European Review for Medical and Pharmacological Sciences 2024; 28: 278-287

Effects of parecoxib on postoperative cognitive dysfunction and serum levels of NSE and S100β in elderly patients undergoing surgery

W.-Y. YIN, T. PENG, B.-C. GUO, C.-C. FAN, J. XU, X.-M. LIU, X. LI

Department of Anesthesiology, Baoshan Branch, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

Abstract. – OBJECTIVE: To investigate the effects of parecoxib on postoperative cognitive dysfunction, and serum levels of neuron-specific enolase (NSE) and S100β protein (S100β) in elderly patients undergoing surgery.

PATIENTS AND METHODS: The retrospective cohort study method was used to collect the clinical data of 94 elderly patients who underwent elective orthopedic and general anesthesia surgery in our hospital from September 2020 to February 2022. 94 patients were divided into the control group (47 cases) and the study group (47 cases), according to different intervention methods. In the study group, 40 mg of parecoxib was injected intravenously into patients 30 min before the induction of anesthesia, and the patients in the control group were given the same dose of normal saline intravenously before the operation. The basic clinical data of the patients were collected. The levels of the indexes before operation and 6 hours after operation were compared between the two groups, including the Montreal Cognitive Scale (MoCA) score, inflammatory factor indicators [tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), C-reactive protein (CRP), interleukin-10 (IL-10), interleukin-1β (IL-1β), monocyte chemokine-1 (MCP-1), and inducible nitric oxide synthase (iNOS)], serum cortisol (CORT), beta-amyloid (β-AP), adiponectin (ADP), NSE, and S100β.

RESULTS: No significant differences in the preoperative MoCA score, TNF-α, IL-6, CRP, IL-10, IL-1β, MCP-1, iNOS, CORT, β-AP, ADP, NSE, and S100β levels were observed between the two groups ($p>0.05$). The postoperative MoCA score in the study group was significantly higher than that in the control group ($p<0.05$). The postoperative levels of TNF-α, IL-6, CRP and IL-1β in the study group were significantly lower than those in the control group ($p<0.05$), and the postoperative levels of IL-10, MCP-1 and iNOS in the study group were significantly higher than those in the control group ($p<0.05$).

CONCLUSIONS: Parecoxib can notably inhibit the levels of postoperative inflammatory cytokines, improve neurological dysfunction, and reduce the occurrence of postoperative cognitive dysfunction in patients. The contents of serum NSE and S100β have potential value in the diagnosis of postoperative cognitive dysfunction in elderly patients.

Key Words:
Parecoxi, Elderly surgical patients, Postoperative cognitive impairment, NSE, S100β.

Introduction

Postoperative cognitive dysfunction is a central nervous system complication and is mainly characterized by impairment of attention, concern, learning, and problem-solving. With the development of the social economy, the social population is gradually aging, concomitant with the increases in the incidence[1]. The occurrence of postoperative cognitive dysfunction not only prolongs the hospitalization time and increases the economic burden of patients, but also enhances the risk of death in the perioperative period of patients, thereby leading to a serious impact on the quality of life and health of elderly patients. Therefore, the timely detection and intervention of postoperative cognitive dysfunction play an important role in improving the prognosis of patients.

At present, the pathological mechanism of postoperative cognitive dysfunction remains unclear. It is believed that various factors may cause postoperative cognitive dysfunction, such as the patient's own factors, surgical trauma factors, and the use of anesthetic drugs[2]. As a cyclooxygenase-2 (COX-2) inhibitor, parecoxib exerts important effects on analgesia and inhibition of inflammatory factors[3]. Some studies[4] have confirmed that COX-2 is implicated in the progression of neurodegenerative diseases. Moreover, parecoxib has been proven to reduce the occurrence of postoperative cognitive dysfunction after hip

Corresponding Author: Xue Li, MD; e-mail: lixue@shbsdcyy.com

replacement[5]. High concentrations of neuron-specific enolase (NSE) are present in neuronal cells and neuroendocrine cells, which can specifically reflect neuronal damage and are considered the most sensitive indicator of brain tissue damage[6]. S100β protein (S100β) is highly located in glial cells of the central nervous system and can specifically reveal the severity of brain glial cell damage[7]. NSE and S100β are closely related to cognitive dysfunction. Some scholars8 have substantiated that the levels of NSE in cerebrospinal fluid in patients with vascular dementia are positively correlated with the severity of disease, indicating that NSE can not only be used as a sensitive indicator to reflect the severity of brain injury but also be used as an intelligence factor to participate in cognitive activities. Furthermore, the serum levels of S100β in patients with cognitive impairment of brain tumors are inversely related to cognitive function scores9. However, the effects of parecoxib on serum levels of NSE and S100β and their diagnostic values in the elderly suffering from postoperative cognitive dysfunction are still unclear.

In this study, the effect of parecoxib on postoperative cognitive dysfunction and serum NSE and S100β after surgery in elderly patients, as well as the value of serum NSE and S100β alone or in combination diagnosis on postoperative cognitive dysfunction in elderly patients, were discussed, and analyzed.

