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Pharmacological methods of pain relief during labor

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Abstract

Labor pain and methods of its alleviation constitute the main problem in contemporary obstetrics, both for the patients themselves, as well as for the medical staff. Concerns

associated with pain are not meaningless to the course of labor, are inextricably linked to the quality of perinatal care and to a large extent affect the costs of functioning of the health care system. Moreover, concerns about labor itself are strongly associated with fear of pain at all. Most women are aware of pain during labor, but they expect that it should be soothed with currently available methods, ensuring safety for the mother and the child. In this paper pharmacological methods of labor pain relief, including inhaled analgesia, opioid analgesics, non-opioid drugs, pudendal nerve block and epidural anesthesia were described.

Key words: epidural anesthesia, inhaled analgesia, labor, non-opioid drugs, opioid analgesics, pain relief, pudendal nerve block.

Labor pain and methods of its alleviation constitute the main problem in contemporary obstetrics, both for the patients themselves, as well as for the medical staff [1]. Concerns associated with pain are not meaningless to the course of labor, are inextricably linked to the quality of perinatal care and to a large extent affect the costs of functioning of the health care system. Moreover, concerns about labor itself are strongly associated with fear of pain at all. [2]. Most women are aware of pain during labor, but they expect that it should be soothed with currently available methods, ensuring safety for the mother and the child [3].

The essence of inhaled analgesia used during labor is the inhalation of anesthetics in concentrations ensuring the preservation of full awareness and laryngeal reflex in the patient [4]. There are many anesthetics that can be administered by inhalation, including: isoflurane, sevoflurane, trichlorethylene, methoxyflurane, cyclopropane or nitrous oxide. Trichlorethylene can not be administrated with CO_2 as an absorber because it is flammable while using of cyclopropane, even at subanesthetic concentrations, is dangerous due to the risk of explosion. None of these drugs are currently used for analgesia in modern medicine and they have only historical significance. Also sevoflurane is not used for inhaled analgesia during labor because it does not analgesic effect in subanesthetic concentrations. However, subanesthetic concentrations of nitrous oxide, enflurane, isoflurane and methoxyflurane have no significant effect on uterus contractions and are therefore preferred.

In modern obstetric practice, only nitrous oxide is widely used for intrapartum anesthesia. The reasons for this situation are to be seen in several of its features, which include: ease of administration and dosage, non-flammability, lack of acute odor, no effect on

uterus contractions, low toxicity, no depressive effects onto the cardiovascular system and minimal risk of inducing hyperthermia [4-6]. Nitrous oxide was used for the first time during labor in 1881 by Stanialav Klikovich, who studied the effectiveness of mixture of this gas with 20% pure oxygen [7], while a device for self-dosing of nitrous oxide was introduced into obstetric practice by Minnitt in England in 1934 [6]. Currently, nitrous oxide is used in a mixture with pure oxygen at 1: 1 ratio and can be administered via a mask to the respiratory system of laboring woman, from a device that mixes both gases immediately before aspiration, (Nitronox), or as a ready gas mixture in one container, through the mouthpiece (Entonox). The mouthpiece and the mask have a valve which allows the gas mixture to flow to the patient only if there is a negative pressure in the mouthpiece or in a well-sealed mask during inspiration. The dosing valve eliminates the flow of gas when the patient does not inhale in and limits the exposure of medical personnel to the effect of this medicine. The Nitronox device additionally allows for the capture of gases exhaled by the patient. This is important, because prolonged exposure to nitrous oxide (especially in the case of medical personnel) disturbs the metabolism of vitamin B_{12} by converting monovalent cobalt into its bivalent form, which can not serve as a coenzyme for the synthesis of methionine and methylmalonyl-CoA mutase. Patients who chronically abuse nitrous oxide may develop clinical symptoms resembling complex subacute spinal cord degeneration, megaloblastic anemia and increased incidence of spontaneous abortions [8,9]. The mechanism of analgesia of nitrous oxide results from impulse inhibition in the spinal cord as well as on the supraspinal level. In addition, it causes the release of endorphins and enkephalins in the central nervous system [10]. Nitrous oxide has a weak anesthetic effect in high doses and analgesic and sedative effects in low doses. The efficacy, safety and the risk of adverse reactions depends on the dose which is a derivative of the drug concentration and the time of exposure [8]. After the initial instruction, the laboring woman can use the mask or mouthpiece without any additional help. This form of analgesia can be used continuously or intermittently - with the beginning of the moment of increasing the contraction force and at the end, when the contraction stops. The maximal effect of analgesic effect in the case of nitrous oxide is reached in about 30-40 seconds after the start of inhalation, and the disappearance of its effects appears after 3-4 exhalations [11]. Intrapartum analgesia with nitrous oxide has no side effects or threatens the safety of the mother and the fetus. It does not require intravenous

access and continuous monitoring of fetal well-being, which additionally increases the comfort of the woman [8].

