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A preliminary study of the effects of ulinastatin on early postoperative cognition function in patients undergoing abdominal surgery

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HIGHLIGHTS

- IL-6 and S100β increased after abdominal surgery in elderly patients.
- Ulinastatin reduced the incidence of POCD.
- Ulinastatin decreased S100β and IL-6 level.
- Ulinastatin may prevent the occurrence of POCD by inhibiting the release of IL-6.

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ABSTRACT

Purpose: Ulinastatin, a urinary trypsin inhibitor, is widely used to treat acute systemic inflammatory disorders. However, its effects on early postoperative cognitive function have not been fully elucidated. The objective of this study was to investigate the effect of ulinastatin on serum IL-6, TNF-α, CRP and S100β protein concentration and early postoperative cognitive function in patients after abdominal surgery.
Methods: Eighty ASAI-II patients older than 65 years, scheduled for elective abdominal surgery were randomly divided into 2 groups ($n = 40$ each): ulinastatin and control. After induction of anesthesia, the ulinastatin group received 10,000 units/kg of ulinastatin intravenously before surgical incision and 5000 units/kg on post-op days 1–3. Cognitive function was assessed preoperatively and on post-op day 7 using a battery of nine neuropsychological tests. Serum IL-6, TNF-α, CRP and S100β protein levels were determined preoperatively, at the end of surgery and on post-op days 1–3.
Results: There were significant decrements in each neuropsychological test, except for the Digit Span Backward Test between groups. Based on neuropsychological testing, the ulinastatin group had a lower incidence of postoperative cognitive dysfunction (POCD) than the control group (2.5% versus 27.5%, $p < 0.05$). In the control group, serum S100β protein and IL-6 concentrations increased at the end of surgery and on post-op days 1 and 2. The ulinastatin group had lower serum S100β protein and IL-6 concentrations than those in the control group ($p < 0.05$).
Conclusion: Ulinastatin may be effective in reducing the incidence of early postoperative cognitive dysfunction.

1. Introduction

Ulinastatin is a multivalent Kunitz-type serine protease inhibitor found in human urine and serum that inhibits the activation of human leukocyte elastase. It has been widely used in patients with inflammatory disorders, including shock and pancreatitis. It suppresses human leukocyte elasetase activity and inhibits the production of proinflammatory cytokines such as TNF-α and IL-6. Animal studies [3,1] demonstrate that cytokines such as IL-1β and IL-6 are involved in cognitive dysfunction. Simultaneously, emerging evidence indicates that the inflammatory response represents a potential pathogenic factor in many central cognitive disorders.

Little is known, however, on whether ulinastatin has any beneficial effects on postoperative cognitive dysfunction (POCD). The current study was conducted to examine the correlation between ulinastatin, serum S100β protein, IL-6, TNF-α, and CRP levels with early POCD in patients undergoing abdominal surgery.

2. Materials and methods

This was a prospective, randomized, double-blind trial. Approval was obtained from the Local Research Ethics Committee

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and informed consent was obtained from each patient. Eighty-three ASA I-II patients aged greater than 65 years scheduled for abdominal surgery participated in the study. Three patients were discharged from hospital before post-op day 7 and were excluded from the study. Patients with a score of 23 or less on the Mini-Mental State Examination (MMSE) [5] before surgery, diabetes mellitus, cardiovascular or cerebrovascular disease, hyperlipidemia, osteoarthritis, neurological or psychiatric disease, abnormal renal or hepatic function, taking multiple drug medications for underlying diseases, and any known sensitivity to study medications were also excluded. Patients who were hearing or vision impaired, illiterate, with mental retardation, previous sedative and antidepressant medication use and a history of alcoholism or past anesthesia were also excluded. Patients received no anesthetic premedication. Patients were allocated randomly (by computer-generated random numbers) to receive either an infusion of ulinastatin or placebo. Study drugs (ulinastatin and placebo) were prepared by the hospital pharmacy in identical containers marked with the name of the project, the investigator's name, and consecutive numbers. Patients and investigators were blinded to the infusion.

Following placement of an intravenous (IV) line, all patients received atropine 0.01 mg/kg IV. Subsequently, induction of anesthesia was performed in all patients with midazolam 0.04 mg/kg, propofol 1–2 mg/kg, and remifentanil 0.5 μg/kg. Cisatracurium 0.15 mg/kg was administered to facilitate endotracheal intubation and intermittent positive pressure ventilation. Anesthesia was maintained with an infusion of remifentanil 0.2 μg/kg/min and inhalation of sevoflurane (1–2% end-tidal concentration) with oxygen. Depth of anesthesia was maintained by adjusting the concentration of sevoflurane to achieve a Bispectral Index Score of 40–60. Heart rate (HR), mean arterial pressure (MAP), respiratory rate (RR), $P_{ET}CO_2$ and hemoglobin oxygen saturation (SpO_2) were recorded every 5 min. Muscle relaxant reversal medications were not administered at the end of the surgery. The endotracheal tube was removed when patients were breathing spontaneously and awake. After inducing anesthesia, ulinastatin 10,000 units/kg diluted in normal saline to a volume of 100 mL (group U) or 100 mL of normal saline (group P) was administered intravenously over a period of 30 min before surgical incision and 5000 units/kg after surgery on days 1–3. The control group received the same volume of normal saline. All patients received intravenous patient-controlled analgesia (IVPCA) postoperatively. 1000 μg fentanyl was diluted with 100 ml of normal saline. It was administered at a basic basal infusion rate of 2 ml/h, bolus 2 ml, and lockout time 6 min. The incidence of postoperative complications such as nausea and vomiting and arrhythmia were recorded.

