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THE ROLE OF INTRAVENOUS ACETAMINOPHEN IN TREATMENT OF ACUTE PAIN: LITERATURE REVIEW AND FIRST-HAND EXPERIENCE

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Abstract. *The paper is based on the literature review and first-hand experience and deals with the efficacy and safety of intravenous acetaminophen in treatment of acute pain syndromes, including a severe multitrauma.*

Keywords*: acetaminophen, intravenous, acute pain, multitrauma.*

Literature review. Acetaminofen (paracetamol) was synthesized in 1878, investigated in a clinic in 1887 and has been widely used in medicine since 1950 [1]. Since then, it was recognized as a safe and efficient analgesic and antipyretic in children and adult patients [1-4]. Since 2001, acetaminophen became available in Europe for intravenous injection under the trade mark Perfalgan (Bristol-Myers Squibb). Since 2011, the use of intravenous form of acetaminophen (Infulgan, Yuria-Pharm) has become possible, which allowed to expand its application for treatment of pain syndromes of various etiology.

An efficient pain management is crucial for achieving and maintaining the patient's comfort and for achieving good clinical outcomes [5]. Insufficient control of acute pain results in extension of the recovery period, delay in patient's mobilization [6], which increases the risk of development of venous thromboembolism [7-9]. Mental implications of an uncontrolled pain are insomnia, depression, anxiety. They lead to deterioration of the quality of life, unfavorable treatment results and decline in patient satisfaction [9-11]. Inefficient pain management substantially increases health spending [6, 12].

In spite of the improvement of analgesic therapy owing to the use of new analgesics and their combinations, of new technologies – a prolonged infusion, patient-controlled analgesia [13] etc., acute pain remains a complicated medical problem [14]. Comparison of two epidemiological studies of acute pain (1995 and 2003) indicates that the results of pain treatment did not improve during this period. Warfield C.A. et al. [15] found out, following a telephone inquiry of operated patients that ≈ 77% of patients suffer from postoperative pain, and 80% assess it from moderate to severe. Apfelbaum J.L. et al. [16] in a similar study in 250 adult patients found out that ~ 80% of patients report an acute postoperative pain, and 86% classified their pain as moderate to extreme.

An inefficient treatment of acute pain increases the risk of its chronization [10, 13]. Kehlet et al. [17], when studying the frequency of pain chronization after frequent surgical procedures (coronary artery bypass surgery, surgery of breast and chest, plastic repair of inguinal hernia, leg amputation), found out that pain can be present during several months and even years after healing of surgical wound.

History of usage of opioids stretches back more than 2,000 years, and they remain a key element of pain management of acute pain of a medium and severe degree. However, the use of opioids may cause side effects such as constipation, nausea and vomiting, excessive sedation, respiratory depression [18]. Another problematic issue is an opioid-induced hyperalgesia [19-21]. A systematic review of opioid-induced adverse effects in postoperative patients was conducted: 31% of patients had them on the side of

gastrointestinal tract (intestinal distension, nausea, vomiting, constipation); 30.3% - on the side of central nervous system (insomnia, sedation); 18.3% had itching; 17.5% - retention of urine; 2.8 % - respiratory depression. These side effects are unpleasant to such an extent that some patients are willing to accept a less adequate anesthesia to avoid them [23, 24].

For the purpose of enhancing the quality of pain relief, a strategy of multimodal anesthesia [25, 26] was proposed in the early 1990s; this strategy implies a simultaneous administration of several analgesics with different mode of action thus allowing improving anesthesia using lower drug doses. The multimodal anesthesia may consist of the application of opioid and non-opioid pharmacological agents as well as of regional anesthesia and extended blockades of peripheral nerves.

ASA recommends the use of multimodal anesthesia in the postoperative period with administration, on 24-hours a day basis, of acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) in the absence of contraindications, and a regional anesthesia. Numerous studies have shown that the multimodal anesthesia plan significantly reduces the opioid doses [27]. In recent time, anti-seizure medications (gabapentin, pregabalin) were added to the regimen of acute pain treatment; these medications contribute to reduction of doses of other analgesics and prevent pain chronization [28]. The multimodal approach allows to reduce postoperative pain, enhance the patient's satisfaction, accelerate mobilization and rehabilitation, as well as to reduce health spending [29, 30].

