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MORPHOLOGICAL CHANGES OF THE SKIN IN A POSTOPERATIVE WOUND AT THE SYNDROME OF OPIOID-INDUCED HYPERALGESIA

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Resume

The article describes the morphological changes of the skin in the area of postoperative wound. It has been found that the use of high doses of fentanyl (10-20 mcg/kg/hr) by continuous infusion for analgesia in the early postoperative period in children operated on for tumors of abdominal cavity can cause opioid-induced hyperalgesia, which is accompanied by morphological changes in the skin around the postoperative wound with the development of necrosis in the center of it, with expressed perifocal reactive changes in the form of significant inflammation and violations of microcirculation with the formation of the small nerve fibers on the 14^{th} day. There was fibrosis of the derma with the formation of large amount of collagen fibers with their edema and lamination.

Key words: analgesia, hyperalgesia, skin biopsy.

Introduction. Pain, that feels a child in early postoperative period, changes the development of the nociception system and results in irreversible functional and structural changes in CNS, which change "program" of response to the pain in the future [1]. Pain syndrome in early postoperative period is an actual problem of clinical surgery, anesthesiology and resuscitation. In the literature devoted to pain management in postoperative period there is an evidence that from 33% to 75% of patients, who underwent scheduled or emergency surgery, suffered from postoperative pain. Damage of tissues during surgical invasion starts a cascade of pathophysiological changes in peripheral and central nervous system, which lead to the formation of post-surgical chronic pain syndrome (CPS). Despite the wide range of drugs and analgesia techniques most patients experience pain of varying intensity during the postoperative period [1,2]. An inadequate analgesia in early postoperative period impairs the course and prognosis of this period and contributes to the development of hyperalgesia. Hyperalgesia is a state of the increased sensitivity to pain that is caused by intensive nociceptive stimulation or can be induced by opioid analgesics. Hyperalgesia is realized mainly at the level of spinal cord and is associated with increased intensity of pain and accordingly the stress response to pain is developed, risk of chronic pain is increased and promotes the development of tolerance to opioids and necessity in increasing doses [3,5,8,10]. For the diagnostic of hyperalgesia determining of pain in the area of postoperative wound threshold von Frey monofilaments is used. By using monofilaments in the ascending order to the slightest pressure force which is perceived by patients as pain [4,6,9]. In treatment of early postoperative period in children using of continuous infusion of fentanyl is necessary to ensure an adequate level of anesthesia, postoperative stress reduction and adaptation to the mechanical ventilation (MV). Fentanyl (or other opiate analgesic) is used as a continuous infusion at a constant speed in all cases in early postoperative period.

The **aim** of the study was to determine the morphological changes in the area of skin in postoperative wound in early postoperative period in children with opioid induced hyperalgesia.

Materials and methods. 14 children (average age 14,4±2,4 years) with tumors of abdominal cavity in early postoperative period. Before determining the threshold of pain fentanyl infusion was stopped for 60 minutes, which is sufficient to finish drug action. To determine the mechanical pain threshold was used a set of von Frey's monofilamnets (VFMs), calibrated to exert pressure on skin with increasing strength of 4g (39.216 mN) to 300g (2941.176 mN) (Touch-Test Sensory Evaluator, North Coast Medical Inc., CA, USA). Monofilaments were pressed to the skin surface at the angle of 90º, while they were bend for

