Chapter

Intravenous Lidocaine in Non-Opioid Multimodal Perioperative Pain Management: Current Controversy and Future Perspectives

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Abstract

In the perioperative setting, intravenous lidocaine moderately reduces postoperative pain, opioid consumption and inflammatory response. Under laboratory conditions, lidocaine has been shown to inhibit cancer cell behaviour and exerts beneficial effects on components of the inflammatory and immune responses that are known to affect cancer biology. New evidence suggests that it might minimize the impact of surgery on NK cells and could augment NK cell cytotoxicity and improve survival in patients after pancreatic oncosurgery. Given the narrow therapeutic index, potential toxicity and inconclusive evidence about its Enhanced Recovery After Surgery benefits, however, currently intravenous lidocaine is not routinely use for perioperative pain control. It should be administered after considering with the patient of its clear benefits over risks, in a dose of 1-2 mg/kg/h, not more than 24 hours and under a high dependency unit monitoring. Patients groups where the risk-benefit balance is tilted towards benefit include patients who are already on high doses of opioids, intolerant of opioids, and those who are at high risk of chronic postoperative pain. The upcoming role for intravenous lidocaine in oncosurgery might shift its place from a second line non-opioid adjuvant to a first line option in the context of improving oncological outcomes.

Keywords: lidocaine, perioperative pain management, ERAS, oncosurgery, outcomes

1. Introduction

Lidocaine (Xylocaine®) was first synthesized in 1942, approved for use in human medicine and launched in 1948 in Sweden [1], patented in USA in 1948, and launched in 1949 after Food and Drug Administration approval [2]. Since 1958, intravenous (i.v.) lidocaine infusions have been used for postoperative analgesia as well [3]. The i.v. lidocaine is administered as an adjuvant in multimodal perioperative pain management for its analgesic, anti-inflammatory, and anti-hyperalgesic properties [4]

in many clinical settings. They include the operating theater, recovery room, high dependency unit (HDU), intensive care unit (ICU), and surgical ward [5]. Currently, the Enhanced Recovery After Surgery (ERAS) society guidelines recommend lidocaine as a continuous intravenous infusion in some ERAS protocols (colorectal surgery, hysterectomy, and pancreaticoduodenectomy) when epidural regional analgesia is not feasible or opioids may be contraindicated [6]. Under laboratory conditions, lidocaine has been shown to inhibit cancer cell behavior and exerts beneficial effects on components of the inflammatory and immune responses which are known to affect cancer biology [7]. The promising immune-modulatory and antinociceptive properties of i.v. lidocaine expand its role beyond the immediate perioperative period targeting the prevention of chronic postsurgical pain (CPSP) and the improvement of oncological outcomes as well.

In this chapter, the mechanism of action of i.v. lidocaine, its pharmacokinetics, pharmacological and clinical considerations of perioperative i.v. lidocaine infusions in terms of their current controversy and future perspectives in the field of acute and chronic non-opioid multimodal pain management and beyond will be presented.

2. Mechanism of action

2.1 Sodium channels

The primary mechanism of action of i.v. lidocaine is through blockade of voltage-gated sodium channels (VGSCs) leading to reversible block of action potential propagation. After a rapid state of depolarization activated VGSCs pass to a nonconductive state of inactivation, when VGSCs are closed and not capable of opening during a certain period, followed by resting state when VGSCs are still closed but capable of opening. Repetitive pulses from afferent fibers with a high-frequency abnormal firings produce an additional VGSC block, the so-called use-dependent block/frequency-dependent block, when the availability of VGSC to reopen decline [8, 9]. These different states of VGSC (open, resting, and inactivated) have different binding affinity for local anesthetics, and the affinity of the inactivated state is the highest [10]. Thus, i.v. lidocaine preferentially binds to the inactivated state, thereby enhancing use-dependent block and suppressing the high-frequency abnormal firings in injured dorsal root ganglion (DRG) or peripheral nerves [11]. The higher the frequency, the more intense the block is. The i.v. lidocaine blocks the sodium currents during the resting state of VGSC, the so-called tonic block, as well [12].

