



Effect of flurbiprofen axetil pretreatment on the pain degree as well as stress hormone and mediator secretion after abdominal surgery

Ying Chen[✉]

Anesthesiology Department, Combine Traditional Chinese and Western Medicine Hospital of Liangshan Prefecture in Sichuan Province, Liangshan, Sichuan Province, 615000

ARTICLE INFO

Article history:

Received 14 Jul 2017
Received in revised form 17 Jul 2017
Accepted 24 Jul 2017
Available online 28 Jul 2017

Keywords:

Flurbiprofen axetil
Pain
Cytokine
Stress

ABSTRACT

Objective: To study the effect of flurbiprofen axetil pretreatment on the pain degree as well as stress hormone and mediator secretion after abdominal surgery. **Methods:** Patients undergoing abdominal surgery in our hospital between May 2015 and March 2017 were selected and randomly divided into two groups, intervention group received flurbiprofen axetil pretreatment combined with routine intravenous anesthesia, and the control group only accepted conventional intravenous anesthesia. The levels of pain neurotransmitters and cytokines, stress hormones and mediators in serum were detected before operation as well as 12 h and 24 h after operation. **Results:** 12 h and 24 h after operation, serum NPY, SP, Glu, TNF- α , IL-2, IL-6, IL-10, ACTH, Cor, Ins, NE and E levels of both groups of patients were significantly higher than those before operation while SOD, GHS-Px and HO-1 levels were significantly lower than those before operation, and serum NPY, SP, Glu, TNF- α , IL-2, IL-6, IL-10, ACTH, Cor, Ins, NE and E levels of intervention group 12 h and 24 h after operation were significantly lower than those of control group while SOD, GHS-Px and HO-1 levels were significantly higher than those of control group. **Conclusion:** Flurbiprofen axetil pretreatment can reduce the pain degree and stress response after abdominal surgery.

1. Introduction

Abdominal incision pain after surgery is the important factor influencing the postoperative functional recovery, and persistent incision pain will on the one hand, affect the patient's autonomous activity, and then go against gastrointestinal functional recovery, and on the other hand, also cause the body in a persistent stress state, lead to the abnormal secretion of a variety of endocrine hormones and result in internal environment disturbance[1,2]. Flurbiprofen axetil is an intravenous non-steroidal drug that is wrapped by lipid microspheres and can target the location of pain and produce non-selective inhibition on cyclooxygenase to reduce the synthesis of prostaglandins, relieve inflammation and restrain perception of pain. There are studies about flurbiprofen axetil preemptive analgesia

for orthopedic surgery and breast surgery[3,4], but it is not yet clear about the analgesic effect of flurbiprofen axetil preprocessing for abdominal surgery. The effect of flurbiprofen axetil pretreatment on the pain degree as well as stress hormone and mediator secretion after abdominal surgery was analyzed in the following study.

2. Case information and research methods

2.1 General information of enrolled cases

Patients undergoing abdominal surgery in our hospital between May 2015 and March 2017 were selected, all patients received surgery under general anesthesia for abdominal benign disease, ASA grading was I-II, and the patients with malignant tumor, those with mental illness and those with autoimmune diseases were excluded. A total of 184 cases were enrolled and divided into intervention group and control group by random number table, each with 92

[✉]Corresponding author: Ying Chen, Anesthesiology Department, Combine Traditional Chinese and Western Medicine Hospital of Liangshan Prefecture in Sichuan Province, Liangshan, Sichuan Province, 615000.
Tel: 17721951413
Fund Project: College Talent Training Project of Sichuan Province No: 2011018B.

cases. Intervention group received flurbiprofen axetil pretreatment combined with routine intravenous anesthesia, including 52 men and 40 women that were 38-55 years old; the control group only received routine intravenous anesthesia, including 55 men and 37 women that were 36-53 years old. There was no significant difference in general information between the two groups ($P>0.05$).

2.2 Anesthesia methods

Before the operation, patients received intramuscular injection of scopolamine 0.01 mg/kg and phenobarbital 2 mg/kg, and after they entered the operating room, the normal intravenous access was opened and the monitoring instrument was connected. Intervention group received intravenous injection of flurbiprofen axetil 1 mg/kg five minutes before anesthesia induction, control group received intravenous injection of same dose of saline at the same point in time, then midazolam 0.05 mg/kg, propofol 2.2 mg/kg, sufentanil 0.5 μ g/kg and cis atracurium 0.15 mg/kg were used for anesthesia induction, and micro pump injection of propofol + cis atracurium was adopted for anesthesia maintenance.

