ONCOLOGY

Concentration of β-Endorphin in Blood Plasma and Cerebrospinal Fluid During Various Types of Anesthesia in the Early Postoperation Period and in Incurable Oncological Patients

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Early postoperative syndrome in oncological patients is accompanied by a pronounced increase of plasma β-endorphin irrespectively on the type of surgery. By contrast, chronic pain syndrome in incurable patients is characterized by a decrease of β-endorphin in the plasma and cerebrospinal fluid. In patients with early postoperative syndrome, efficient epidural morphine analgesia and central epidural electrical neurostimulation reduce plasma β-endorphin. By contrast, in incurable patients with chronic pain syndrome, the content of β-endorphin in the plasma and cerebrospinal fluid increases under the effect of efficient spinal morphine analgesia (epidural or subarachnoidal). Changes in the plasma content of β-endorphin directly depend on the type of pain syndrome, its intensity, and efficiency of analgesia, and may serve as a criterion of analgesia.

Key Words: *β-endorphin; pain; cancer; analgesia*

Surgical intervention accompanied by mechanical damage to tissues, peritumoral inflammation, tumor-induced compression and damage to organs, tissues, nerve trunks, plexuses, spinal cord, and brain promotes the release of active substances and stress hormones that play an important role in the development of acute and chronic pain syndrome in oncological patients.

Endogenous opioid peptides (endorphins) play an important role in nociception and concomitant nociceptive reactions. Endorphins are functionally related to the system of opioid receptors involved in the nociceptive reactions.

High density of opiate receptors in the substantia gelatinosa of the dorsal spinal horns of the cord provides the basis for spinal epidural and subarachnoidal opioid analgesia. These methods are based on the blockade of nociceptive signals at the spinal level by morphine binding to opioid receptors.

Epidural or subarachnoidal injection of morphine even in a minimal dose produced pronounced analgesia, which favored wide application of these analgesic procedures in clinical practice. Similar effect on the nociceptive synaptic transmission is probably produced by central epidural electrical neurostimulation (CEENS) based on activation of antinociceptive structures in the spinal cord and brain as a part of comprehensive analgesic approach [4].

Our aim was to study the effect of spinal morphine analgesia and CEENS on the content of β-endorphin in the plasma and cerebrospinal fluid (CSF) in oncological patients with early postoperative and chronic pain syndromes.

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MATERIALS AND METHODS

Three groups of patients were studied. Groups 1 and 2 comprised oncological patients with postoperative pain syndrome, while group 3 consisted of inoperable incurable oncological patients with chronic pain.

Group 1 (n=22) consisted of patients subjected to pneumonectomy and lobectomy (14), thoracotomy (3), extirpation and plasty of a esophagus (3), and transpleural gastrectomy and proximal stomach resection (2).

Postoperative epidural analgesia was made by injection of 5 mg morphine in 10 ml isotonic sodium NaCl an implanted catheter. Puncture and catheterization of the epidural channel were made prior to operation at the T_{II}-T_V level depending on planned surgery. Pain intensity and analgesia efficiency were scored. The analgesic effect was considered as sufficient if pain score decreased to 0-1 and was insufficient if the pain score was 2 and more points.

In each patient, the duration of analgesia was determined. Plasma level of β-endorphin was determined before and after operation against the background of pain and 1 h after epidural morphine.

Group 2 (n=30) consisted of patients with stomach carcinoma subjected to gastrectomy (20) and subtotal stomach resection (10). In this group, postoperative analgesia was performed by CEENS (15 patients, test subgroup) or subcutaneous promedol (15 patients, control subgroup).

On the day of operation, active electrode (a PEPD-1 wire in Teflon isolation) was transcutaneously introduced into the epidural channel at the L_{III}-L_V level, while indifferent (passive) electrode was placed on the forehead. We used rectangular current pulses with negative phase generated by a Delta-301 neurostimulator. Electrical stimulation was started immediately after pain in the postoperative wound appeared and continued for 3-5 days. Stimulation parameters were chosen according to subjective sensations of the patients. Analgesia was considered effective if pain was completely cut or if a weak pain that did not restrict movements appeared during cough. If this level of analgesia was not achieved, promedol was additionally administered. In the control group the intervals between promedol injections were shortened.

In addition, analgesia efficiency was evaluated on the basis of the amount of administered narcotics. Analgesia was rated as excellent, if no additional injections of narcotics were needed; otherwise it was considered good or poor, if the amount of additional analgetic drugs decreased by 70-75%, 25-50%, and 25%, respectively, in comparison with the control.

The plasma level of β-endorphin was measured prior to operation, after operation at the highest pain score, 1 h after the start of analgesia, and at the end of postoperation days 1 and 3.

Group 3 (n=30) consisted of patients with pronounced chronic pain syndrome, in which the tumor process of various localization was generalized.