A brief battery of neuropsychological tests [24] was administered within 2 days before surgery and on post-op day 7. Neuropsychological assessment was performed in a quiet room with only the patient and the psychometrician present. Each examiner was trained on psychometric test administration and relevant interview techniques by the neuropsychologist involved in the protocol. All tests were administered and scored in a standardized manner to minimize differences between test administrators. Project investigators trained in neuropsychological assessment completed all data scoring and interpretation. The test battery, which included seven tests with nine subscales, was selected on the basis of demonstrated efficiency in similar subject populations [16]. Specific tests used included: the Mental Control and Digit Span (forward and backward) subtests of the Wechsler Memory Scale measuring attention and concentration; the Visual Retention and Paired Associate Verbal Learning subtests of the Wechsler Memory Scale, measuring figural memory and verbal learning/memory; the Digit Symbol subtest of the Wechsler Adult Intelligence Scale-Revised, measuring psychomotor speed; the Halstead-Reitan Trail Making Test (Part A), measuring hand–eye coordination, attention, and concentration; and the Grooved Pegboard Test (favored and unfavored hand), measuring manual dexterity. Parallel forms of tests were used in sequential testing in a randomized way, when available, to minimize any practice effect. A postoperative deficit in any test was defined by a decline of 20% or more from the preoperative value of that test [17]. Any patient demonstrating a deficit in 2 or more tests was considered as having POCD.

To observe changes in the level of S100β, IL-6, TNF-α, and CRP, venous blood samples were obtained before inducing anesthesia (T0), at the end of surgery (T1) and 1 d (T2), 2 d (T3), and 3 d (T4) after surgery. Blood samples (3 ml) were centrifuged at 4000 rpm for 20 min at −4 °C and the serum was stored at −70 °C. S100β levels were measured using an enzyme linked immunosorbent assay (ELISA) kit (Uscn Life Science Inc., USA), IL-6, TNF-α, and CRP levels were measured using an enzyme linked immunosorbent assay (ELISA) kit (R&D system, Minneapolis, MN, USA).

2.1. Statistical analysis

SPSS 15.0 (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. Sample size was calculated to detect a 25% reduction in the incidence of POCD in the ulinastatin group compared to the control group. With $\alpha = 0.05$ and $\beta = 0.80$, 38 patients were needed in each group. All data is normally distributed using Kolmogorov–Smirnov test. Numerical data, including IL-6, TNF-α, CRP and S100β concentrations between groups were analyzed with the Student's *t*-test and intragroup numerical data were analyzed with repeated measures ANOVA. Nominal data were analyzed by χ^2 test. Statistical significance was accepted as $p < 0.05$. The correlation between changes in blood biomarkers with significant differences between groups and cognitive function were evaluated by multivariate logistic regression analysis.

3. Results

There were no significant differences in patient characteristics between groups ($p > 0.05$) (Table 1). There were no significant differences in HR, MAP, RR, $ETCO_2$, and SpO_2 during surgery between groups ($p > 0.05$). There were significant differences in the occurrence of postoperative decline in each neuropsychological test except the Digit Span (backward) between groups (Table 2). The ulinastatin group had a lower incidence of postoperative cognitive dysfunction than the control group (2.5% versus 27.5%, $p < 0.05$) (Table 3). The incidence of postoperative complications, such as nausea and vomiting and arrhythmia, were not significantly different between groups ($p > 0.05$) (Table 4). In the control group, serum S100β protein and IL-6 concentration increased at the end of surgery and on post-op days 1 and 2. However, the ulinastatin group had lower serum S100β protein and IL-6 concentrations than those in the control group ($p < 0.05$). There were no significant differences between groups in TNF-α or CRP concentrations

Table 1
Group demographics (the degree of freedom = 78).

	Group U ($n = 40$)	Group P ($n = 40$)	*p*-Value
Gender (male/female)	21/19	22/18	
Age (year)	75.6 ± 7.2	74.1 ± 8.1	0.687
Weight (kg)	54.5 ± 7.4	57.8 ± 10.2	0.542
ASA (I/II)	19/21	20/10	
Duration of surgery (min)	73 ± 12	75 ± 14	0.733

No statistical significance was present in these parameters. Mean ± SD was given in age, weight and duration of surgery.