1-1,5s. The monofilaments were used in the ascending order. Between the studies was withstand an interval of 10s. Mechanical pain threshold was defined as the smallest power of pressure, which causes the pain reaction in patients (4 points or more for Behavioral Pain Scale (BPS). Pain threshold was measured on the surface around the postoperational wound. Simultaneously was assessed neurological status, indicators of hemodynamic and respiratory system. Received daily dose of fentanyl was also fixed. We were investigating histological changes in the structure and nature of the tissue reactions in the wounds in children at application of different types of anesthesia. The first (control) group included healthy children with normal skin. The second group included children with the presence of wounds, which underwent anesthesia by continuous infusion of fentanyl. On the 3^{rd}, 7^{th} and 14^{th} day were performed a biopsy of wounds – were taken fragments of skin with underlying tissues in the wound, stepping 0.5 cm from its borders. The collected materials were fixed with 10% aqueous solution of neutral formalin during 48 hours, than it was washed under running water, thereafter dehydration in system of multiatomic alcohols was conducted and standard procedure of pouring into paraffin. Prepared semi light slices of 7–8mm were stained with hematoxylin and eosin (main method of staining histological preparations) for the evaluation of pathological changes and reactions of tissues during occurrence and wound healing (assessment of the state and composition of tissues in edges and the bottom of the wound, the presence and nature of pathological and reparative changes in skin wound), the character of microhaemocirculation violations. The histological preparations from slices of tissue was made on the 14^{th} day of the experiment the method of staining with hematoxylin and eosin was used and silvered by the Foote method for the determination of the development in tissues in process of healing of small nerve endings and their pathological changes. Microscopy of histological preparations was carried out by using a light microscope OLIMPUS BX 41 with the use of increments of 40, 100, 200 and 400 times.

Results and discussion. All 14 patients included in the study were operated on abdominal tumors and were in early postoperative period. For all patients were performed respiratory support by device “Hamillton C2” – ASV mode with the following parameters - FiO2, 30%, PEEP 2 cm H_20, PIP 15-20 cm H_20; at the moment of the study hemodynamics were stable. For all patients in early postoperative period were performed anesthesia by continuous fentanyl infusion. Fentanyl dose was ranged from 10 to 20 mg/kg/hr and the average dose per day was 16,4±3,2 mcg/kg/hr (corresponding to the daily dose 600-7200 mcg/day). Average duration of the anesthesia was 54,4±4,2 hours.

In first (control-intake patients) group skin had standard histological structure: from outside skin is represented by the layer of stratified squamous epithelium – the epidermis. Underlying connective tissue basis – derma (skin) with no sharp boundary moves into the subcutaneous tissue – hypodermis. Derma includes two types of connective tissues that form papillary and reticular layers. The clear border between layers is absent. The papillary layer is formed by loose connective tissue, and is expressed unevenly. In some places it is nearly invisible, and sometimes outer epidermis relief, that follows the contours of the connective tissue papillae, is greatly protrudes in relation to nearby skin. Reticular layer is well developed, submitted by dense fibrous unformed connective tissue. This layer contains skin appendages – hair, closely associated sebaceous gland. The basis of hypodermis is adipose tissue. Adipocytes, which form adipose tissue, are composed into particles of different size and shape – compact clusters of fat cells. Between themselves particles are separated by layers of loose connective tissue, where blood vessels and nerves passing. Derma is delimited inside by platysma.

In patients of the second group in 3 days after fentanyl infusion was observed the following morphological changes: area of injury was widespread with no precise borders, with the development of necrosis in its center (thickness of the layer of necrotic tissue was up to 5 mm) with expressed perifocal reactive changes in the form of significant inflammation (thickness of the area of reactive changes was up to 7 mm), there were serious violations of microcirculation. Vessels in derma in affected area around the wound channel were paretic dilated with the expressed degenerative changes in the endothelium, plethoric, with marginal standing of leukocytes in them. Around skin appendages and perivascular was defined small clusters of mononuclear cells – lymphocytes and monocytes with the presence of single leukocytes. Structure of the underlying hypodermis was disrupted due to necrosis and substantial cellular inflammatory infiltration. In the dermis and hypodermis was observed accumulation of the edematous liquid as a manifestation of the disorder of microhaemocirculation with lamination of collagen and elastic fibers of dermis. In edematous liquid was also found mononuclear cells like blood monocytes, lymphocytes, and segmented leukocytes in large quantities (Fig. 1).