2.3 Serum index detection

Before operation as well as 12 h and 24 h after operation, cubital venous blood was collected from two groups of patients and centrifuged at 2 000-3 000 r/min to separate upper serum, enzyme-linked immunosorbent assay kit was used to detect NPY, SP, TNF- α , IL-2, IL-6, IL-10, ACTH, Cor, Ins, NE and E levels, and high performance liquid chromatography was used to determine the contents of Glu, and radioimmunoprecipitation kit was used to detect SOD, GHS-Px and HO-1 contents.

Table 1.

Serum pain neurotransmitter levels before and after operation.

Groups	n	Time	NPY	SP	Glu
Intervention group	92	Before operation	157.5 \pm 22.4	99.3 \pm 11.6	6.82 \pm 0.85
		12 h after operation	215.2 \pm 28.5 [#]	132.6 \pm 16.8 [#]	8.61 \pm 1.06 [#]
		24 h after operation	284.5 \pm 35.6 [#]	158.9 \pm 19.3 [#]	11.35 \pm 1.82 [#]
Control group	92	Before operation	161.2 \pm 19.4	101.2 \pm 12.4	6.91 \pm 0.91
		12 h after operation	275.8 \pm 31.2 [*]	189.7 \pm 22.6 [*]	12.46 \pm 1.52 [*]
		24 h after operation	315.2 \pm 44.8 [*]	231.2 \pm 32.9 [*]	18.87 \pm 2.25 [*]

*: compared with same group before operation, $P<0.05$; #: comparison between two groups at the same point in time, $P<0.05$.

Table 2.

Serum pain-related cytokine levels before and after operation (pg/mL).

Groups	n	Time	TNF- α	IL-2	IL-6	IL-10
Intervention group	92	Before operation	12.52 \pm 1.85	10.25 \pm 1.84	30.21 \pm 4.58	17.68 \pm 2.03
		12 h after operation	16.57 \pm 2.03 [#]	15.41 \pm 1.89 [#]	41.28 \pm 5.86 [#]	25.51 \pm 3.94 [#]
		24 h after operation	20.33 \pm 2.89 [#]	19.28 \pm 2.25 [#]	48.58 \pm 5.24 [#]	31.24 \pm 3.85 [#]
Control group	92	Before operation	12.71 \pm 1.78	10.41 \pm 1.75	30.82 \pm 4.14	18.02 \pm 1.76
		12 h after operation	23.82 \pm 3.26 [*]	19.45 \pm 2.04 [*]	57.85 \pm 7.69 [*]	45.46 \pm 6.46 [*]
		24 h after operation	31.25 \pm 4.29 [*]	32.15 \pm 4.45 [*]	69.21 \pm 9.24 [*]	62.12 \pm 7.75 [*]

*: compared with same group before operation, $P<0.05$; #: comparison between two groups at the same point in time, $P<0.05$.

2.4 Statistical methods

SPSS 19.0 software was used to input and analyze data, data comparison between two groups was by t test and test results $P<0.05$ indicated statistical significance in differences.

3. Results

3.1 Serum pain neurotransmitter levels

Before operation as well as 12 h and 24 h after operation, analysis of serum pain neurotransmitters NPY (ng/L), SP (ng/L) and Glu (μ mol/L) levels between two groups of patients was as follows: serum NPY, SP and Glu levels were not significantly different between two groups of patients before operation ($P>0.05$); 12 h and 24 h after operation, serum NPY, SP and Glu levels of both groups of patients were significantly higher than those before operation ($P<0.05$), and serum NPY, SP and Glu levels of intervention group 12 h and 24 h after operation were significantly lower than those of control group ($P<0.05$).

3.2 Serum pain-related cytokine levels

Before operation as well as 12 h and 24 h after operation, analysis of serum pain-related cytokines TNF- α , IL-2, IL-6 and IL-10 levels between two groups of patients was as follows: serum TNF- α , IL-2, IL-6 and IL-10 levels were not significantly different between two groups of patients before operation ($P>0.05$); 12 h and 24 h after operation, serum TNF- α , IL-2, IL-6 and IL-10 levels of both groups of patients were significantly higher than those before operation ($P<0.05$), and serum TNF- α , IL-2, IL-6 and IL-10 levels of intervention group 12 h and 24 h after operation were significantly lower than those of control group ($P<0.05$).

Table 3.

Serum stress-related endocrine hormone levels before and after operation.

