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**Review**
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# Management of Trauma Pain in the Emergency Medicine

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**ABSTRACT** The literature review is devoted to modern principles of acute pain management of traumatic genesis in the practice of emergency medical care. It describes the capability of pain intensity evaluation, and available methods of analgesia and pain relief medication. Special emphasis is laid on current data on inhaled methoxyflurane analgesia.

**Keywords:** acute pain, analgesia, emergency medical care, methoxyflurane
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EMS — emergency medical services
NRS — Numeric Rating Scale
NSAIDs — non-steroidal anti-inflammatory drugs
PHS — prehospital stage
VAS — visual analogue scale

Pain accompanies a significant portion of pathological conditions and is related to a negative biological need that forms the perceptual and motivational component of the functional system that controls two important adaptive results: the integrity of the integumentary membranes and the level of oxygen supply to the tissues [1].

Pain can be defined as unpleasant sensations and emotions associated with actual or potential tissue damage [2]. Often it becomes the leading subjective factor for the patient, determining the “quality of life” both in the acute period and during chronification of the process [3, 4]. At the same time, insufficient pain relief, including in cases of traumatic injuries, remains a significant problem in the early stages of medical care — both at the prehospital stage (PHS) and in the emergency medical service (EMS) department [5–7].

In 1989, the term oligoanalgesia was proposed to describe the lack of adequate pain management in terms of dosage and rate of administration of analgesic drugs in patients in EMS departments [8].

Continuing pain not only prolongs the suffering of patients, but also contributes to the objective aggravation of their condition due to pathological stimulation of the neurovegetative, endocrine and mediator systems with subsequent decompensation, and also forms a chronic pain syndrome [3, 9]. Persistence of pain syndrome can complicate the conditions for carrying out treatment and diagnostic measures, including at the PHS, for example, limiting the implementation of adequate transport immobilization in case of skeletal trauma [10].

Moreover, the persistence of pain after seeking medical help often becomes the reason and argument for lawsuits against doctors and medical institutions [11].

Despite the objectivity of its existence, pain is always subjective [2], which dictates the need for medical personnel to assess the initial severity of the pain syndrome and the effectiveness of its treatment. In an emergency, for ease of use, one-dimensional pain intensity scales such as the 100-mm Visual Analogue Scale (VAS) and the 11-point Numeric Rating Scale (NRS) are most widely used. They allow physicians to better control the situation and adjust analgesia at various stages of medical care, and are also extremely convenient for most patients [7]. In particular, it has been shown that a difference of 2 points on the NRS [12] or a change of 13 mm on the 100 mm VAS [13] in the dynamics of pain therapy are already clinically significant. To facilitate the interpretation of the results, it is possible to translate the quantitative indicators of pain scales into verbal categories, such as mild, moderate or severe pain [4].

Early and complete correction of pain syndrome should be one of the main tasks of primary care medical personnel, including mobile EMS teams [14]. Modern diagnostic methods available in hospital settings allow for full relief of acute pain syndrome at the site of the patient's initial contact with medical personnel, rather than "preserving" ongoing pain as the main diagnostic criterion for internal injuries [15]. The literature emphasizes the need to shift priorities from a preliminary full diagnosis of the underlying condition causing pain to its immediate relief [16]. Pain treatment should be carried out in parallel with diagnosis, and its intensity should be assessed initially and again after therapy [7].

In the Russian Federation, pain syndrome is a reason for calling EMS in an emergency [17]; and the professional competencies of medical personnel allow for adequate analgesia in acute and chronic pain of various origins [18–20]. To achieve complete pain relief at the PHS, various analgesic methods and a wide range of painkillers are currently available. The equipment of the mobile EMS team for this purpose includes the following drugs: inhalation anesthetics (nitrous oxide), opioids (fentanyl, morphine, tramadol), non-steroidal anti-inflammatory drugs (ketorolac, ketoprofen), general anesthetics (ketamine), local anesthetics in parenteral form and for topical use (spray, gel) [21].

It is necessary to take into account that the concept of rational analgesia, along with efficiency, also includes safety, which is most important when providing EMS outside a medical organization, especially in critically ill patients with unstable hemodynamics and respiratory disorders. In these conditions, including during mass incidents, technical difficulties with timely provision of vascular access are possible, and the lack of medical resources at the initial stage limits the constant monitoring of the condition of patients who have received potent drugs. This dictates certain requirements for analgesics used in emergency medical care: convenient routes of administration, rapid achievement of a sufficient level of pain relief, controllability, minimal depressing effect on vital functions of the body, especially in critical conditions [22].

Previously widespread conduction methods of pain relief for skeletal trauma using local anesthetics, such as fracture site block, circular block, paravertebral block [23, 24], are currently practically not used at the PHS. This is largely due to the fear of potential development of technical and purulent-septic complications. Much attention in the literature is also given to the systemic toxicity of local anesthetics [25]. At the same time, in foreign practice

there is a certain renaissance of regional analgesia, performed, for example, in cases of hip fractures by paramedics at the scene of the incident [26, 27].