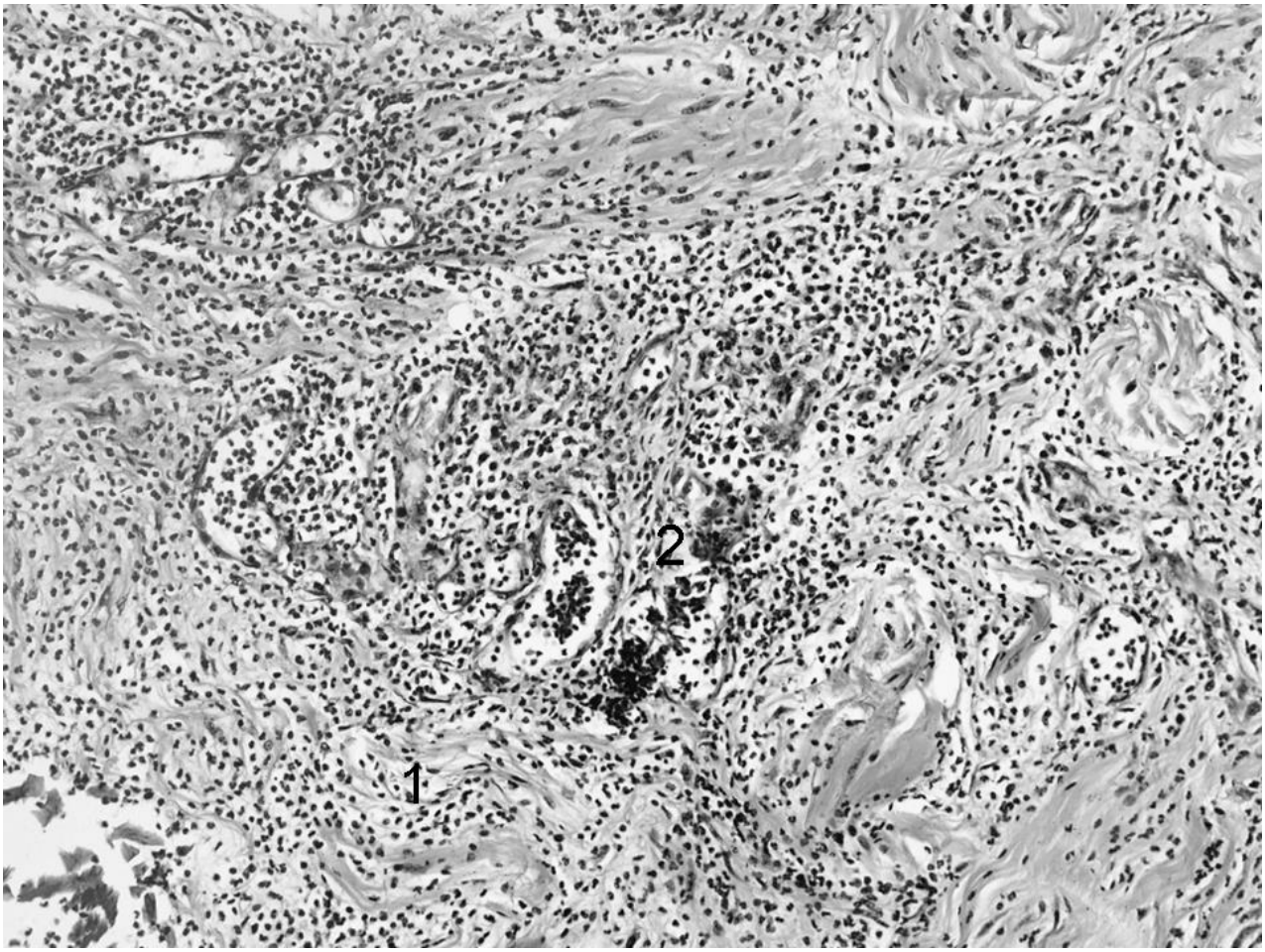

Fig. 1. Skin in the wound after 3 days of treatment, second group. Hematoxylin-eosin. X200.

1 - Abundant polymorphocellular diffuse inflammatory infiltration in the dermis;

2 - Leukostasis in vessels.