The patients were subdivided into three subgroups depending on the type of analgesia: the 1st subgroup (n=10) was treated with epidural morphine (5 mg), while the 2nd (n=11) and the 3rd (n=9) groups were treated with subarachnoidal morphine (2 mg and 5 mg, respectively). Puncture and catheterization of the epidural channel were performed by routine methods. Puncture of the spinal cord was made at the L_{II}-L_{III} level. Morphine was injected in above specified doses in 10 ml isotonic NaCl.

Concentration of β-endorphin in the plasma and cerebrospinal fluid was determined against the background of pain and 1 and 3 h after injection of morphine by radioimmunological method with Immuno Nuclear Corporation kits.

Pain intensity and efficiency of analgesia was scored using a 4-point scale: no pain (0), weak pain (1), moderate pain (2), severe pain (3), and very strong pain (4).

Surgery in the 1st and 2nd groups was performed under endotracheal narcosis (neuroleptanalgesia+ nitrous oxide:oxygen 2:1 mixture). The data were analyzed statistically using Student's t test.

RESULTS

In group 1, a good analgesic effect was achieved with epidural morphine in 15 patients (1st subgroup), while in 7 patients (2nd subgroup) analgesia was insufficient, although there was no significant difference in the intensity of postoperative pain syndrome (Table 1). One hour after injection of morphine, pain intensity markedly decreased in the 1st and, to a lesser degree, in the 2nd subgroup.

There was a significant difference in the duration of morphine-induced analgesia.

Plasma level of β-endorphin before operation varied in all patients. A pronounced decrease in plasma β-endorphin was revealed in the patients with good analgesic effect (1st subgroup) 1 h postinjection. In the 2nd subgroup, the concentration of β-endorphin remained at a high level and little differed from the corresponding value before analgesia (Table 1).

In group 2, plasma β-endorphin also markedly increased during postoperative pain syndrome (Table 2). One hour after the start of CEENS a pronounced decrease in plasma β-endorphin content was observed against the background of efficient analgesia. At the end of postoperative day 1 the level of β-endorphin approached the initial values (p<0.05).

In group 3 patients the level of β-endorphin was 17.3±3.3 pg/ml. In all patients spinal morphine irrespective of the dose reduced pain 1 and 3 h postinjection, which was accompanied by an increase of β-endorphin concentration in CSF and plasma (Table 3).

The patients in all 3 subgroups demonstrated good analgesic effect after 10-18, 8-22, and 12-72 h, respectively.

In the 3rd group, the concentration of β-endorphin did not depend on the type of analgesia and morphine dosage.

Pronounced analgesic effect was accompanied by a pronounced increase in cerebrospinal and plasma content of β-endorphin 1 and 3 h after procedure in comparison with its level during pain, while the level of this neuropeptide correlated with analgesic effect.

Epidural or subarachnoidal injection of morphine produced higher concentration of this agent in comparison with intramuscular injection and determines more potent analgesia with a pronounced increase of cerebrospinal β-endorphin [12,13].

Due to its high concentrations and hydrophilic properties, morphine was present in CSF for a longer period, which provided a prolonged analgesic effect. There is evidence that the half-elimination periods of morphine from CSF and plasma are similar, but elimination of morphine proceeds more slowly in CSF than in the plasma [11].

Therefore, in incurable oncological patients with acute postoperative and chronic pain syndrome spinal analgesia was highly efficient.

Acute pain syndrome accompanied by activation of hypothalamic endorphin mechanisms promoted the release of β-endorphin in the pituitary and increased its plasma and cerebrospinal levels [2].

Plasma content of β-endorphin increased during pain syndrome in the early postoperative period probably due to its enhanced synthesis and release in response to pain stress [9,14].

The studies in the early postoperative period showed that during effective opiate- and CEENS-induced analgesia the content of β-endorphin returned to the ini-

TABLE 1. Plasma Concentration of β-Endorphin and Efficiency of Morphine Epidural Analgesia in Early Postoperative Period in Thoracic Oncological Patients ($M\pm\sigma$)

Patient subgroups	End-points	β-Endorphin, pg/ml	Pain syndrome, points
Group 1: good analgesic effect of morphine (5 mg, n=15)	Before operation	65.8±9.6	0
	Pain on postoperation day 1	164.0±22.5	3.07±0.15
	One hour after morphine injection	82.4±10.2	0.53±0.08
Group 2: insufficient analgesic effect of morphine (5 mg, n=7)	Before operation	80.7±12.2	0
	Pain on postoperation day 1	159.6±25.2	3.05±0.22
	One hour after morphine injection	127.7±18.3	2.44±0.11

TABLE 2. Plasma Concentration of β-Endorphin and Efficiency of CEENS Analgesia in Early Postoperative Period in Patients with Stomach Carcinoma ($M\pm\sigma$)