Intravenous administration of lidocaine as an alternative to opioids for pain relief, which is also gaining popularity abroad both in anesthesiology practice [28, 29] and in the EMS department [30, 31], in this country is considered an off-label indication, and there are no publications on its use by EMS.

The main parenteral analgesics administered at the PHS for acute severe pain of traumatic genesis in all age groups remain morphine and fentanyl [32]. The effectiveness of these drugs for pain relief is undeniable, but characteristic side effects (respiratory depression, vasoplegic shock, depression of consciousness, addiction, high potential for abuse) force specialists to use them in EMS conditions with caution and look for alternative solutions [9, 14]. Unfortunately, a number of pharmacological forms of analgesic drugs that are effectively used abroad (for example, intranasal fentanyl spray [33]) are not registered in the Russian Federation.

Tramadol can be an alternative to traditional opioids in the relief of moderate pain of traumatic genesis at the PHS [34]. Being a central analgesic, it does not cause opioid-associated respiratory depression in therapeutic doses, but has a weaker analgesic effect than morphine and fentanyl. A significant side effect of parenteral tramadol administration is vomiting [35].

A review of foreign literature demonstrates a revival of interest for the use of ketamine in severe trauma as an effective painkiller with minimal impact on respiratory and circulatory functions [36, 37]. Concerns about an increase in intracranial pressure in victims with traumatic brain injury when using ketamine were not confirmed [38]. Moreover, the technique of fractional administration of subnarcotic doses of ketamine in case of combined shock-producing trauma and preserved consciousness made it possible, while avoiding its iatrogenic suppression, to achieve complete pain relief [39].

To relieve pain of mild to moderate intensity in non-severe trauma, non-steroidal anti-inflammatory drugs (NSAIDs) are used in EMS practice. The most suitable for the PHS in this pharmacological group is ketorolac, which has a rapid analgesic effect, superior to other NSAIDs and tramadol, and similar in strength to morphine [40].

The side effects of ketorolac described in the literature, such as dyspeptic phenomena, gastrointestinal bleeding, and acute renal failure, are more expected with long-term course administration rather than with a single parenteral administration, and developed less frequently than with other NSAIDs [41].

Despite publications showing minimal clinical impact of ketorolac on hemostasis [42], it should be used with caution at the PHS if ongoing internal bleeding is suspected.

A recent publication showed that the analgesic effect of intravenous ketorolac in acute pain of severe and strong intensity was the same for doses of 30 mg (the recommended single dose) and 10 mg [43]. According to the authors, reducing the effective dose of ketorolac may reduce the potential for adverse effects of the drug.

In case of greater pain intensity, multimodal analgesia is advisable, which involves a combination of analgesics that simultaneously affect different links in the conduction and perception of pain impulses [44]. Along with the high pain-relieving potential, the combination of opioids (fentanyl or tramadol) and ketorolac allows for prolonged pain relief without additional re-prescription of drugs during medical evacuation, and thereby minimizes the side effects of these pharmacological groups [45].

Inhalation analgesia also continues to be widely used at the PHS. Its advantages over parenteral administration of analgesics are as follows: non-invasiveness, good controllability, and absence of drug dependence [46].

Nitrous oxide is an inorganic gas stored in a cylinder in a liquefied state and is a weak anesthetic with a strong analgesic potential [47]. In PHS conditions, nitrous oxide is used in spontaneously

breathing patients mixed with oxygen in a 2:1 or 1:1 ratio, causing pain relief in the 2nd–4th minute of inhalation from the anesthesia machine through a face mask. The use of nitrous oxide mixed only with air is contraindicated. To avoid the development of diffusion hypoxia, the analgesia technique requires mandatory breathing of 100% oxygen for 2–4 minutes after switching off nitrous oxide. The high rate of diffusion of nitrous oxide in body cavities limits its use in pneumothorax, acute intestinal obstruction, and the risk of intracranial hypertension [48].

Another inhalational analgesic used at the PHS is methoxyflurane, which is a volatile halogenated hydrocarbon stored in vials as a vaporizing liquid. Methoxyflurane was widely used in clinical practice as a general anesthetic for surgical procedures in the 1960s, but in the following decades, its use in anesthesiology gradually decreased and was completely discontinued due to reports of severe dose-dependent nephrotoxicity [49]. The mechanism of renal dysfunction was linked to damage to the proximal tubules as a result of the release of fluoride ions following enzymatic metabolism of the drug during prolonged use in high (anesthetic) doses [50].