Patients and Methods

Basic Information

A total of 94 elderly patients who experienced elective general anesthesia surgery in our hospital from September 2020 to February 2022 were retrospectively enrolled in the present study. Using the retrospective cohort study method, 94 patients were divided into the control group (47 cases) and the study group (47 cases), according to different intervention methods. Inclusion criteria: (1) All patients met the surgical indications for general anesthesia surgery[10]; (2) Patients were over 60 years old and under 85 years old; (3) Patients could cooperate with treatment; (4) Patients without obvious allergic history to the drugs used in the study; (5) All patients had given the informed consent and voluntarily participated in this experiment; (6) All subjects had normal preoperative cognitive function. Exclusion criteria: (1) Patients with serious damage in liver and kidney and/or cardiac insufficiency; (2) Pregnant or breastfeeding patients; (3) Patients with infectious diseases or a history of drug allergy; (4) Patients with incomplete clinicopathological data or could not cooperate with the study; (5) Patients with a history of mental illness; (6) Patients with coagulation disorders. This study conformed to the relevant principles of medical ethics and was approved by the hospital Ethics Committee (Approval number: 2020-skt-003) on August 30, 2020. The flow chart of general data is shown in Figure 1.

Methods

All patients fasted for 6 hours and forbade drinking water for 4 hours before the operation. The venous access was opened, and the electrocardiograph (ECG), blood pressure, and blood oxygen saturation were routinely monitored.

The study group

The patients underwent tracheal intubation. Before induction of anesthesia, 0.04 mg/kg midazolam (Jiangsu Nhwa Pharmaceutical Co., Ltd., production batch number: 20181037, specification: 2 mL: 2 mg), 0.02 g/kg propofol (Sichuan GuoRui Pharmaceutical Co., Ltd., production batch number: 20180079, specification: 10 mL: 0.1 g), 0.2 μg/kg sufentanil (Yichang Renfu Pharmaceutical Co., Ltd., production batch number: 20184172, specification: 2 mL: 100 μg) and Atracurium (Jiangsu Hengrui Pharmaceutical Co., Ltd., production batch number: 20180869, specification: 10 mg) were used for anesthesia induction. After successful endotracheal intubation, the anesthesia machine was mechanically ventilated, with a tidal volume of 6-8 ml/kg and a respiratory rate of 10-12 breaths/min. Then, 0.01 g/kg propofol and 10 μg/kg remifentanil (Jiangsu Nhwa Pharmaceutical Co., Ltd., production batch number: 120183314, specification: 1 mg) were used for anesthesia maintenance, and the target-controlled concentration was adjusted according to hemodynamic changes. All anesthetics were discontinued postoperatively. The airway secretions were aspirated, and the endotracheal tube was removed when the patients were conscious. The patients in the study group received an intravenous infusion of 40 mg parecoxib (Pharmacia and Upjohn Company, production batch number: 20180044, specification: 40 mg). The recommended dose was 40 mg, and the total daily dose did not exceed 80 mg with the intravenous or intramuscular administration[11] 30 minutes before the start of induction of surgical anesthesia.

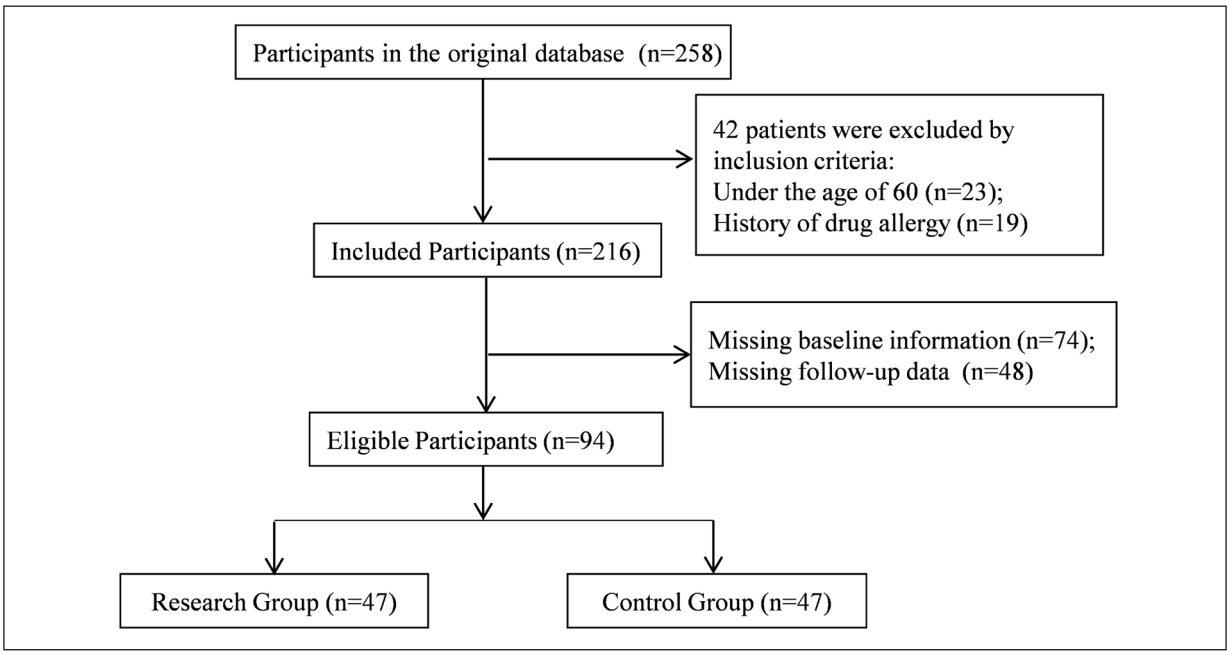

Figure 1. Flow chart of general data selection.

The control group

The patients in the control group were given an equal dose of normal saline intravenously 30 minutes before surgery. The anesthesia induction procedure was performed as above.

