be reduced, and mobidity be reduced also. However, UTI's effect on skeletal muscle relaxants used in general anesthesia should be considered. Also due to its comparative high cost, we should avoid reckless and indiscrete usage.

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