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Review

PERSONALISED PAIN TREATMENT IN INTENSIVE CARE UNITS - MONITORING OF NOCICEPTION

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SUMMARY – The personalization of pain treatment in intensive care units was developed due to the interindividual variability and heterogeneity of critically ill patients. A personalized approach to pain is based on the prediction and continuous assessment of pain. In critically ill patients, this approach includes the knowledge of the underlying cause of pain related to the primary diagnosis, the causes of procedural pain and previous chronic pain conditions of the patient, in order to apply a specific therapeutic approach. Available treatment recommendations emphasize the use of adaptive or dynamic analgesia, with titration of analgesics according to changes in the clinical state of patients. They indicate the necessity of pain assessment with tools for pain intensity assessment and therapy evaluation, as well as the need for assessment at regular time intervals. Despite treatment guidelines, clinical practice shows significant deviations from evidence-based recommendations. The reasons are primarily the non-recognition of pain, insufficient knowledge of analgesics (type and dose), lack of regular assessment and inadequacy of the applied tools for pain assessment. In terms of personalization, there is a need to develop objective pain assessment methods, such as sensitive and pain-specific tools that do not rely on the patient's ability to communicate and are independent of assessors, disease characteristics and pharmacological interventions in critically ill patients.

Key words: *pain; nociception; personalization; monitoring; intensive care medicine*

Introduction

The personalization of pain treatment in Intensive Care Units (ICUs) was developed due to the interindividual variability and heterogeneity of patients in ICUs. Analgesic recommendations emphasize the use of adaptive or dynamic analgesia. One imperative of the clinical approach is to assess pain intensity at regular time intervals and titrate analgesics based on changes in the patient's clinical condition.

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The personalized pain approach is based on continuous pain assessment, knowledge of the disease mechanism, and the application of specific treatment options. In addition to the causes of pain related to the primary diagnosis, the causes of procedural pain and previous chronic pain conditions should be known[1]. Despite treatment guidelines, clinical practice shows significant deviations from evidence-based recommendations. The reasons are the non-recognition of pain, insufficient knowledge of analgesics (type and dose), lack of regular assessment and inadequacy of the applied tools for pain assessment.

The frequency of pain in ICU patients ranges up to 50%, and in 50% of them it is of medium to severe intensity during treatment, both at rest and with

procedural pain[2,3]. The main reasons for the ineffective treatment of pain in ICU are related to the deficit of knowledge regarding the pathophysiological effects of pain and related therapeutic principles, as well as the assignment of low priority to pain therapy compared to other therapeutic procedures in ICU[4]. The staff often underestimate the severity of pain, believing that no pain assessment at regular time intervals is necessary[5].

In addition to the pain related to the underlying disease, the treatment of pain in the ICU should include the treatment of periprocedural pain, pain related to invasive therapeutic procedures, patient care and changes related to sensory disorders and delirium[4]. At the same time, pain related to the underlying disease should be treated continuously, while bolus techniques of analgesic therapy are applied in the treatment of intermittent/periprocedural pain[6].

The goal of pain treatment in the ICU is to reduce the harmful effects of acute pain on organs and organ systems, thereby influencing the treatment outcome.

Assessment of pain intensity is carried out as a self-assessment, usually using one-dimensional pain scales in patients who can communicate. In patients unable to do so (cognitive dysfunction, sedation), other validated tools for assessing pain intensity are required[7]. The inconsistency in the selection of validated assessment tools is an obstacle to the successful treatment of pain in the ICU[8]. Therefore, in terms of personalization, there is a need to develop objective pain assessment methods as well as sensitive and pain-specific tools that do not rely on the patient's ability to communicate and are independent of assessors, disease characteristics and pharmacological interventions in critically ill patients.

The importance of monitoring pain and regular assessment is also evident from the effect of the implementation of pain assessment tools in ICU on the outcome of patient treatment. In 2015, Gerorgiu et al. conducted a systematic review of studies on the effect of pain assessment in critically ill patients on the outcome of treatment. Ten studies were included and all showed that pain assessment positively affected the outcome, including a reduction in duration of mechanical ventilation and number of days of hospitalization in an ICU, as well as reduction in the frequency of adverse events and mortality[9].

ICU pain management recommendations also emphasize pain monitoring. In 2018, updated recommendations from The American College of Critical Care Medicine (ACCM) for managing pain, agitation and delirium were published, supplementing the guidelines published in 2013. They indicate the necessity of both pain assessment with pain assessment tools and the need for assessment at regular time intervals[10,11].

An ideal pain assessment tool should be able to determine the presence of pain intensity in patients that are awake and nociceptive stimulation in patients unable to respond[12].

Despite the recommendations, clinical practice shows that less than 50% of ICU physicians and other health professionals assess the severity of ICU pain. Moreover, even those that do also rarely assess the severity of pain. In addition, insufficient education to assess pain intensity is considered one of the most frequent factors for its poor treatment[13].