Observation Indicators

(1) Clinical data analysis: the basic clinical data of patients were collected, including age, gender (male, female), body mass index, education level (below junior high school, high school, college and above), type of surgery (open disc surgery, hip replacement, open fracture surgery), smoking history, drinking history, operation time, anesthesia time, preoperative blood pressure (diastolic blood pressure, systolic blood pressure), American Society of Anesthesiologists classification (grade I, grade II), comorbidities (coronary heart disease, diabetes, hypertension, others). The recovery time, eye-opening time, and extubation time of patients in the two groups were recorded.

(2) The changes in Montreal Cognitive Scale (MoCA) scores before and 6 hours after surgery were compared between the two groups[12]. Eleven items in 8 cognitive domains were scored, including visuospatial function (1 point for alternately connected test instruction), 1 point for visual structure skills (copy cube) instruction and executive function [3 points for visual structure skills (clock drawing) instruction], naming ability (3 points), memory (no score), attention (5 points), language ability (2 points of repetition, and 1 point of fluency), abstract ability (2 points), delayed recall (5 points), and orientation ability (6 points), of which the total score was 30 points, and the ≥26 points were normal. Patients with higher MoCA scores indicate better cognitive function.

(3) Comparison of the expression of inflammatory factors before and 6 h after surgery between the two groups of patients: the concentrations of inflammatory cytokines, including tumor necrosis factor-α (TNF-α) (Shanghai Fuyu Biotechnology Co., Ltd., Jiading Industrial Zone, Shanghai, China, catalog number: FY-03218H2), interleukin-6 (IL-6) (Wuhan Huamei Bioengineering Co., Ltd., CUSABIO®, Wuhan High-tech Development Zone, Hubei Province, China, catalog number: CSB-E04638h), C-reactive protein (CRP) (Wuhan Huamei Bioengineering Co., Ltd., CUSABIO®, catalog number: CSB-E08617h), interleukin-10 (IL-10) (Wuhan Huamei Bioengineering Co., Ltd., CUSABIO®, catalog number: CSB-E04593h), interleukin-1β (IL-1β) (Wuhan Huamei Bioengineering Co., Ltd., CUSABIO®, catalog number: CSB-E08053h), and monocyte chemokine-1 (MCP-1) (Wuhan Huamei Bioengineering Co., Ltd., CUSABIO®, catalog number: CSB-E06921Rb) were determined by enzyme-linked immunosorbent assay (ELISA). The serum level of inducible nitric oxide synthase (iNOS) was measured by the chemical colorimetry method. The kit was purchased from Hepeng

Biotechnology Co., Ltd. (Jinshan District, Shanghai, China, catalog number: HPBIO-JM7338).

(4) The expressions of serum cortisol (CORT) (Wuhan Huamei Bioengineering Co., Ltd., CUSABIO®, catalog number: CSB-E07968h), β-amyloid protein (β-AP) (Wuhan Fein Biotechnology Co., Ltd., Wuhan, Hubei Province, China, catalog number: FN-EH0933) and adiponectin (ADP) (Wuhan Huamei Bioengineering Co., Ltd., CUSABIO®, catalog number: CSB-E07270h) in the two groups before and 6 h after the operation were detected by ELISA.

(5) The expression levels of NSE and S100β were compared between the two groups before and 6 h after surgery. The expression levels of NSE and S100β were detected using the chemiluminescence method. The kit was purchased from Wuhan Elirete Biotechnology Co., Ltd. (Jiangxia District, Wuhan City, Hubei Province, China, catalog number: E-BC-K271-M).

Statistical Analysis

SPSS software (version 24.0, IBM Corp., Armonk, NY, USA) was used for the statistical data analysis. The enumeration data were expressed as [n (%)], and compared by χ^2. The measurement data were first subjected to the normality test (Shapiro-Wilk test, S-W test), and the measurement data that met the normal distribution were expressed by mean ± standard deviation ($\bar{x}\pm s$). The paired *t*-test was used to compare preoperative and postoperative data between the same group, and the independent sample *t*-test was used to compare the control group and the study group. Wilcoxon's signed rank test was used for preoperative and postoperative MoCA scores between the same group, Wilcoxon rank sum test was used for the MoCA score in the control group and study group, and Sidak or Bonferroni correction was used for data comparison between groups. The statistically significant was defined as $p<0.05$.

Results

Comparison of Basic Clinical Data Between the Two Groups

No prominent differences were observed in the two groups, including age, gender, body mass index, education level, type of surgery, smoking history, drinking history, operation time, anesthesia time, blood pressure, and American Society of Anesthesiologists classification and comorbidities ($p>0.05$). There were no significant differences in spontaneous breathing recovery time, eye-opening time and extubation time between the two groups ($p>0.05$, Table I).

Comparison of MoCA Scores Between the Two Groups

There was no remarkable difference in the preoperative MoCA score and total scores between the control and study groups ($p>0.05$). However, postoperative MoCA scores and total scores in both groups were notably decreased compared with those before surgery ($p<0.05$). Moreover, postoperative MoCA scores and total scores in the study group were increased relative to the control group ($p<0.001$, Table II).

Comparison of the Levels of Inflammatory Factors Between the Two Groups

Two-factor repeated measures of variance were used to analyze the changes in inflammatory factors before and after surgery between the two groups. The results showed that the intervention effect was significant ($F=50.77$, $p<0.001$) and the temporal effect was significant ($F=39.20$, $p<0.001$). The measured levels of TNF-α, IL-6, CRP, IL-10, IL-1β, MCP-1 and iNOS before and after surgery were statistically significant with the group interaction ($F=33.89$, $p<0.001$). The postoperative concentrations of TNF-α, IL-6, CRP, and IL-1β in the study group were remarkably lower than those in the control group ($p<0.05$). The postoperative levels of IL-10, MCP-1, and iNOS in the study group were observably higher than those in the control group ($p<0.05$, Table III).