So, after 3 days of fentanyl infusion in the affected tissue was observed early stages of inflammatory process in the form of expressed signs of alteration and significant manifestations of exudation process are determined. In children by 7^{th} day after fentanyl infusion inflammatory changes in skin tissue were seen. Among inflammatory cells were determined young forms of fibroblasts. In the hypodermis reactive inflammatory infiltration were observed. The cellular composition of infiltrate was presented by segmented leukocytes, among which were determined a small number of lymphocytes and monocytes (macrophages, polynuclear giant cells of foreign bodies). The vessel reaction in the form of moderate hyperemia, edema of hypodermis and reticular layer of dermis were observed in the area of inflammation. There were determined single bundles of collagen fibers of dense fibrous

framed connective tissue of the dermis with signs of swelling, lamination, fragmentation of fibers (Fig. 2).

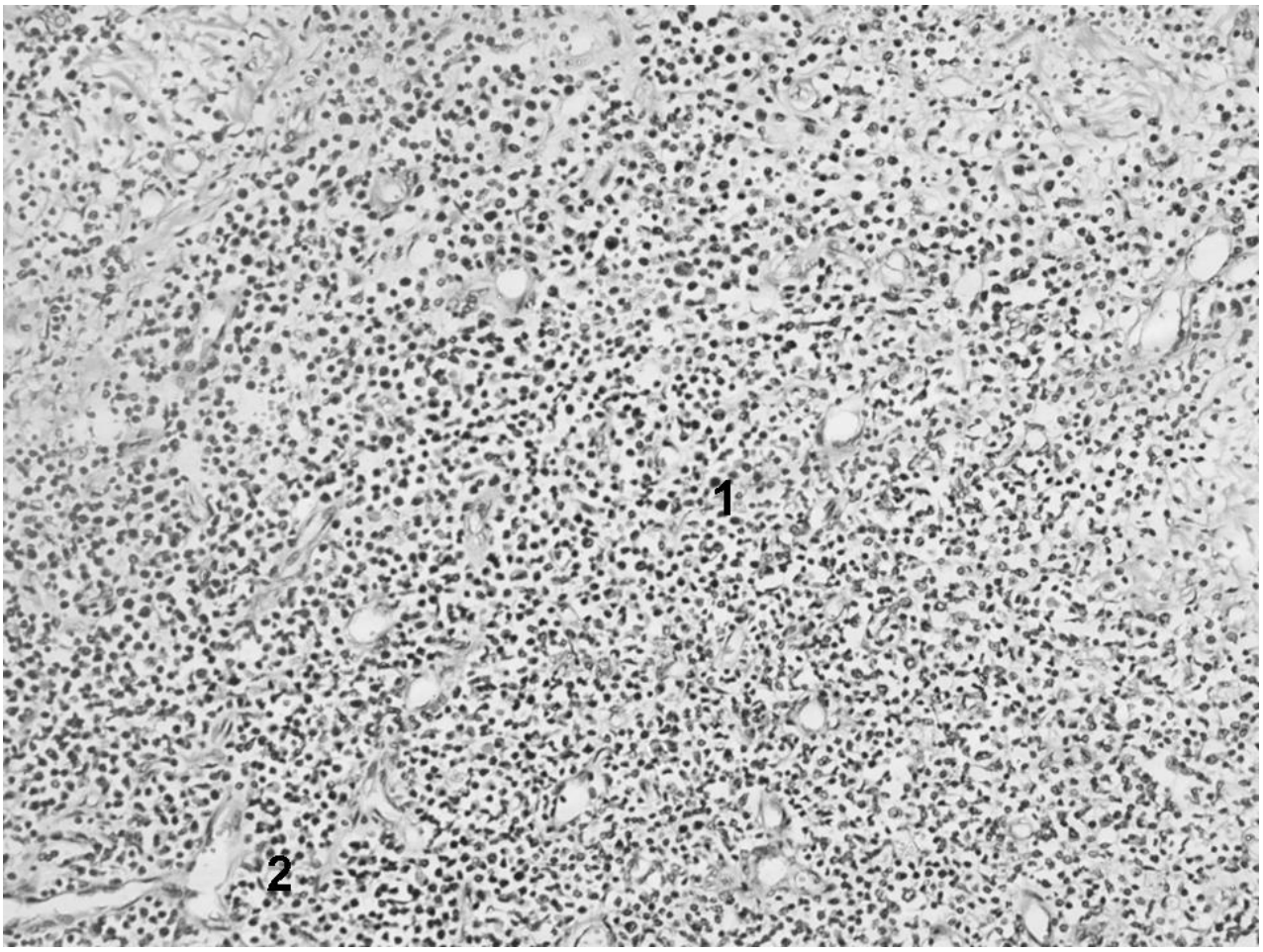

Fig. 2. The piece of skin in the area of wound after 7 days of treatment. Second group. Hematoxylin-eosin. X200.

1 – young granulation tissue with polymorph cellular inflammatory infiltration;

2 – small newly formed vessels.

On 14th day in the second group children were noted almost complete resolution of inflammation and wound healing. In the former area of inflammation connective tissue scar was formed, which was completely cuticularizated. Under the scar tissue was determined the layer of framed fibrous connective tissue. The scar tissue partially was replaced by structural elements of the skin that are inherent in the norm. Normal dermal nipples, hair follicles, sebaceous and sweat glands were not determined. The scar tissue was composed of a large

number of fibrocytes and collagen fibers. In hypodermis were observed slight signs of microhaemocirculation violation in a form of plethora of vessels.

So, these changes indicated almost complete resolution of inflammatory changes with the formation of connective tissue scar, in which remodeling process was observed. In the second group of children on 3rd and 7th days as a result of fentanyl infusion was developed expressed inflammation with significant changes in microcirculation, significant polymorphocellular inflammatory infiltrate, the maximum of which was developed on the 3rd day. In this group of patients as a result of wound healing and inflammation resolution almost complete scar was formed, but without applications of skin, maintaining slight inflammatory-cellular infiltration and slight violations of microcirculation.

On 14th day in patients of the second group in the area of scar tissue formation was occurring formation of small nerve fibers, but in small quantities. There were a significant fibrosis of derma with formation of large number of collagen fibers with their edema and lamination were observed. There were determined significant perineural edema, fragmentation of certain neural fibers (Fig. 3).