Using algorithms that emphasize adequate analgesia before sedation reduces the requirements for sedatives and the duration of mechanical ventilation, without increasing the frequency of accidental extubations or post-traumatic stress disorder. This improves outcomes and, regardless of the algorithm used, analgesia should be targeted and titrated to this effect. Therefore, guidelines and protocols should be available in every intensive care unit[6].

Tools for pain assessment

Vital signs

Vital signs (elevated blood pressure, increased heart rate, changes in breathing rate) are considered poor indicators of pain intensity. In clinical practice, however, they are often used for its assessment. They are not specific for pain assessment; they can change in correlation with pathophysiological conditions that are not correlated with pain[14]. Precisely because of this fluctuation, they should be understood as an unwanted event in severe pain rather than as an indicator for pain assessment[15]. Therefore, they have not even been validated as a pain assessment tool[11].

Scales for assessing pain intensity

Self-report pain scales allow patients to express their own subjective experience of pain. They are considered the standard for patients who can communicate independently and reliably. The reasons for this are that the assessment of pain intensity by healthcare workers is imprecise and significantly underestimates the intensity of pain for very high scores[11]. Unidimen-

sional scales evaluate one aspect of pain, usually intensity, and can be categorical or numerical. NRS – the numerical scale – is the most commonly applied. It allows patients to evaluate their pain on a numerical axis from 0, no pain, to 10, the most significant possible pain. NRS has proven to be the most feasible and has the best negative predictive value of 90%[5].

Multidimensional scales for self-assessment of pain better reflect the experience of pain[16].

In conditions where self-assessment of pain by the patient is not possible, different tools are used that incorporate behavioral and physiological variables. Both the Behavioural Pain Scale (BPS) and Critical Care Pain Observation Tool (CPOT) were validated in ICUs. Both scales can be used in patients with an established artificial airway. The BPS evaluates three behavioral domains: facial expression, upper extremity movements and ventilatory compliance in response to movement or a painful stimulus. Each of these domains is ranked from 1 (no response) to 4 (complete response), with a possible score of 3 to 12[17]. The CPOT evaluates four behavioral domains: facial expression, movements, muscle tension and ventilator compliance. Each component is ranked from 0 to 2, with a total score of 0 to 8[18].

Monitoring of nociception

Unlike pain, which is a subjective feeling and subject to self-assessment, nociception implies the processing of nociceptive stimuli. It is a sequence of physiological events in the body that occurs due to harmful stimuli[19]. The nociception reaction is closely connected with the "surgical" response to stress, with a shift towards sympathetic activity and a decrease in parasympathetic tone[20]. Painful stimuli cause a series of peripheral and central changes that activate the sympathetic part of the autonomic nervous system. The sympathetic system originates from the spinal cord and, stimulated by various chemical messengers, acts on several organ systems, including the heart (increased heart rate), lungs (increased respiratory rate), blood vessels (vasoconstriction), eye (pupil dilation) and skin (increased work sweat gland). Therefore, in unconscious patients, tools have been used to measure the sympathetic response to stressful stimuli in these locations[21,22]. The problem with measuring the sympathetic response to a specific painful stimulus is that several other stimuli can act on the sympathetic system at the same time, which can either decrease the response or increase it. Various drugs affecting the autonomic nervous system can, for example, reduce the heart rate (beta blockers) or increase it (atropine). A pacemaker or arrhythmia can also interfere with the measurement of the sympathetic response[23].

According to Ledowski et al., pain and nociception monitoring can be divided into tools that simultaneously measure one, two or more parameters. In addition to pupillometry, which is a tool that measures one component, there is also the Analgesia Nociception Index (ANIa skin conductance measurement and the nociceptive flexion reflex threshold. The two-component tools, in addition to the Surgical Plethysmographic Index (SPI), also include qNOX, which integrates electromyographic and electroencephalographic samples. The only tool with more parameters is the Nociception Level (NOL) Index[20].

Pupillometry is a tool that tries to objectify the pain level by measuring pupil changes. Parameters necessary for pain assessment are pupil diameter and pupil constriction speed[24]. Pupillometry can assess pain intraoperatively, postoperatively and in intensive care units[25]. It has proven to be a suitable method for assessing the pain level and, therefore, for titrating analgesics, primarily opioids. Studies have shown that achieving optimal analgesia without causing hemodynamic instability with an excess of opioids and avoiding inadequate analgesia with a lack of analgesics is possible[26]. Confounding factors in the interpretation of pupillometry include pupillary miosis caused by opioid analgesics, the patient's emotional state and pupil diameter, and lesions of the mesencephalon and pons[27].

The Surgical Plethysmographic Index (SPI) is a noninvasive type of monitoring based on calculating the pain level according to an algorithm with variables comprising heart rate and peripheral vasoconstriction. The calculation requires a GE Healthcare pulse oximeter placed on the patient's fingers. According to the algorithm, the result of the measurement is a value from 0 to 100, without a measurement unit[28].

The most common range of SPI values that must be maintained for satisfactory analgesia is 20-50. Given that SPI measures the body's sympathetic autonomic nervous response to a painful stimulus, certain drugs can lead to a wrong interpretation of the measured values. SPI values appear to be influenced by mean arterial blood pressure and heart rate. Low blood pressure leads to a weaker signal in the periphery and

thus affects the measurement algorithm[29].