Comparison of the Expressions of CORT, β-AP and ADP Between the Two Groups

Two-factor repeated measures of variance were used to analyze the changes of CORT, β-AP and ADP before and after surgery between the two groups. The results showed that the intervention effect was significant ($F=61.36$, $p<0.001$) and the temporal effect was significant ($F=74.20$, $p<0.001$). The measured levels of CORT, β-AP and ADP before and after surgery were statistically significant with the group interaction ($F=42.56$, $p<0.001$). However, the concentrations of CORT and β-AP were lower in the study group than those in the control group ($p<0.05$), while the concentrations of ADP were markedly higher in the study group relative to the control group ($p<0.05$, Table IV).

Comparison of the Expression Levels of NSE and S100β between the Two Groups

Two-factor repeated measures of variance were used to analyze the changes of NSE and S100β before and after surgery between the two groups. The results showed that the intervention effect

Table I. Comparison of basic clinical data between the two groups ($\bar{x}$±s), [n (%)].

Indicators	The control group (n=47)	The research group (n=47)	χ^2/t	*p*
Age (year)	69.73±6.49	67.82±5.75	1.510	0.134
Gender (%)			0.386	0.535
Male	24 (51.06)	27 (57.45)		
Female	23 (48.94)	20 (42.55)		
Body mass index (kg/m^2)	21.94±2.85	22.52±2.73		
Type of surgery			0.446	0.800
Open disc surgery	18 (38.30)	15 (31.91)		
Hip replacement	16 (34.04)	17 (36.17)		
Open fracture surgery	13 (27.66)	15 (31.91)		
Education level (%)			3.014	0.222
Below junior high school	14 (29.79)	14 (29.79)		
High school	15 (31.91)	22 (46.81)		
College and above	18 (38.30)	11 (23.40)		
Smoking history (%)	7 (14.89)	14 (29.79)	3.005	0.083
History of drinking (%)	7 (14.89)	10 (21.28)	0.646	0.421
Operation time (min)	144.29±9.76	141.35±11.97	1.305	0.195
Anesthesia time (min)	152.76±12.75	148.64±11.80	1.626	0.107
Blood pressure (mmHg)				
Diastolic blood pressure	121.63±11.51	123.26±10.22	0.726	0.470
Systolic blood pressure	73.74±7.52	74.35±6.29	0.427	0.671
American Society of Anesthesiologists classification (%)			0.389	0.533
Class I	28 (59.57)	25 (53.19)		
Class II	19 (40.43)	22 (46.81)		
Comorbidities (%)			0.613	0.894
Coronary heart disease	11 (23.40)	14 (29.79)		
Diabetes	10 (21.28)	9 (19.15)		
Hypertension	15 (31.91)	15 (31.91)		
Others	11 (23.40)	9 (19.15)		
Spontaneous breathing recovery time (min)	5.52±1.87	5.42±1.77	0.266	0.791
Eye opening time (min)	9.12±2.35	9.21±3.00	0.162	0.872
Extubation time (min)	13.52±4.78	13.27±4.19	0.270	0.788

t, χ^2 and *p* represented the comparison of data between the control group and the study group, and the comparison between the groups used the Bonferroni correction.

was significant (F=85.26, $p<0.001$) and the temporal effect was significant (F=56.02, $p<0.001$). The measured levels of NSE and S100β before and after surgery were statistically significant with the group interaction (F=74.26, $p<0.001$). The levels of NSE and S100β were lower in the study group than those in the control group after the operation ($p<0.001$, Table V).

Discussion

Postoperative cognitive dysfunction is an age-related disease and is more prevalent in elderly patients. With the development of the economy and the improvement of the medical level, China is gradually entering an aging society with an increasing proportion of the elderly population. In recent years, the number of elderly patients in clinical practice has memorably increased. Thus, the incidence of postoperative cognitive dysfunction is gradually increasing due to the gradual decline of the organ system and immune function in elderly patients[13]. Neuropathic pain caused by somatosensory system lesions or diseases often affects the elderly population with multiple comorbidities, and due to cognitive impairment and concurrent diseases, the elderly often underestimate the pain, which seriously affects the treatment effect and quality of life of patients[14]. In addition, sarcopenia is a common disease in the elderly, which can cause irritation of the pain receptors of the peripheral nerves and central nervous system that leads to pain, physical disability and impaired ability to perform activities of daily living, thereby reducing the quality of life and

Table II. Comparison of MoCA scores between the two groups ($\bar{x} \pm s$).

MoCA score	Time	The control group (n=47)	The research group (n=47)	Z	p
Visuospatial function	Preoperative	1.14±0.37	1.16±0.43	-1.076	0.093
	Postoperative	0.87±0.31	0.97±0.12	-4.536	0.001
Executive function	Preoperative	2.88±0.23	2.90±0.56	-0.282	0.778
	Postoperative	1.12±0.28*	1.35±0.44*	-2.424	0.015
Naming ability	Preoperative	2.77±0.49	2.80±0.55	-0.795	0.427
	Postoperative	1.15±0.26*	1.79±0.52*	-2.666	0.008
Attention	Preoperative	4.76±0.33	4.70±0.42	-1.281	0.200
	Postoperative	3.46±0.47*	4.12±0.16*	-6.053	0.001
Language ability	Preoperative	2.85±0.36	2.78±0.32	-1.487	0.137
	Postoperative	2.01±0.52	2.40±0.37	-7.483	0.001
Abstract ability	Preoperative	0.71±0.30	0.73±0.26	-1.628	0.104
	Postoperative	0.35±0.19	0.50±0.30	-2.460	0.014
Delayed recall	Preoperative	4.39±0.36	4.42±0.19	-0.653	0.513
	Postoperative	3.13±0.39*	3.71±0.20*	-2.720	0.007
Orientation ability	Preoperative	4.10±0.26	4.12±0.76	-0.167	0.868
	Postoperative	3.26±0.49*	3.75±0.65*	-2.452	0.014
Total score	Preoperative	23.60±2.70	23.61±3.49	-1.528	0.170
	Postoperative	15.99±2.91	17.95±2.76	-3.861	0.001

Z and *p* indicated that the Wilcoxon rank sum test was used for the comparison of the data between the control group and the research group; **p*<0.05 indicated a preoperative comparison with the same group with the Wilcoxon's signed rank and Sidak correction.