Groups	n	Time	ACTH	Cor	Ins	NE	E
Intervention group	92	Before operation	2.52±0.35	131.2±14.6	7.21±0.93	42.31±6.83	55.24±7.84
		12 h after operation	3.41±0.46 [#]	178.7±20.3 [#]	10.23±1.75 [#]	50.38±7.82 [#]	66.12±7.85 [#]
		24 h after operation	3.98±0.52 [#]	193.1±22.5 [#]	13.02±1.99 [#]	55.52±7.24 [#]	69.31±8.02 [#]
Control group	92	Before operation	2.47±0.36	130.9±16.8	7.61±0.93	41.98±6.24	55.96±7.24
		12 h after operation	4.77±0.51 [#]	254.4±31.8 [#]	14.52±1.78 [#]	59.62±7.44 [#]	72.41±8.94 [#]
		24 h after operation	5.85±0.78 [#]	289.3±36.8 [#]	20.31±3.28 [#]	68.27±8.92 [#]	80.35±9.25 [#]

^{*}: compared with same group before operation, $P<0.05$; [#]: comparison between two groups at the same point in time, $P<0.05$.

Table 4.

Serum stress-related endocrine mediator levels before and after operation (U/L).

Groups	n	Time	SOD	GSH-Px	HO-1
Intervention group	92	Before operation	103.51±13.52	84.51±9.35	52.37±7.85
		12 h after operation	87.85±10.26 [#]	72.13±8.96 [#]	44.21±5.62 [#]
		24 h after operation	79.31±9.42 [#]	66.41±8.92 [#]	38.49±5.26 [#]
Control group	92	Before operation	102.98±14.62	84.23±10.24	53.02±7.71
		12 h after operation	74.52±9.34 [#]	61.03±8.94 [#]	34.57±4.57 [#]
		24 h after operation	66.51±8.35 [#]	55.21±6.86 [#]	29.31±3.48 [#]

^{*}: compared with same group before operation, $P<0.05$; [#]: comparison between two groups at the same point in time, $P<0.05$.

3.3 Serum stress-related endocrine hormone levels

Before operation as well as 12 h and 24 h after operation, analysis of serum stress-related endocrine hormones ACTH, Cor, Ins, NE and E levels between two groups of patients was as follows: serum ACTH, Cor, Ins, NE and E levels were not significantly different between two groups of patients before operation ($P>0.05$); 12 h and 24 h after operation, serum ACTH, Cor, Ins, NE and E levels of both groups of patients were significantly higher than those before operation ($P<0.05$), and serum ACTH, Cor, Ins, NE and E levels of intervention group 12 h and 24 h after operation were significantly lower than those of control group ($P<0.05$).

3.4 Serum stress-related endocrine mediator levels

Before operation as well as 12 h and 24 h after operation, analysis of serum stress-related endocrine mediators SOD, GSH-Px and HO-1 levels between two groups of patients was as follows: serum SOD, GSH-Px and HO-1 levels were not significantly different between two groups of patients before operation ($P>0.05$); 12 h and 24 h after operation, serum SOD, GSH-Px and HO-1 levels of both groups of patients were significantly lower than those before operation ($P<0.05$), and serum SOD, GSH-Px and HO-1 levels of intervention group 12 h and 24 h after operation were significantly higher than those of control group ($P<0.05$).

4. Discussion

Incision pain is the most important pathological factor affecting recovery after abdominal surgery, and intraoperative operation traction and extrusion to the incision can cause local tissue inflammation activation, then cause the increase of afferent nerve impulses to local sensors and lead to corresponding perception of pain. Preemptive analgesia is a newly developed analgesic mode in recent years, which provides analgesic drugs before operation to relieve the pain caused by operation and trauma. Flurbiprofen axetil is an intravenous non-steroidal drug with nonspecific inhibitory effect on cyclooxygenase, it is wrapped by lipid microspheres, and therefore, it has strong targeting and penetrating power towards the inflammatory area, and can target and gather in the incision site, quickly cross the cell membrane, and exert analgesic and anti-inflammatory effect in a short period of time[5,6]. Studies have confirmed that flurbiprofen axetil pretreatment before anesthesia can reduce the pain after orthopedic surgery, cardiothoracic surgery as well as gynecological and obstetric surgery, and meanwhile, it can inhibit the prostaglandin synthesis and the inflammatory cytokine secretion[3,4,7]. In spite of this, there is no clear report about the analgesic effect of flurbiprofen axetil pretreatment for abdominal surgery, and the flurbiprofen axetil pretreatment effect on abdominal pain after the operation was analyzed in this study.