The inhaled supply of anesthetic drugs may also in some cases be a supplement to the parenteral use of opioid analgesics. Nowadays, in most developed countries, parenteral use of opioid drugs is a common practice for the treatment of labor pain [12]. Parenteral administration of opioid drugs, apart from regional anesthesia, is the most common method of pain relief during labor [12]. The most commonly used opioid drug is pethidine produced in 1939 [12]. In the second half of the 20th century, newer opioids, characterized by better pharmacokinetic and pharmacodynamic parameters, were introduced for clinical use. Despite of this, perhaps because of the long-term rooting in the awareness of the medical staff working in delivery wards, pethidine is the most-used opioid. In some parts of the world, however, this trend is changing in favor of fentanyl, ramifentanil or nalbuphine [13]. Opioid drugs are often criticized because of their limited analgesic effect and clearly marked side effects from the mother and the fetus. The most frequently mentioned maternal side effects are: weakened ability to make informed decisions, sedation, hypotension, nausea and vomiting, urinary retention, prolonged delivery or delayed gastric emptying [14,15]. The delay of intestinal transit significantly increases the risk of aspiration of the gastric contents in a situation where it is necessary to use general anesthesia. In addition, sedation and the feeling of drowsiness in the laboring woman makes her reluctant to take a vertical position during labor, which prolongs its duration and increases the perception of pain [16]. Opioids cross the placenta easily by a passive diffusion. This is very important that the elimination of the most commonly used pethidine and its active metabolite norpethidine out of the newborn's body can last from three up to even six days [17]. Pethidine has a negative impact on the variability of the fetal heart rate, it reduces the number of accelerations and is a risk factor for the occurrence of decelerations in the CTG record [18]. The results of observational studies also indicate that opioids significantly affect the newborn, which is expressed by the impairment of the sucking reflex and the reduced alertness of the newborn child. This leads to delay the effective breastfeeding [19]. Pethidine may be administered by the intramuscular route - then the single dose ranges from 25-150 mg (0.6-1.2 mg / kg) or intravenously (usually a single dose is 50 mg). The maximum therapeutic effect is achieved about 30-40 minutes after administration of the drug and the next dose, if necessary, is given after 3 to 6 hours. The half-time of the drug in adults is 3 hours, whereas in neonates it is extended to 23 hours due to the

immaturity of the enzymatic pathways responsible for the processes of hydrolysis of pethidine to meperidine acid [20]. Relatively high number of side effects and uncontrolled action after the intramuscular administration was a contribution to the creation of a new generation of opioid drugs with a more favorable profile of action [21]. Fentanyl is a synthetic opioid, of structure similar to that of pethidine, but with a 50-100 times stronger effect. Due to the strong lipophilic properties, it penetrates the blood-brain barrier very quickly, where after about 3-5 minutes it reaches a concentration 10-fold higher than in the blood plasma. The high concentration of fentanyl in the brain is responsible for its rapid elimination and thus short duration of action. The rapid onset of action and rapid elimination of the drug represent its additional advantage - the ease of titration and predictable profile of action, which is extremely useful in clinical practice [22]. Taking into account the pharmacokinetics, pharmacodynamics, greater patient satisfaction, less sedation, shorter duration of labor and less difficulty in starting breastfeeding, fentanyl seems to be a much more beneficial alternative to parenteral administration of pethidine [23].

In contrast to centrally acting opioids, non-opioid analgesics act peripherally, directly at the level of nociceptors of damaged tissues [24]. For this reason, they are referred to as "peripheral analgesics", which is not exactly the right statement due to the recently discovered their central mechanism of action. Among non-opioid analgesics, we distinguish three basic subgroups: carboxylic acid derivatives (acetylsalicylic acid and non-steroidal anti-inflammatory drugs), pyrazolone derivatives (metamizole, phenylbutazone, phenazone) and aniline derivatives (paracetamol). Drugs from the first two groups have antipyretic and anti-inflammatory properties in addition to analgesia, while paracetamol has no anti-inflammatory activity [24]. Non-opioid drugs differ from the opioids with several important features: the former exhibit the so-called "ceiling effect", which means that there is a maximum dose of the drug, beyond which the analgesic effect no longer increases, they do not produce tolerance and in the case of long-term use they do not lead to addiction. Non-opioid analgesics are used in many countries as monotherapy to avoid opioid-induced nausea and sedation [25]. The second significant difference between opioid and non-opioid drugs are the side effects of these latter. While short-term use of non-opioid drugs in the acute pain is relatively safe, in the case of chronic use they may damage the mucous membrane of the gastrointestinal tract, the kidneys or less frequently other organs [26,27]. Using non-opioid drugs, an analgesic effect corresponding to 10 mg of morphine can be achieved. It follows that they are relatively

weak analgesics and therefore have limited usefulness in the treatment of severe and very severe pain [28].