Table III. Comparison of the levels of inflammatory factors in the two groups ($\bar{x} \pm s$).

Groups	Inflammatory factors	The control group (n=47)	The study group (n=47)	t	p
Preoperative	TNF-α (ng/mL)	0.90±0.26	0.97±0.25	1.331	0.187
	IL-6 (pg/mL)	12.36±1.68	11.85±1.59	1.512	0.134
	CRP (mg/L)	3.62±1.58	3.57±1.24	0.171	0.865
	IL-1β (pg/mL)	21.17±3.39	20.33±3.28	1.221	0.225
	IL-10 (pg/mL)	25.72±3.28	25.13±3.26	0.875	0.384
	MCP-1 (pg/L)	25.23±3.12	25.74±2.85	0.827	0.410
	iNOS (mmol/L)	371.38±77.49	373.38±78.47	0.124	0.901
Postoperative	TNF-α (ng/mL)	1.71±0.40*	1.52±0.35*	2.451	0.016
	IL-6 (pg/mL)	24.38±2.64*	17.73±2.04*	13.665	<0.001
	CRP (mg/L)	42.26±6.69*	25.39±4.47*	14.374	<0.001
	IL-1β (pg/mL)	44.47±5.54*	32.47±4.68*	11.344	<0.001
	IL-10 (pg/mL)	20.19±3.14*	22.94±3.38*	4.087	<0.001
	MCP-1 (pg/L)	17.82±3.25*	20.89±3.62*	4.326	<0.001
	iNOS (mmol/L)	253.84±56.31*	280.27±58.18*	2.238	0.028
F		33.89			
p		<0.001			

F and *p* indicated the group interaction effect on the measured levels before and after surgery; **p*<0.05 indicated preoperative comparison with the same group. Tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), C-reactive protein (CRP), interleukin-10 (IL-10), interleukin-1β (IL-1β), monocyte chemokine-1 (MCP-1), inducible nitric oxide synthase (iNOS).

functional independence of patients, and increasing the need for long-term care services[15]. Therefore, early detection, diagnosis, and treatment to further clarify the pathogenesis of postoperative cognitive dysfunction and pain are important for judging the prognosis of patients, improving their quality of life, and prolonging their survival time.

Parecoxib is a specific COX-2 inhibitor. Relevant data[16] show that parecoxib is a safe and potent COX-2 inhibitor of nucleus pulposus cells, which can prevent apoptosis of nucleus pulposus cells by inhibiting endoplasmic reticulum stress. A previous study[17] revealed that the levels of COX-2 were related to neuronal damage. COX-2

Table IV. Comparison of CORT, β-AP and ADP expression between the two groups ($\bar{x} \pm s$).

Groups	Indicators	The control group (n=47)	The study group (n=47)	*t*	*p*
Preoperative	CORT (nmol/L)	289.18±27.96	290.24±25.74	1.180	0.577
	β-AP (pg/mL)	78.22±20.14	78.88±15.11	1.777	0.054
	ADP (g/L)	13.97±3.48	14.29±2.46	0.515	0.607
Postoperative	CORT (nmol/L)	376.43±30.27*	313.16±24.68*	11.106	<0.001
	β-AP (pg/mL)	155.86±76.19*	92.58±41.28*	3.407	<0.001
	ADP (g/L)	4.33±2.13*	9.86±2.14*	12.556	<0.001
F		42.56			
p		<0.001			

F and *p* indicated the group interaction effect on the measured levels before and after surgery; **p*<0.05 indicated preoperative comparison with the same group. Serum cortisol (CORT), beta-amyloid (β-AP), adiponectin (ADP).

Table V. Comparison of the expression levels of NSE and S100β between the two groups ($\bar{x} \pm s$).

Groups	Indicators	The control group (n=47)	The study group (n=47)	*t*	*p*
Preoperative	NSE (μg/L)	11.27±1.58	11.76±1.32	1.433	0.226
	S100β (ng/mL)	1.47±0.35	13.41±1.60*	1.727	0.067
Postoperative	NSE (μg/L)	15.46±1.86*	1.52±0.46	5.728	<0.001
	S100β (ng/mL)	3.94±0.72*	2.83±0.68*	7.684	<0.001
F		74.26			
p		<0.001			

F and *p* indicated the group interaction effect on the measured levels before and after surgery; **p*<0.05 indicated preoperative comparison with the same group. Neuron-specific enolase (NSE), S100β protein (S100β).