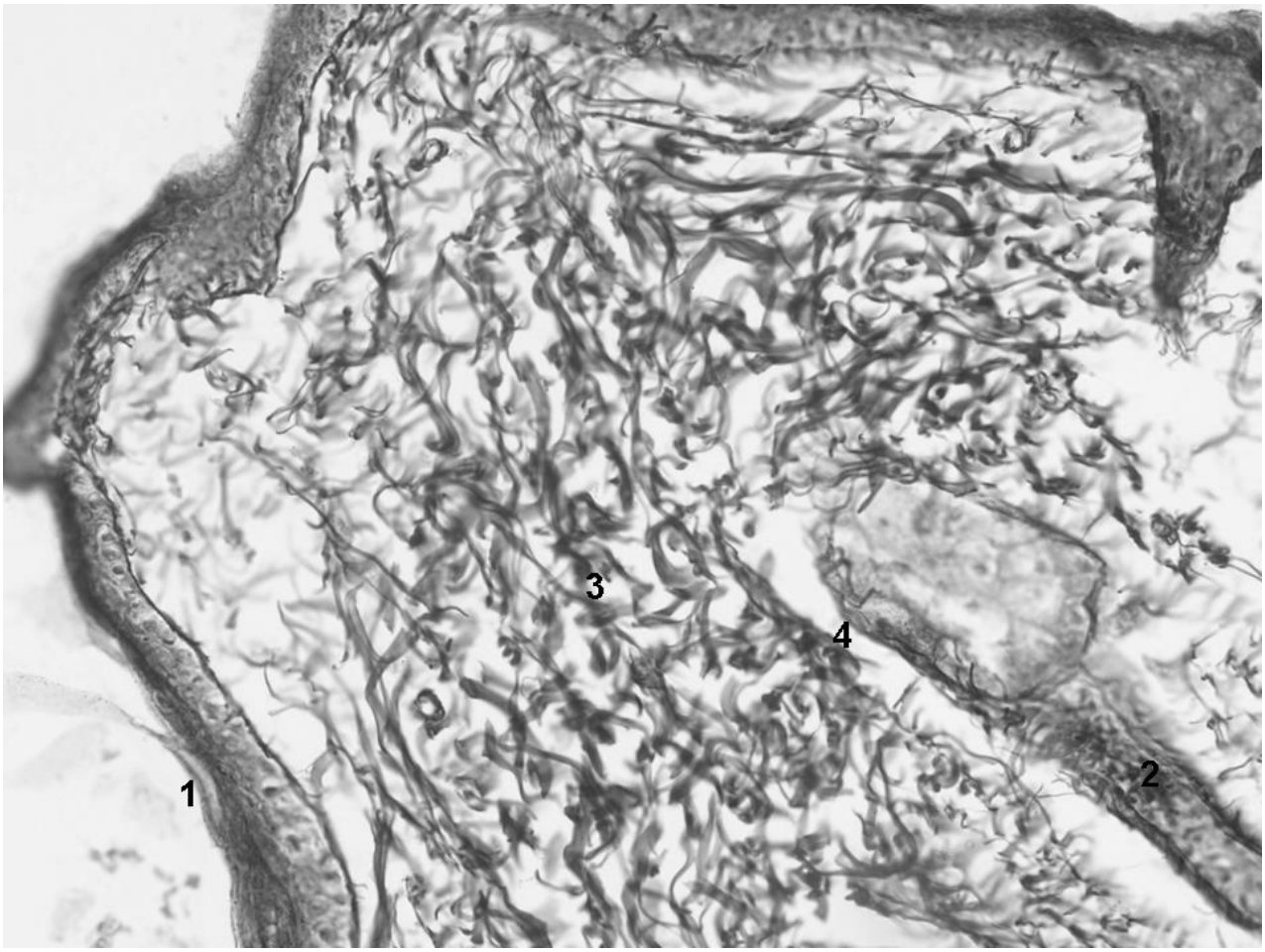

Fig. 3. The skin in the area of scar on the 14th day. The second group. Silvering by Foote. X400.

1 – epidermis;

2 – applications of skin (hair follicles);

3 – collagen fibers;

4 – fragmented small nerve fibers in small quantity, significant perineural edema.

So, in children after fentanyl infusion in the wound area tissues were determined the most expressed alternative and inflammatory changes with significant violations of microhaemocirculations. In the process of wound healing almost complete scar was formed, but with insufficient development of nerve fibers and small quantity of skin derivatives in it.

Conclusions

1. The high doses of fentanyl (10–20 mcg/kg/hr) used by the method of continuous infusion for the anesthesia in early postoperative period in children were

contributed to opioid induced hyperalgesia which was accompanied by morphological changes in the skin around postoperative wound.

2. On the 3rd and 7th days after fentanyl infusion the next morphological changes in tissues were observed: area of injury was widespread without clear borders with the development of necrosis in the center (necrotic tissue thickness was up to 5mm) with expressed perifocal reactive changes in the form of significant inflammation (zone of reactive changes thickness was up to 7mm) with significant violations of microcirculations.

3. On the 14th day on the background of fentanyl use in the area of scar tissue formation there was a small nerve fibers formation. There was an expressed fibrosis of derma with formation of plenty collagen fibers with edema and lamination. There were a significant perineural edema and fragmentation of certain nerve fibers.

4. Further studies are required for optimizing and choosing of schemes of adequate method of anesthesia in children with the use of opioid analgesics and anesthetics of other groups.

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