In the autoanalgesic mode, methoxyflurane continued to be used for self-analgesia by the patient using a disposable hand-held inhaler in the form of a plastic cylinder with a mouthpiece [51]. This use of low (analgesic) doses of methoxyflurane in a short-term intermittent flow regimen, typical of the autoanalgesic technique, was not accompanied by the achievement of potentially toxic fluoride concentrations in the blood of patients. Evidence of safety of blood fluoride concentrations in patients using a methoxyflurane inhaler for pain relief during painful procedures was recently received in a controlled clinical study [52] demonstrating the achievement of a maximum individual blood fluoride level of 10 μmol/L, which is significantly lower than the recognized upper safety limit of 40–50 μmol/L [50]. This confirms the data on the absence of an increased risk of nephro- and hepatotoxicity of methoxyflurane at analgesic doses obtained in previous studies [53, 54].

The use of methoxyflurane for analgesia has remained widely available in Australia and New Zealand, and has been widely used there since 1975 for the relief of acute pain of various origins by EMS teams and in emergency rooms, for injuries at work and on sports grounds, and for pain relief during medical procedures such as dressing changes for burns, colonoscopy, bone marrow biopsy, and prostate biopsy [51]. Recently, methoxyflurane has been registered in the UK and many European countries for analgesia in moderate to severe pain of traumatic origin in adults [22].

Methoxyflurane with a hand-held inhaler can be self-administered by the patient after receiving brief instructions by inhaling through the device to achieve adequate pain relief. The initial dose is one vial containing 3 ml of 99.9% methoxyflurane filled into an inhaler. Pain relief occurs very quickly – after 6–10 inhalations, with one bottle providing pain relief for 25–30 minutes with continuous inhalation (or longer with intermittent use). The lowest dose of the drug necessary for effective pain relief should be used. The maximum single dose of methoxyflurane is 6 ml (2 vials). Its use for several days in a row is not recommended, and the total weekly dose should not exceed 15 ml [22].

Methoxyflurane is not suitable for the treatment of frequently recurring episodes of traumatic pain in the same patient or for exacerbation of pain in patients with chronic pain syndromes. It is contraindicated in cases of impaired consciousness or its altered state of any genesis (including head injury, use of psychotropic drugs or alcohol) and in cases of risk of malignant hyperthermia [55].

The use of methoxyflurane in analgesic doses in the EMS setting had no effect on cardiovascular and respiratory parameters [46, 56, 57]. Although the latest study did not find any specific pattern of changes in systolic blood pressure in patients after analgesia with methoxyflurane in different age groups, caution should be exercised when using the drug in elderly patients taking beta-blockers due to the possibility of lowering blood pressure [55].

When using methoxyflurane, the most common adverse reactions that did not, however, lead to discontinuation of treatment were transient dizziness, headache, and drowsiness [54].

Methoxyflurane analgesia is provided by open circuit, but there are no published reports in the literature of cases of nephrotoxicity associated with occupational exposure to methoxyflurane. According to a study measuring methoxyflurane exposure in a hospital-based healthcare setting, exposure levels for all workers per work shift were significantly below the estimated maximum exposure limit [58, 59].

Analysis of the efficacy of methoxyflurane in various studies has demonstrated its high analgesic potential in relieving acute pain of traumatic genesis in the early stages of EMS. In a randomized, double-blind study (STOP!), methoxyflurane was associated with statistically significant reductions in pain scores compared with placebo in patients presenting to the EMS department with acute pain due to trauma [54]. The median time to significant analgesia with methoxyflurane was short (4 minutes) and comparable to the time to onset of analgesia observed in other studies with intranasal fentanyl (11 minutes) and intravenous morphine (5 minutes) [56, 60, 61].

Although methoxyflurane was less effective than intravenous morphine or intranasal fentanyl for the relief of moderate to severe pain in the EMS setting, a large (n=42,844) retrospective analysis [62] found that it provided faster and/or greater pain relief than intramuscular tramadol at the PHS or in the EMS department [63].

An indirect comparative study of the effectiveness of pain relief in trauma with methoxyflurane and nitrous oxide did not reveal statistically significant differences between the two drugs, although after 15 minutes the proportion of patients experiencing pain relief was higher with methoxyflurane [22]. In another study, when comparing the quality of pain relief during dressing changes in burn patients, methoxyflurane showed greater effectiveness compared to nitrous oxide [64]. Methoxyflurane also proved to be more effective than nitrous oxide in pain relief for trauma at the PHS in another clinical study, noting, however, that the use of methoxyflurane is more expensive than traditional analgesics per patient treated [65]. It is necessary to note the fundamental differences in the ease of use of the two methods of inhalation analgesia available at the PHS. Methoxyflurane is dosed through a compact disposable inhaler, including by the patient himself in the form of autoanalgesia, while analgesia with nitrous oxide in domestic practice is carried out only by medical personnel using a rather heavy anesthesia apparatus. Ease of portability is especially desirable when providing EMS in remote or hard-to-reach places, and in situations with mass casualties.

## CONCLUSION

Thus, the modern arsenal of analgesics available at the early stages of EMS for trauma patients allows for rational pain relief taking into account the medical situation and the specific clinical situation. In particular, inhalational analgesia with methoxyflurane is an effective and safe alternative to parenteral analgesics due to its non-invasive route of administration, ease of use and rapid onset of action, which is especially important in mass disaster situations.

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