The multimodal strategy of the postoperative pain management implies a phased and staggered approach. For treatment of mild postoperative pain, paracetamol is administered as a base analgesic, with addition of NSAIDs as well as of tissue infiltration with a local analgesic before surgical incision. The additional administration of analgesics with different modes of action is based on increase or an expected increase of pain intensity. For treatment of moderate postoperative pain opioids are added where applicable. For treatment of severe pain, injection of opioids is indicated, in case of growing ("breakthrough") pain, a continuous regional anesthesia and modified routes of opioids' administration in case of a long-term pain [31].

Intravenous paracetamol is not associated with increased frequency of nausea, vomiting, respiratory depression which can accompany the use of opioids, or with dysfunction of thrombocytes, gastropathy and nephrotoxicity which are sometimes associated with NSAIDs [32, 33]. It is characterized by a quick onset of action and leads to more predictable effects than its oral or rectal dosage forms [1, 34]. In the study of Singla N.K. et al., adult subjects received intravenous, oral and rectal paracetamol; mean maximum plasma concentration was two times higher at intravenous injection than oral paracetamol, and four times higher than rectal paracetamol. The intravenous paracetamol group demonstrated its earlier and higher peak concentrations in plasma and cerebrospinal fluid. Metabolism in blood plasma and in cerebrospinal fluid was much higher for oral and rectal forms.

The advantage is that intravenous acetaminophen can be injected before or during operation allowing starting an efficient analgesia at an early stage of the postoperative period [36, 37]. The intravenous administration route can be replaced by the oral one when patients will be ready to come over to the oral drug administration [38].

The intravenous paracetamol injection bypasses the portal blood flow and makes it possible to avoid the effect of its first passage through liver that can decrease the potential risk of liver damage [39]. In the therapeutic dosage (up to 4000 mg a day) [40],

intravenous paracetamol seldom possesses hepatotoxicity and is safe for many patients with co-existing diseases of liver [41, 42]. Nevertheless, intravenous paracetamol is contraindicated for patients with severe damage of liver and severe active diseases of liver [43].

Method of administration and dosage. The maximum single dose amounts to 1000 mg of paracetamol. The maximum daily dose is 4 g. The interval between injections should be at least 4 hours. Generally between 1-4 infusions are applied during first day from the beginning of pain syndrome; the duration of treatment can be extended, however, it should not exceed 72 hours (3 days); the overall number of infusions should not exceed 12 [44).

CLINICAL STUDIES OF INTRAVENOUS ACETAMINOPHEN ADMINISTRATION

Preemptive analgesia. A number of studies demonstrated a preemptive effect of 1000 mg acetaminophen intravenously 30 minutes before incision at abdominal histerectomia [45], Caesarean section [46], laparoscopic cholecystectomy [47] and in bariatric surgery [48].

Acute postoperative pain. The efficacy of intravenous paracetamol for treatment of postoperative pain in adults has been studied in numerous studies around the world which demonstrated an efficient pain management and opioid-saving effect [49-51]. Macario A. et al. [52] in systemic review of 16 studies (1,464 patients, 780 of them received acetaminophen intravenously) concluded that intravenous paracetamol significantly reduces consumption of opioids, increases the analgesia duration and only seldom requires administration of additional analgesics.

Total hip or knee joint endoprosthetics. Sinatra R.S. et al. [50, 53] reported on the outcomes of the study on pain relieving effect of single and repeated IV application of 1000 mg acetaminophen in combination with PCA morphine compared to placebo during 24 hours in 101 patients with moderate and severe pain after a total hip or knee joint endoprosthetics. Patients who received paracetamol had less pain and required less morphine (46% reduction during 6 hours and 33% reduction during 24 hours) compared to those who received placebo. Patient satisfaction with analgesia was substantially higher in IV paracetamol group: 79.6 % of patients assessed analgesia as excellent compared to 65.4% in placebo group.