is not only an inducible enzyme, but also an important inflammatory mediator. The levels of cytokines will increase when patients are traumatized by surgery. It is known that CRP, IL-6, IL-1β and TNF-α are important inflammatory factors and play an important role in the acute phase response. TNF-α is a multipotent pro-inflammatory factor and one of the first elevated factors in the inflammatory response. For the experiments on postoperative cognitive dysfunction in aged Sprague Dawley (SD), the elevated level of TNF-α in the hippocampus exerts an important role in neuroinflammation and cognitive function[18]. However, it has also been suggested[19] that although perioperative parecoxib did not provide significantly better postoperative pain control or reduce the need for opioids compared with placebo, its use resulted in a shorter hospital stay. In addition, TNF-α can induce the production of IL-6 that will further evoke the release of CRP by the liver[20,21]. IL-6 is a vital inflammatory factor that can participate in various immune responses. The level of IL-6 plays a crucial role in cognitive function, which may affect cognitive function by changing the morphology of hippocampal neurons and neurodevelopment[22]. IL-1β, as a multifunctional cytokine, mediates the inflammatory response to infection and injury, thereby affecting the memory function of the hippocampus in the brain. The expression levels of IL-10, MCP-1, and iNOS are notably decreased during the process of the inflammatory response, and these indicators have an important efficacy in inhibiting the inflammatory reaction[23,24]. The results of this study disclosed that the concentrations of TNF-α, IL-6, CRP, and IL-1β were distinctly enlarged between the two groups after the operation compared with those before surgery, and their levels in the study group were notably lower than those in the control group, concomitant with the inverse results in the concentrations of IL-10, MCP-1 and iNOS. These results indicated that parecoxib could significantly inhibit the excessive release of inflammatory factors, such as TNF-α, IL-6, CRP, and IL-10, and suppress the excessive reduction of anti-inflammatory factor IL-1β, MCP-1, and iNOS. This may be because the stimulation of surgery can activate inflammatory cells, produce a cascade reaction, activate the peripheral and central immune systems, and release a large

number of inflammatory factors to result in the occurrence of cognitive dysfunction, while parecoxib can significantly inhibit the inflammatory factor expression, thus reducing the occurrence of postoperative cognitive dysfunction.

CORT is a glucocorticoid and is involved in the body's learning and memory function. A previous study[25] revealed that the levels of CORT in aged rats were significantly increased after surgery, which may be caused by the decrease of glucocorticoid receptors and increase of cortisol secretion in the elderly population. β-AP is a polypeptide molecule, and its level has an important relationship with the content of its precursor protein. Under normal conditions, the expression level of β-AP is extremely low; however, its increase will evoke an inflammatory response and induce nerve cell injury. ADP is a protein secreted by adipose tissue and exerts multiple characteristics, such as anti-oxidative stress and anti-inflammatory response. In addition, it has been reported that ADP can reduce the risk of central nervous system diseases[26]. In this study, the levels of CORT and β-AP in the two groups after the operation were significantly increased compared with those before surgery, in which those in the study group were observably lower than those in the control group, accompanied by the reverse outcomes in the concentration of ADP. These results suggested that the levels of CORT, β-AP and ADP may be related to postoperative cognitive dysfunction. Moreover, CORT, β-AP and ADP may be the important indicators that can reveal the cognitive function of patients, while parecoxib can regulate the levels of CORT, β-AP, and ADP.

A distinctive feature of cognitive decline is the large number of activated glial cells (microglia and astrocytes) surrounding Aβ plaques[27]. It has been demonstrated that the sustained activation of microglia and astrocytes may be associated with the progression of cognitive function[28]. Wu et al[29] used RNA-seq to quantitatively analyze the characteristic gene expression of activated astrocytes in the dorsolateral prefrontal cortex (DLPFC) of 1,076 elderly people and found that the higher degree of sleep fragmentation was related to the higher expression level of the characteristic gene of activated astrocytes. Moreover, the higher level of characteristic genes of activated astrocytes was correlated with the lower the cognitive function and the faster the decline. It has also been confirmed[30] that astrocyte dysfunction can lead to memory loss, even if neurons and other cells are otherwise healthy. Therefore, S100β, a marker of astrocyte damage, is selected for analysis. The NSE and S100β are both indicators related to neurological function. NSE mainly exists in neurons and neuroendocrine cells. Once injury occurs, NSE will be released into blood, and the serum NSE level will greatly increase. Thus, the NSE level can be used as an important indicator to reflect the degree of neuronal damage in patients to a certain extent. The study[31] of cognitive dysfunction in elderly dogs after periodontal surgery confirms that the serum concentrations of NSE in control dogs after surgery are uplifted, indicating that there is nerve damage in elderly dogs after surgery. As a marker protein of glial cells, S100β is mainly synthesized and secreted by glial cells and mainly exists in neurons and glial cells. It is a fact that S100β enters the blood through the damaged blood-brain barrier when the nervous system is damaged[32]. Additionally, the expression levels of S100β are closely related to the degree of brain injury[33]. According to a meta-analysis conducted by Huang et al[34] parecoxib showed a remarkable effect in reducing the incidence of postoperative cognitive dysfunction and could significantly reduce the concentrations of S100β from the end of the operation to postoperative day 2. This report suggests that parecoxib may alleviate postoperative cognitive dysfunction by inhibiting the production of S100β. This may play a key role in controlling the pathogenesis of postoperative cognitive dysfunction. Consistent with this research, our study found that the levels of NSE and S100β in the two groups after the operation were significantly increased compared with those before surgery, and their levels in the study group were observably lower than those in the control group. Additionally, the postoperative MoCA scores decreased, and these scores in the study group were lower than those in the control group. These data indicated that postoperative patients had cognitive dysfunction, which may be ameliorated after parecoxib treatment.

Conclusions

In conclusion, parecoxib can inhibit the levels of postoperative inflammatory factors, repair neurological dysfunction, and reduce the occurrence of postoperative cognitive dysfunction in patients. Moreover, NSE and S100β have high diagnostic value in postoperative cognitive dysfunction in patients. However, the time of this study was short, and the sample size was small. Only patients in our hospital were included, and

the sample was not representative. In addition, future research will focus on preoperative risk stratification to effectively prevent or reduce the occurrence of postoperative cognitive dysfunction, so the candidate research process will continue to study in this field.