The sensation of pain in the body depends on a variety of neurotransmitters that transmit the external noxious stimuli to the central nervous system in the form of nerve impulses. NPY, SP, and Glu are the neurotransmitters associated with pain signal transmission. SP is a tachykinin widely distributed in the nervous system, which is abundantly expressed in dorsal root ganglion

neurons, and can reduce the pain threshold of noxious stimuli and make the body more vulnerable to perception of pain[8]. NPY is a neuropeptide specifically expressed in the spinal cord neurons, which is of important value for the completion of the cell depolarization process, and can mediate the nerve impulse conduction from the peripheral to the central and cause pain[9]. Glu is a kind of amino acid with nervous excitation effect, and Glu accumulation in the synaptic cleft will act on the N - methyl - D - aspartate receptor of postsynaptic membrane, cause calcium influx, thus promote the transmission of nerve impulses, and cause corresponding pain feelings[10]. In the study, analysis of the perioperative pain-related neurotransmitter content changes showed that serum NPY, SP and Glu levels of both groups of patients increased significantly 12 h and 24 h after operation, and serum NPY, SP and Glu levels of intervention group were significantly lower than those of control group. This indicates that the secretion of pain neurotransmitters increases after abdominal surgery, and the flurbiprofen axetil pretreatment can reduce the secretion of pain neurotransmitters and reduce the degree of pain.

The surgical operation trauma will cause inflammatory response activation in local incision, and the massive release of inflammatory mediators will increase the sensitivity to pain, which in turn causes postoperative pain in the incision. TNF- α , IL-2, IL-6 and IL-10 are the inflammatory cytokines that are closely related to the incision pain and hyperalgesia[11]. TNF- α is a cytokine that changes in the early stage of inflammation and has the effect of triggering inflammatory response[12]; IL-2 is secreted by T cells and NK cells, and mainly involved in activation of humoral immunity and cascade activation of inflammatory response; IL-6 is a cytokine with pro-inflammatory activity, which can act on peripheral nerve tissue, reduce pain threshold and increase sensitivity to pain; IL-10 is a cytokine with inhibitory action, it can inhibit the secretion of multiple inflammatory mediators in multiple links, and its compensatory secretion increases in the activation of inflammatory response[13]. In the study, analysis of the perioperative pain-related cytokine content change showed that serum TNF- α , IL-2, IL-6 and IL-10 levels of both groups of patients significantly increased 12 h and 24 h after operation, and serum TNF- α , IL-2, IL-6 and IL-10 levels of intervention group were significantly lower than those of control group. This means that the secretion of pain-related inflammatory cytokines increases after abdominal surgery, and flurbiprofen axetil pretreatment can reduce the secretion of inflammatory cytokines, improve the hyperalgesia caused by inflammation, and relieve pain.

Persistent postoperative incision pain can cause the body to be in stress and cause a variety of endocrine hormones to change. Adrenal gland is an endocrine gland that plays an important role in stress. The adrenal cortex synthesizes Cor under the action of hypothalamic trophic hormone ACTH, which on the one hand, can

enhance the ability of the body to endure trauma, and on the other hand, has glycemic effect and promotes the compensatory secretion of Ins at the same time of elevating blood sugar[14]. The adrenal medulla massively synthesizes and secretes NE and E on the basis of sympathetic nerve excitement, which can cause hemodynamic fluctuation[15]. The stress state not only causes changes in endocrine hormones, but also causes oxidative stress reaction activation and massively consumes SOD, GSH-Px, HO-1 and other anti-oxidases[16]. In the study, analysis of the perioperative stress hormone and mediator contents showed that serum ACTH, Cor, Ins, NE and E levels of both groups of patients significantly increased while SOD, GSH-Px and HO-1 levels significantly decreased 12 h and 24 h after operation, and serum ACTH, Cor, Ins, NE and E levels of intervention group were significantly lower than those of control group while SOD, GSH-Px and HO-1 levels were significantly higher than those of control group. This indicated that the stress response is significantly activated after abdominal surgery, and the flurbiprofen axetil pretreatment is able to inhibit the stress response. Flurbiprofen axetil pretreatment can decrease the pain extent and stress reaction, reduce the generation of pain-related neurotransmitters and cytokines, and inhibit the secretion of stress-related endocrine hormones and mediators after abdominal surgery.

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