Abdominal laparoscopic surgery. Wininger S.J. et al. [51] reported on the outcomes of the efficacy study of IV acetaminophen (1000 g every 6 hours, or 650 mg every 4 hours during 24 hours) versus placebo in 244 patients with moderate and severe pain after a laparoscopic surgery (histerectomia, cholecystectomy, plastic repair of hernia). Patients in both IV acetaminophen groups, statistically significant, had less pain compared to placebo.

Major abdominal and proctological operations. Memis D. et al. [49] evaluated the effect of IV acetaminophen versus placebo in 40 adults after major operations. In the IV acetaminophen group, visual analogue scale (VAS) values of pain were lower, postoperative consumption of opioids was less, time prior to extubation ≈ 3 hours less, and postoperative nausea and vomiting as well as sedation degree were lower than in placebo group.

Safety profile. Good tolerance of IV paracetamol is indicated in 1,375 patients (1,020 adults and 355 children) in clinical studies [43, 49, 50, 51, 53]. Out of 1,020 adult patients, 380 (37%) received at least five doses and 173 (17%) – more than ten doses. 87% (n=886) of patients received 1000 mg acetaminophen IV every 6 hours, and

remaining 134 patients - 650 mg acetaminophen every 4 hours. 15 % of patients were older than 65 years, and 5% - older than 75 years. According to postmarketing surveillance data, hepatic toxicity associated with acetaminophen was fewer than 1 in 500,000 treated patients [50]. In the pooled analysis of eight studies (n=1064) conducted in the USA to evaluate the hepatic safety of IV acetaminophen versus placebo, liver enzyme levels in patients treated with IV acetaminophen were similar to those who received placebo. In one of the studies in which patients received repeated doses over 48 hours, the placebo group demonstrated a higher rate of liver enzyme elevations than the IV acetaminophen group. Nonetheless, administration of acetaminophen in doses higher than recommended may result in liver injury, including the risk of severe hepatotoxicity and death. One must be careful in prescribing acetaminophen to patients with liver dysfunction, active liver disease, alcoholism, chronic malnutrition, severe hypovolemia, or severe kidney dysfunctions [43].

To reduce the risk of severe liver injury from paracetamol overdosing, a coalition on safety "Know Your Dose" has been established (the Acetaminophen Awareness Coalition "Know Your Dose" (www.knowyourdose.org) [54]. In addition, in January 2011, the FDA asked manufacturers of over-the-counter-drugs to limit the maximum amount of paracetamol to 325 mg per dosage unit (e.g., tablet, capsule) [55].

FIRST-HAND EXPERIENCE

Our study was conducted in 20 adult patients (2 groups of 10 patients each) with a severe multitrauma (thoracic-abdominal, orthopedic). The analgesia scheme included: in the first group – administration of intravenous acetaminophen (Infulgan, Yuria-Pharm) in doses recommended by the manufacturer simultaneously with a thoracic epidural analgesia with Naropin and additional IM morphine injection in case of insufficient analgesia. Patients of the second group did not receive any acetaminophen.

The pain syndrome assessment was conducted according to VAS and requirements in morphine administration; hemodynamic and respiratory parameters were controlled. The study demonstrated that the use of acetaminophen enhances the analgesia quality by reducing pain level under VAS by 25-30%, and reduces the need to apply morphine reducing its daily requirement by 30-50% in patients with severe multitrauma. The use of IV acetaminophen was characterized not only by a high efficacy but also by a good tolerance and did not affect hepatic functions. It should be noted that only multimodal approach ensures maximum efficacy in management of severe pain related to multiple traumatic injuries of skeleton, abdomen and chest organs, soft tissues.

CONCLUSIONS

According to literature data intravenous paracetamol is an efficient analgesic for treatment of moderate and mild pain, and an important component of a multimodal approach to management of acute pain. Our study confirms the efficacy of intravenous paracetamol's inclusion into a multimodal analgesia scheme in case of severe multitrauma. When using paracetamol in recommended doses and in case of a right selection of patients, no toxic effects of the medication are observed.

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