Funding
The study was supported by Shanghai special research project on aging and women and child health (Project ID: 2020YJZX0127).

Availability of Data and Materials
The data supporting the results or analyses presented in the paper could be obtained from the corresponding author on reasonable request.

Ethics Approval
This study conformed to the relevant principles of medical ethics and was approved by the Hospital Ethics Committee (Approval number: 2020-skt-003) on August 30, 2020.

Informed Consent
All patients signed the informed consent form.

Authors' Contributions
WYY carried out the Clinical data analysis and performed the main detection of indicators. TP and BCG collected data and processed the data. CCF and JX participated in study concepts and data acquisition. XML conducted the statistical analysis. XL is a guarantor of integrity of the entire study and was a major contributor in writing the manuscript. WYY and XL confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Conflict of Interest
The authors declare that they have no competing interests.

ORCID ID
Xue Li: 0000-0003-2543-3235.

References

1) Zhou XY, Liu J, Xu ZP, Fu Q, Wang PQ, Wang JH, Zhang H. Dexmedetomidine ameliorates postoperative cognitive dysfunction by inhibiting Toll-like receptor 4 signaling in aged mice. Kaohsiung J Med Sci 2020; 36: 721-731.
2) Xie X, Shen Z, Hu C, Zhang K, Guo M, Wang F, Qin K. Dexmedetomidine Ameliorates Postoperative Cognitive Dysfunction in Aged Mice. Neurochem Res 2021; 46: 2415-2426.
3) Zhuang Q, Tao L, Lin J, Jin J, Qian W, Bian Y, Li Y, Dong Y, Peng H, Li Y, Fan Y, Wang W, Feng B, Gao N, Sun T, Lin J, Zhang M, Yan S, Shen B, Pei F, Weng X. Postoperative intravenous parecoxib sodium followed by oral celecoxib post total knee arthroplasty in osteoarthritis patients (PIPFORCE): a multicentre, double-blind, randomised, placebo-controlled trial. BMJ Open 2020; 10: e030501. doi: 10.1136/bmjopen-2019-030501. Erratum in: BMJ Open 2020; 10: e030501corr1.
4) Wang RD, Zhu JY, Zhu Y, Ge YS, Xu GL, Jia WD. Perioperative analgesia with parecoxib sodium improves postoperative pain and immune function in patients undergoing hepatectomy for hepatocellular carcinoma. J Eval Clin Pract 2020; 26: 992-1000.
5) Zhao M, Ning L, Kong Y, Li XX. Celecoxib versus parecoxib versus oxycodone in pain control for transcatheter chemoembolization in patients with hepatocellular carcinoma[J]. J Clin Oncol 2020; 38: 509.
6) Papuć E, Rejdak K. Increased cerebrospinal fluid S100B and NSE reflect neuronal and glial damage in Parkinson's disease[J]. Front Aging Neurosci 2020; 12: 156.
7) Langeh U, Singh S. Targeting S100B protein as a surrogate biomarker and its role in various neurological disorders[J]. Curr Neuropharmacol 2021; 19: 265-277.
8) Gao Y, Duan J, Ji H, Lu W. Levels of S100 calcium binding protein B (S100B), neuron-specific enolase (NSE), and cyclophilin A (CypA) in the serum of patients with severe craniocerebral injury and multiple injuries combined with delirium transferred from the ICU and their prognostic value[J]. Ann Palliat Med 2021; 10: 3371-3378.
9) Yu D, Liu B, Jiang G, Pei S, Pan H. Correlation of changes in serum S100β, NSE and inflammatory factor levels with MMSE and MoCA in intracranial tumor patients with cognitive impairment[J]. Oncol Lett 2020; 20: 1968-1972.
10) Hanna K, Khan M, Ditillo M, Hamidi M, Tang A, Zeeshan M, Saljuqi AT, Joseph B. Prospective evaluation of preoperative cognitive impairment and postoperative morbidity in geriatric patients undergoing emergency general surgery[J]. Am J Surg 2020; 220: 1064-1070.
11) Zallipalli SN, Bethi RR, Kandru M, Dendukuri NK, Gandla G, Vemuri SSS, Peri H, Linga S. Effect of Parecoxib on postoperative pain management after total knee/hip arthroplasty: A systematic review and meta-analysis. Cureus 2022; 14: e32339.
12) Suda S, Muraga K, Ishiwata A, Nishimura T, Aoki J, Kanamaru T, Suzuki K, Sakamoto Y, Katano T, Nagai K, Hatake S, Satoi S, Matsumoto N, Nito C, Nishiyama Y, Mishina M, Kimura K. Early cognitive assessment following acute stroke: feasibility and comparison between mini-mental state examination and montreal cognitive assessment[J]. J Stroke Cerebrovasc Dis 2020; 29: 104688.
13) Zhao S, Chen F, Wang D, Han W, Zhang Y, Yin Q. NLRP3 inflammasomes are involved in the progression of postoperative cognitive dysfunction:

from mechanism to treatment[J]. Neurosurg Rev 2020; 44: 1815-1831.

14) Giovannini S, Coraci D, Brau F, Galluzzo V, Loreti C, Caliandro P, Padua L, Maccauro G, Biscotti L, Bernabei R. Neuropathic Pain in the Elderly[J]. Diagnostics (Basel) 2021; 11: 613.