Unlike SPI and pupillometry, the Analgesia nociception index (ANI) measures changes in heart rate as a reflection of parasympathetic activity. The result is expressed as a number from 0 to 100, where a higher number reflects more significant parasympathetic activity and a lower level of pain and nociception. It has been reported that a value greater than 57 has an excellent negative predictive value for excluding acute pain[30]. Similar results were described in a study of pain assessment in critically ill patients conducted by Chanques et al[31].

Skin conductance measurement is possible with a device such as the Med-Storm algesimeter via three electrodes placed on the palmar, and plantar skin marked C (current), R (reference) and M (measurement). The sympathetic system innervates the sweat glands on the skin. Acetylcholine is released at the nerve endings, which acts on muscarinic receptors. Activation of muscarinic receptors leads to the production of sweat, which causes a decrease in skin resistance and increases skin conductivity. Since sympathetically modulated skin conductance has an emotional component to an extent, there is an intraindividual variability based on the patient's emotional state. The obtained value is specifically related to pain and painful stimulus and is less influenced by hemodynamic changes or drugs[32,33].

Nociceptive flexion reflex threshold (NFR) is a polysynaptic spinal withdrawal reflex triggered by activation of nociceptive A delta afferent fibers[34]. The reflex threshold is measured by monitoring the electromyographic activity of the biceps femoris caused by stimulation of the sural nerve at different intensities. The NRF threshold is defined according to the absolute power that drives the reflex. Unlike other methods, such as skin conductance and pupillometry, it seems that anxiety as an emotional state has no significant influence on the NFR threshold[35].

Factors that can affect the NFR threshold are related to the equipment and include electromagnetic interference, the use of muscle relaxants or some neurological problems in the patient. Some of these shortcomings have led to the relatively rare use of the NFR threshold in clinical practice[36].

qNOX is two-component monitoring that monitors the depth of anesthesia (qCON) and the level of analgesia (qNOX). The hypnotic index (qCON) is based on the measurement of EEG brain activity during anesthesia and correlates well with other similar indices, such as BIS (bispectral index). The measurement result is displayed as a number from 0 to 99, where a number less than 40 indicates a very low probability of response to a painful stimulus[37].

The Nociception Level (NOL) Index is the only multiparameter system for assessing nociception. It is based on the measurement of skin conductivity and changes in heart rate and photoplethysmography, all through a single probe placed on the patient's finger. All variables are entered into an algorithm that then displays a value from 0 to 100, where 0 indicates the absence of nociception and 100 indicates a state of extreme nociception. So far, several studies have shown the usefulness of the NOL Index intraoperatively in detecting painful stimuli and adequate response to analgesia[38].

Conclusion

The personalization of pain treatment in the ICU has developed due to the interindividual differences of patients, in order to reduce the harmful effects of pain on the outcome of the treatment of critically ill patients. In terms of personalization, there is a need to develop objective pain assessment methods that do not rely on the patient's ability to communicate and are independent of assessors, disease characteristics and pharmacological interventions in critically ill patients. The development and implementation of nociception monitoring in clinical practice, pain assessment at regular time intervals and a therapeutic approach in line with the relevant recommendations are the basis of personalized pain treatment for critically ill patients.

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Sažetak

PERSONALIZIRANO LIJEČENJE BOLI U JEDINICAMA INTENZIVNOG LIJEČENJA - PRAĆENJE NOCIPCIJE

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Personalizacija liječenja boli u Jedinicama intenzivne medicine svoje izvorište nalazi u interindividualnoj varijabilnosti i heterogenosti kritično oboljelih. Personalizirani pristup boli temelji se na predviđanju i kontinuiranoj procjeni boli. Kod kritično oboljelih obuhvaća poznavanje osnovnog uzroka boli vezanog uz glavnu dijagnozu, uzroke proceduralne boli kao i prethodna kronična bolna stanja oboljelog kako bi se primijenio specifični terapijski pristup. Dostupne preporuke za liječenje naglašavaju primjenu adaptivne ili dinamičke analgezije, sa titracijom analgetika u odnosu na promjenu kliničke situacije pacijenata. One ukazuju na neophodnost procjene boli alatima za procjenu jačine boli i evaluaciju terapije, tako i potrebu procjene u regularnim vremenskim intervalima.Unatoč smjernicama za liječenje klinička praksa pokazuje značajna odstupanja od preporuka temeljenih na dokazima. Razlozi su primarno prisutni u neprepoznavanju boli, nedostatnom poznavanju analgetika (tip i doza), neregularnoj procjeni i neadekvatnosti primijenjenih alata za procjenu boli. U smislu personalizacije nameće se potreba razvoja objektivnih metoda procjene boli, alata osjetljivih i specifičnih za bol koji se ne oslanjaju na sposobnost komunikacije od strane bolesnika, neovisni su od procjenitelja, karakteristika bolesti, te farmakoloških intervencija kod kritično oboljelih.

Ključne riječi: *bol, nocicepcija, personalizacija, monitoring, intenzivna medicina*