EVALUATION OF THE EFFICACY AND SAFETY OF INTRAVENOUS LIDOCAINE FOR THE MANAGEMENT OF ACUTE POSTOPERATIVE PAIN - CURRENT STATE OF KNOWLEDGE

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ABSTRACT

The management of acute post-operative pain is an integral part of surgical procedures. Untreated pain leads to many complications. In anesthetic procedures, multilevel formation and processing of a pain stimulus requires multidirectional treatment. This concept of proceedings is called multimodal analgesia. On the one hand, it enables the effective pain control and on the other hand, minimizes the number of complications resulting from side effects of the drugs used. The basic group of drugs applied to fight acute post-operative pain are opioids, which are according to the concept of multimodal treatment supplemented with non-opioid analgesics, regional anesthesia or a group of drugs called adjuvants. Adjuvants, or supportive medicines, are the basic substances given in other cases. This group includes intravenous (i.v.) lidocaine. The first report on an attempt to use i.v. lidocaine in the management of acute surgical pain comes from 1954. Some recommendations for the management of postoperative pain from 2014 contain i.v. lidocaine, which has been included as a drug from the group of adjuvants. Its optimal way of administration, however, is still an open question. Based on current scientific reports, it seems that the anesthetic procedure involving the supply of i.v. lidocaine as an adjuvant drug in the postoperative pain therapy is justified by clinical benefits in specific surgical procedures. It is limited, however, to the field of abdominal surgery. The literature review concluded this usage may be beneficial for a specific group of patients, but protocols vary.

BACKGROUND

The postoperative pain treatment is an inseparable part of surgical procedures. It has a significant impact on the time of hospitalization, the costs of treatments and a patient's overall satisfaction. Insufficient managing of postoperative pain, especially in case of major surgical trauma, may result in many complications. Some complications could include an impaired wound healing, immunosuppression, adrenergic activation with gastrointestinal obstruction or even coronary events. Consequently the lack of physical mobilization after surgery due to severe postoperative pain may result in thrombosis and untreated postoperative pain that may transform into chronic pain.

There are many processes involved in the development of postoperative pain. From releasing mediators of the inflammatory process to hyperalgesia in the area of the body in which the surgery was performed. You can accomplish these processes through the modulation of pain in the neurons. The next step is to conduct the pain stimulus from the spinal cord to the pain brain centers where it undergoes the further modulation. In analgesic treatment, this multilevel formation and the processing of the pain stimulus requires and allows a multidirectional interaction. This concept is called multimodal analgesia. On the one hand, it allows effective pain management and, on the other hand, it helps to minimize the number of complications resulting from the drugs side effects. The basic group of drugs for postoperative pain management are opioids, which are often supplemented in accordance with the concept of multimodal treatment with nonopioid analgesics, regional anesthesia or a group of medicines called adjuvants.

Adjuvants, or supportive drugs in the managing of postoperative pain are the basic medicines in other indications. In the case of these drugs it has also been proven some additional effectiveness in relieving of pain. They are most often used intravenously in combination with other analgesics. The group of adjuvants includes drugs from ketamine, clonidine, gabapentanoids or magnesium sulphate, as well as, intravenous lidocaine. Lidocaine is an amide local anesthetic which works by blocking the sodium channel. In addition, it has antinociceptive, antiarrhythmic (inhibits the conduction of stimuli in the cardiac conduction system), anticoagulant, anti-inflammatory features and can help wound healing [1]. The analgesic effect of i.v. lidocaine appears to be independent of the physiological pain pathways and its effect on sodium channels. It is believed, that this curative increases the intracellular calcium ion concentration in the sensory cortex neurons, which may be responsible for the analgesic effect [2]. In addition, this analgesic impact was shown to be significantly more potent in visceral pain than in somatic pain, and its works more as an antihyperalgesic, than direct analgesic [1]. It predestines lidocaine for analgesic use after surgical procedures within the abdominal cavity. In addition, its analgesic effect may be strengthened by capacity of inhibiting the inflammatory response, which is induced by surgery. The result of its use in the postoperative period is plasma concentrations reduction of interleukin-6 (IL-6), interleukin-8 (IL-8), IL-1 receptor antagonists (IL-1ra), CD11b, L-and P selectin [3]. Lidocaine has also been shown to exert a positive effect on the bowel function resumption through direct stimulation of the smooth muscle in the intestinal wall, blocking the conduction of reflexes which are slowing peristalsis and by the, above mentioned, anti-inflammatory effect [4].