15) Giovannini S, Brau F, Forino R, Berti A, D'Ignazio F, Loreti C, Bellieni A, D'Angelo E, Di Caro F, Biscotti L, Coraci D, Fusco A, Padua L, Bernabei R. Sarcopenia: Diagnosis and Management, State of the Art and Contribution of Ultrasound. J Clin Med 2021; 10: 5552.

16) Yang CH, Qi WL, Zhao CW, Cai WJ, Gong Q, Niu JY, Zhao WH, Xu L. Parecoxib prevents nucleus pulposus cells apoptosis by suppressing endoplasmic reticulum stress[J]. Eur Rev Med Pharmacol Sci 2020; 24: 11295-11304.

17) Zhu Y, Yao R, Li Y, Wu C, Heng L, Zhou M, Yan L, Deng Y, Zhang Z, Ping L, Wu Y, Wang S, Wang L. Protective effect of celecoxib on early postoperative cognitive dysfunction in geriatric patients[J]. Front Neurol 2018; 9: 633.

18) Lu Y, Xu Z, Shen F, Lin R, Li H, Lv X, Liu Z. Propofol protects against TNF-α-induced blood-brain barrier disruption via the PIM-1/eNOS/NO pathway[J]. Curr Neurovasc Res 2020; 17: 471-479.

19) Angthong C, Manuwong S, Singh V, Rajbhandari P, Veljkovic A. Efficacy of intravenous perioperative parecoxib administration in the surgical fixation of unstable ankle fracture: a prospective, double-blinded, randomized, placebo-controlled trial[J]. Eur Rev Med Pharmacol Sci 2021; 25: 4779-4784.

20) Liu T, Yin C, Li Y, Gao F, Yu L, Wang Z, Wang Q. Effects of transcutaneous electrical acupoint stimulation on postoperative cognitive decline in elderly patients: A pilot study[J]. Clin Interv Aging 2021; 16: 757-765.

21) Edipoglu I S, Fatma C. The associations between cognitive dysfunction, stress biomarkers, and administered anesthesia type in total knee arthroplasties: prospective, randomized trial[J]. Pain Physician 2020, 22: 495-507.

22) Subramanian S, Pallati PK, Sharma P, Agrawal DK, Nandipati KC. TREM-1 associated macrophage polarization plays a significant role in inducing insulin resistance in the obese population[J]. J Transl Med 2020; 18: 197.

23) Zhu B, Sun D, Yang L, Sun Z, Feng Y, Deng C. The effects of neostigmine on postoperative cognitive function and inflammatory factors in elderly patients-a randomized trial[J]. BMC Geriatrics 2020; 20: 387.

24) Zhang D, Li N, Wang Y, Lu W, Zhang Y, Chen Y, Deng X, Yu X. Methane ameliorates post-operative cognitive dysfunction by inhibiting microglia NF-κB/MAPKs pathway and promoting IL-10 expression in aged mice[J]. Int Immunopharmacol 2019; 71: 52-60.

25) Feinkohl I, Janke J, Slooter A, Winterer G, Spies C, Pischon T. Plasma leptin, but not adiponectin, is associated with cognitive impairment in older adults[J]. Psychoneuroendocrinology 2020; 120: 104783.

26) Zhang NN, Sun L, Chen WT, Yang YL, Wu YM. Effects of edaravone on postoperative cognitive function in elderly patients undergoing hip joint replacement surgery: A randomized controlled trial[J]. Int J Surg (London, England) 2020; 80: 13-18.

27) Romoli M, Sen A, Parnetti L, Calabresi P, Costa C. Amyloid-β: a potential link between epilepsy and cognitive decline[J]. Nat Rev Neurol 2021; 17: 469-485.

28) Araki T, Ikegaya Y, Koyama R. The effects of microglia- and astrocyte-derived factors on neurogenesis in health and disease[J]. Eur J Neurosci 2021; 54: 5880-5901.

29) Wu R, Tripathy S, Menon V, Yu L, Buchman AS, Bennett DA, De Jager PL, Lim ASP. Fragmentation of rest periods, astrocyte activation, and cognitive decline in older adults with and without Alzheimer's disease[J]. Alzheimers Dement 2023; 19: 1888-1900.

30) Armbruster M, Naskar S, Garcia JP, Sommer M, Kim E, Adam Y, Haydon PG, Boyden ES, Cohen AE, Dulla CG. Neuronal activity drives pathway-specific depolarization of peripheral astrocyte processes[J]. Nat Neurosci 2022; 25: 607-616.

31) Zbóril S, Schmidt AP, Oses JP, Wiener CD, Portela LV, Souza DO, Auler JOC Junior, Carmona MJC, Fugita MS, Flor PB, Cortopassi SRG. S100B protein and neuron-specific enolase as predictors of postoperative cognitive dysfunction in aged dogs: A case controlled study[J]. Vet Anaesth Analg 2020; 47: 740-747.

32) Wan Z, Li Y, Ye H, Zi Y, Zhang G, Wang X. Plasma S100β and neuron-specific enolase, but not neuroglobin, are associated with early cognitive dysfunction after total arch replacement surgery: A pilot study[J]. Medicine 2021; 100: e25446.

33) Xi L, Fang F, Yuan H, Wang D. Transcutaneous electrical acupoint stimulation for postoperative cognitive dysfunction in geriatric patients with gastrointestinal tumor: a randomized controlled trial[J]. Trials 2021; 22: 563-563.

34) Huang S, Hu H, Cai YH, Hua F. Effect of parecoxib in the treatment of postoperative cognitive dysfunction: A systematic review and meta-analysis. Medicine (Baltimore) 2019; 98: e13812.