Patient subgroups	End-points	β-Endorphin, pg/ml	Pain syndrome, points
Group 1 (test, n=15)	Before operation	19.0±1.8	0
	Pain after operation	71.6±4.5	3.25±0.2
	At the end of postoperation day 1	42.5±7.4	0.45±0.03
	One hour after the start of CEENS	23.8±1.4	0.3±0.01
	Postoperation day 3	23.8±3.1	0.3±0.001
Group 2 (control, n=15)	Before operation	21.1±1.6	0
	Pain after operation	67.8±4.6	3.34±0.09
	One hour after the start of CEENS	51.2±4.0	2.21±0.1
	At the end of postoperation day 1	37.0±2.6	1.8±0.16
	Postoperation day 3	26.9±1.7	1.0±0.01

TABLE 3. Effect of Various Methods of Analgesia on Concentrations of β-Endorphin in Cerebrospinal Fluid and Plasma of Incurable Patients ($M\pm\sigma$)

Patient subgroups	Analgesia	Parameter	Time of cerebrospinal fluid analysis			Time of plasma analysis	
			during pain	after analgesia		during pain	after 1 h
				after 1 h	after 3 h		
Group 1 (n=10)	Epidural morphine, 5 mg	β-Endorphin, pg/ml	12.2±2.4	27.8±3.8	78.6±7.7		
		Pain, points	3.5±0.1	2.1±0.1	1.8±0.2		
Group 2 (n=11)	Subarachnoidal morphine, 2 mg	β-Endorphin, pg/ml	17.9±4.5	32.3±4.9	85.3±10.9		
		Pain, points	3.7±0.1	2.1±0.1	1.5±0.39		
Group 3 (n=9)	Subarachnoidal morphine, 5 mg	β-Endorphin, pg/ml	18.6±3.1	35.2±3.6	89.1±9.6	1.0±10.3	128.3±29.4
		Pain, points	3.5±0.3	2.0±0.25	1.5±0.25		

tial level. By contrast, the high level of plasma β-endorphin was characteristic of insufficient analgesia and sustained pain syndrome [1,7,8].

There is a hypothesis that opiate receptors normally bind minor amount of β-endorphin [10]. Binding of exogenous opiates to receptors downregulates the synthesis of β-endorphin.

High plasma concentrations of β-endorphin under conditions of insufficient analgesia can be maintained because morphine injected epiduraly or subarachnoidally cannot reach and bind to opiate receptors or its concentration is low for efficient blockade.

CEENS (i. e. electrostimulation of antinociceptive structures in the spinal cord and brain) produces good analgesia and reduces plasma content of β-endorphin to the initial levels [4].

CEENS is a highly efficient method of postoperative analgesia, which makes unnecessary the use of parenteral narcotic analgetics in 53.3% patients. Good and excellent results of CEENS analgesia were attained in 96.7% patients [4]. The total dose of narcotic analgetics administered during 3 postoperative days was 220.0±8.4 mg per patient in the control subgroup and 15.0±4.0 mg in the test subgroup (or 14.7-fold lower).

CEENS is a reliable protection from the damaging effect of postoperative stress reaction. It more efficiently prevents hyperactivation of the pituitary–adrenal and endogenous opioid systems than routine promedol analgesia.

There is evidence that the level of ACTH and hydrocortisone increased at the peak of postoperative pain together with a pronounced increase in β-endorphin (by more than 3 times in comparison with the initial level). The revealed regularity attests to synergistic reactions of the pituitary-adrenal and endogenous opioid systems in response to surgical intervention [5].

Activation of these systems is an adaptive response to stress directed towards inhibition of the pain syndrome, stabilization of cell membranes and intracellular structures, cell protection from proteolysis [3]. Therefore, the dynamics of changes of ACTH, cortisol, and β-endorphin in the postoperative period could be considered as a measure of stress reaction and quality of analgesia for comparison of different methods of analgesia [1,6].

Our data show that in contrast to acute postoperative pain, the long-term pain syndrome in incurable oncological patients is characterized by decreased content of β-endorphin in the liquor and plasma. Neurophysiologists explain this fact by exhaustion and insufficient production of β-endorphin under conditions of persistent chronic nociceptive stimulation. Efficient analgesia increases the level of β-endorphin. This increase directly correlates with the intensity of pain syndrome and can serve as a criterion of effective analgesia in incurable patients.

Thus, irrespective to the type of surgical intervention, the early postoperative pain syndrome in oncological patients is characterized by markedly increased plasma content of β-endorphin. By contrast, chronic pain syndrome in incurable oncological patients is accompanied by a decrease in the level of β-endorphin in the CSF and plasma. In patients with early postoperative pain syndrome, plasma β-endorphin drops under conditions of efficient epidural analgesia with morphine and CEENS. By contrast, in incurable oncological patients with chronic pain syndrome the content of β-endorphin in the plasma and CSF grows after efficient epidural or subarachnoid morphine analgesia. Changes in plasma content of β-endorphin correlate with the type of pain

syndrome, its intensity, and analgesia efficiency and can serve as a criterion of proper analgesia.

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