According to the medical product characteristics, besides its use in regional anesthesia, intravenous supply of lidocaine in life-threatening cardiac arrhythmias is also an option. A single administration of 50 - 100 mg lidocaine is allowed in divided doses of 25 - 50 mg per minute. If the initial dose turns out to be ineffective, the next one can be given after 5 minutes. It should not to be exceed a dose of 200 - 300 mg lidocaine within 60 minutes. It is also allowed to be used in the form of an continuous infusion, not exceeding the dose of 1 - 4 mg / min (20 - 50 mcg / kg body weight / min). The maximum daily dose of lidocaine is not specified [5]. The group of drugs that are routinely used perioperatively does not include substances that can change the metabolism of lidocaine by affecting cytochrome p-450 [6]. After intravenous administration of a single dose (bolus) of lidocaine at the dose of 50 - 100 mg, the onset of action occurs within 45 - 90 seconds and the duration of action is 10 - 20 minutes. If an infusion is started without an initial loading bolus, achieving therapeutic serum concentration is relatively slow and may require 30 - 60 minutes from the start of the infusion. Therefore, in order to achieve this goal faster, the appropriate serum concentration of the drug it is necessary to apply a preliminary bolus dose [7]. In case of i.v. lidocaine delivery regimen: bolus followed by continuous infusion lasting less than 12 hours, its elimination time last 100 minutes. When lidocaine is used for more than 24 hours, this time increases to 3.22 hours. This longer elimination time should be taken into consideration to assess the risk of drug accumulation and the occurrence of side effects [8]. Adverse effects associated with the use of i.v. lidocaine depend on its serum concentration. Among the mild symptoms are (serum concentration 3 - 8 mcg/ml): numbness and tingling of the fingers, numbness around the mouth, metallic taste in the mouth, ringing in the ears, nausea, dizziness, headache. Moderate symptoms (plasma drug concentration: 8 - 12 mcg/ml) are: nausea and vomiting, severe dizziness, convulsions, low blood pressure, arrhythmias. The severe symptoms (drug concentration in plasma > 12 μg / ml) include: muscle tremors, convulsions, loss of consciousness, arrhythmias leading to cardiac arrest [9].

Contraindication to the lidocaine usage is hypersensitivity to lidocaine or other local anesthetics with amide structure. Although standard doses of lidocaine do not usually cause adverse effects in the cardiovascular system, it should not be administrated to patients with high cardiovascular risk, suffering from cardiac conduction blocks (sinoatrial block, second or third degree atrioventricular block) and/or severe form of arterial hypertension. Its usage excludes neurological diseases (i.e. neuromuscular diseases, multiple sclerosis, paraparesis, transverse paralysis). Patients with liver failure should be subjected to special

observation due to lidocaine being mainly metabolized in the liver with cytochrome P450-1A2 [10].

The first report on an attempt to use i.v. lidocaine in the treatment of acute pain comes from 1954 [11]. It was administered intraoperatively as a painkiller, obtaining a good and long-lasting analgesic effect and reducing the incidence of nausea and vomiting in the postoperative period. Another report documenting the effect of intravenous lidocaine during general anesthesia dates back to 1977 [12]. Just before the incision of the skin, a bolus of lidocaine was administered at a dose of 2-2.5 mg/kg i.v., followed by a continuous intravenous infusion at a dose of 3-6 mg/kg/h for another 60 minutes. Despite the lack of opioid analgesics, the authors observed good quality of intraoperative analgesia. They also determined the upper limit and safe concentration of lidocaine in the serum for its analgesic effect, which was 3.5 µg/ml. This concentration has become the reference point for researchers in subsequent years.

The influence of lidocaine administered intravenously only in the postoperative period was not analyzed, but did not produce the expected results. Cepedy's research suggests that i.v. lidocaine, used as adjuvant to postoperative analgesia performed with morphine PCA (patient controlled analgesia) has no effect on the reduction of opioid consumption, pain level and occurrence of side effects in this period [13]. By analogy, i.v. lidocaine alone after a hysterectomy at the initial dose of 1.5 mg/kg i.v. bolus followed by a continuous infusion of 2 mg/kg/h for 2 hours postoperatively had no effect on reducing the intensity of pain experienced by patients. The concentration of lidocaine in blood in this case ranged from 1.5 to 2.0 µg/ml [14].

In 1990 a randomized placebo-controlled trial on a group of 30 patients undergoing laparotomy proved effectiveness of lidocaine administered as an intravenous bolus at a dose of 100 mg 30 min before introduction to general anesthesia, followed by an intravenous infusion at a dose of 180 mg/h and continued for a further 24 hours [15]. After an analysis of the results, it was concluded that there was a faster return of gastrointestinal function and lower demand for opioids in the study group. There were no differences between the groups relating to side effects. This trial proved the safety of using extended i.v. infusions of lidocaine. Modification in the drug administration in this case consisted of the infusion time point onset, continuation of intraoperative as well as post-operative. This way of painkiller supplying is called analgesia in advance. The multistep usage of i.v. lidocaine combines its antinociceptive, antihyperalgesic and antiinflammatory effects. Analgesia applied in advance prevents the development of pain hypersensitivity in the perioperative period. The aim of this method is to minimize or protect the CNS against the increase of afferent pain stimulation occurring during the procedure. As a consequence, this leads to a reduction in peripheral and central sensitivity (sensitization) with simultaneous preservation of the pain perception mechanisms which are necessary for correct interpretation of postoperative complications [16].