Pudendal nerve block and cervical blockade are regional anesthetic methods which are used in obstetrics for decades. The blockage of the pudendal nerve is performed by locally injecting of its trunk with an anesthetic. As a result area of the perineum, anal and 2/3 posterior part of the labia undergo anesthesia. The front part of the labia innervated by the genito-femoral nerve remains not anaesthetized. This method is used for anesthesia in the second stage of labor and for vaginal obstetrical procedures [29]. The blockage of the pudendal nerve can be made through the perineum or vagina, by the administration of 20-25 ml of anesthetic local to the area of the ischial spine. In the common clinical practice, the most frequently used is vaginal access, which is less painful, has fewer complications and better efficacy [28]. The cervical blockade involves injecting the local anesthetic, in 2 to 6 punctures to a depth of 3 to 7 millimeters, into the lateral fornices of the vagina.

The needle must be laid parallel to the vaginal part of the uterus arrays [30]. This treatment affects the conduction of painful stimuli by sensory fibers visceral the lower part of the uterus, cervix and upper vagina (T10-L1), the so-called bottom hypogastric plexus. Due to frequent complication in the form of fetal cardiac arrhythmias including bradycardia, this method is not recommended [24].

Nowadays, the gold standard of intrapartum analgesia is believed to be lumbar epidural anesthesia. The effectiveness of this kind of anesthesia, in comparison to other methods, results from the fact that it takes into account the majority of mechanisms of pain during vaginal delivery. In addition, epidural anesthesia, site of action of which is the spinal cord and roots of the spinal nerves, gives the opportunity to eliminate various functions related to the nerve conduction and allows for selective segmental blocking. Epidural anesthesia is based on the inhibition of the conductivity in the nerve fibers by blocking the calcium channels in the cell membrane of the spinal nerve root neurons. The clinical effect is obtained by administering to the epidural space a solution containing a local anesthetic with or without an opioid drug. The place of access to the epidural space used for obstetrical anesthesia is the middle section of the lumbar spine, due to the horizontal course of spinous processes, the largest width of the epidural space and the location of the spinal cord's core above the injection site [24]. Among local anesthetics, are used almost exclusively amides

local anesthetics: lignocaine, prilocaine, ropivacaine or bupivacine. The clinical effect is achieved after about 10-20 minutes after administration of the drug to the epidural space. Anesthesia should mainly provide sensory blockade, therefore the use of low concentrations of local anesthetics should be sought, which ensures the maintenance of the motor function of the laboring woman. The use of high concentrations of local anesthetics leads to motoric blockage resulting in a lack of mobility, decreased muscle tone of the pelvic floor and less effective pressure in the second stage of labor. It may result in prolongation of the second stage of labor and increase of the percentage of surgical deliveries [31, 32]. In addition, large doses of analgesics may cause sympathetic blockage, which may cause relaxation of vascular system leading to maternal hypotension, defined as a 20% decrease in blood pressure relative to baseline [33]. A sudden episode of severe hypotension may lead to a clinically significant decrease of blood flow in the utero-placental unit, reduced oxygen supply for the fetus , and in fetuses with limited possibilities of compensation, to intrauterine hypoxia [34]. This is prevented by intravenous hydration of the patient before administration of drugs to the epidural space. The combination of opioids administered epidurally with local anesthetics reduces the dosage of both drugs, reduces the risk of motor blockage induced by local analgesia and reduces the risk of side effects from opiates such as urinary retention, pruritus, chills and fever [35]. The analgesic mixture is administered to the epidural space as a bolus, either continuously or by means of a patient-controlled infusion pump [36]. The latter two methods of supplying anesthetic drugs require the placement of a special catheter in the target space that allows the medication to be administered intermittently or continuously. One of the varieties of regional anesthesia used to relieve the pain of labor is the combined subarachnoid - epidural use of opioids, local anesthetics or a mixture of both at the same time. The drugs are initially administered to the subarachnoidal space and then to the epidural space by a catheter placed there. Undoubtedly, the advantage of this method is a quick onset and longer blocking time, but no significant differences in the quality of the anesthesia were observed [37].

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