Another study from 2004 was carried out on a group of 40 patients undergoing laparotomy and the reducing effect of i.v. lidocaine on postoperative pain was evaluated [17]. Lidocaine was administrated as a 10-minute i.v. bolus at a dose of 1.5 mg/kg 30 min before skin incision, followed by an i.v. infusion at a dose of 1.5 mg/kg/h. The infusion was stopped 1 hour after the last suture. Furthermore morphine was used to treat postoperative pain. The authors determined the plasma concentration of lidocaine - intraoperatively and 60 minutes after termination of the infusion. This concentration was significantly lower than 3.5 mcg/ml, and was 1.9 +/- 0.7 mcg/ml in the first sample and 0.9 mcg/ml in the second one. In spite of such low plasma concentrations, postoperative pain reduction was observed as well as lower demand for morphine during this period.

In meta-analysis of randomized placebo-controlled trials in which i.v. lidocaine was used to treat acute post-operative pain was published in 2010. The analysis included a group of 1754 patients from 29 countries [18]. In the studies, lidocaine was used at a dose of 1.5 - 3mg/kg body as an intravenous bolus administered before induction phase of general anesthesia, and then a continuous infusion was started at a dose of 1.5 - 3 mg/kg/h. The infusion was continued according to different schemes - up to 24 hours after the procedure. This meta-analysis showed that the use of i.v. lidocaine according to the above-mentioned dosage in the treatment of acute postoperative period is an effective, safe procedure. It also showed multiple positive clinical effects in terms of postoperative rehabilitation, such as reduced demand for opioids, faster return of gastrointestinal function, reduced frequency of postoperative nausea and vomiting, and shorter hospital stay. There were no significant side effects from the cardiovascular system or the nervous system. Most benefits were observed after abdominal surgery.

Lidocaine is gaining importance as a drug from the group of adjuvants. For example in Polish recommendations for the postoperative pain management from 2014, i.v. lidocaine was included as a component of multimodal therapy. Based on current studies, an i.v. bolus of 1.5 mg/kg is proposed 30 min before surgery, then intraoperatively - continuous i.v. infusion at a dose of 1.5 - 3.0 mg/kg/h and postoperatively - continuous i.v. infusion at a dose of 1.0 - 3.0 mg/kg/h. These above mentioned recommendations do not specify the time of the infusion in the postoperative period. No serious side effects or complications of such therapy have been demonstrated [1].

Based on the data, it can be concluded that there is a tendency for lower and lower doses of i.v. lidocaine, resulting in safe, lower plasma concentrations. Limited toxic plasma concentration of lidocaine is 5 mcg/ml. As mentioned above [17], even a drug concentration of about 1.2 mcg/ml provides a good analgesic effect with minimized risk of side effects. The possibility of opioid dose reduction in the postoperative period due to the use of lidocaine minimizes the incidence of adverse reactions associated with this group of drugs. It seems that the time of i.v. infusion of lidocaine in the postoperative period depends on how long the patient is under the direct supervision of the anesthetist. This approach guarantees the safety of the method, especially in terms of the

potential for side effects. Therefore, the i.v. infusion of lidocaine should be switched off before the patient leaves the postoperative ward.

Based on current scientific knowledge, it seems that the anesthetic approach considering the supply of iv. lidocaine as an adjuvant in the treatment of acute pain in postoperative period is justified by clinical benefits. Advantages include faster recovery of the gastrointestinal tract function, higher level of analgesia obtained with lower doses of opioids, faster mobilization and more effective rehabilitation of patients increasing their level of satisfaction due to less frequent occurrence of adverse effects, mainly nausea and vomiting. Economic factors have no less importance: low cost of the drug, faster rehabilitation of the patient after the surgical procedure, and thus a shorter hospitalization time with a lower risk of complications. The use of intravenous lidocaine is also supported by the relative safety of this drug and the ease of administration - it does not require a central venous line [1, 2, 4]. Some authors think that lidocaine has the potential to be an alternative to epidural analgesia (at least in specific populations of patients) especially because of the beneficial, even if small, impact on a multiplicity of clinical and patient relevant outcomes, such as gastrointestinal recovery, PONV (Postoperative nausea and vomiting), and opioid consumption during postoperative recovery in patients undergoing abdominal surgery [21, 22]. The topic is still up for debate, and new analyses on the efficacy of such therapies are still being published [21, 22].

CONCLUSION

The management of postoperative pain and recovery is still unsatisfactory in clinical practice. The obtained results can provide new information and confirm the current reports on the use of i.v. lidocaine and transfer these experiences to daily clinical practice, improving the quality of patient care. There is also a need for standardization of anesthetic pain protocols including i.v. lidocaine, which are very different in various authors. We have to remember, also, that there is limited evidence that this intervention has an impact on pain scores besides in the early postoperative phase and in other surgical procedures other than in abdominal cavity.

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