Ectopic firing could be suppressed by a systemic i.v. dose of lidocaine far below that required to inhibit nerve impulse propagation along an uninjured nerve [13]. To date, nine isoforms of VGSCs (Nav1.1-Nav1.9) have been identified. The Nav1.8 channel is approximately five times more sensitive to lidocaine than other VGSC isoforms [14]. In addition, in isolated Nav1.8, the half-maximal inhibitory concentration (IC_{50}) for low-frequency block is 319 μM, whereas its IC_{50} for high-frequency block is 50 μM. This may explain why i.v. lidocaine blocks ectopic activity in injured nerves, while normal nociception remains unchanged at the same IC_{50} values [15]. Thus, in vivo, systemic lidocaine suppressed the noxious stimulus evoked discharges in dorsal horn-wide dynamic range neurons, while spontaneous action potentials and activity induced by non-noxious stimuli remained unchanged [16]. The experimental

evidence to date supports the hypothesis that i.v. lidocaine suppresses the ectopic firing in injured peripheral nerves, DRG, and dorsal-horn cells. These findings, however, could only partially explain the possible mechanisms of i.v. lidocaine inhibitory effect on spontaneous chronic pain in clinical settings. The clinical effects of i.v. lidocaine in chronic pain patients outlast its plasma concentrations [17] which points to a supra-spinal mechanism as well (such as a specific site of action in the thalamic region of the brain [18]), involving targets other than VGSC.

2.2 Calcium channels

The voltage-gated calcium channels (VGCCs) are involved in numerous physiological processes, including neurotransmitter release [19]. Their modulation is a potential target in chronic pain control [20]. Experimental data reveal that lidocaine inhibits VGCC in a dose- and voltage-dependent manner [21]. However, much higher doses (approximately 100-fold higher) of lidocaine are needed in order to inhibit VGCC compared to VGSC [22]. Thus, its degree of VGCC blockade is limited [23].

2.3 Potassium channels

The potassium channels are important regulators of membrane resting potential, firing action potentials, and repolarization in neurotransmission [24]. Certain types of potassium channels are involved in pain modulation and inflammation, such as voltage-gated potassium channels (VGPCs), voltage-independent potassium channels, tandem pore domain potassium channels (2P K^+ channels), and ATP-sensitive potassium channels. Although the affinity of i.v. lidocaine for VGPCs is sixfold lower compared to VGSC, the inhibition of outward potassium currents causes partial membrane depolarization and leads to an increased amount of sodium channels which in turns are more sensitive to lidocaine. Thus, inhibition of outward potassium currents promotes sodium channel inactivation. Lidocaine inhibited tandem pore potassium channels at IC_{50} of 1 mM and voltage-independent potassium channels at IC_{50} of 219 μM [9]. Lidocaine modulates mitochondrial adenosine triphosphate (ATP)-sensitive potassium channels and thus reduces cytokine-induced cell injury. In an experimental model of incubated vascular smooth muscle and endothelial cells, the cell survival improved with increasing dosages of lidocaine [25].

2.4 Nonselective cation channels

The nonselective cation channels are members of the transient receptor potential (TRP) family of ion channels and play a distinct role in nociception and neurogenic inflammation [26–30]. The transient receptor potential vanilloid 1 (TRPV1) and ankyrin 1 (TRPA1) channels as typical members of TRP family are expressed on some sensory and dorsal root ganglia [31], are interrelated functionally each other [32], and are involved into the development and sustainability of chronic pain [33]. Lidocaine at concentrations 10–30 mM (> 100 higher than plasma concentrations of i.v. lidocaine) have a greater inhibitory effect on TRP channels in rodents than in humans and may have a desensitizing effect on TRP channels as well [34]. The desensitized TRP channels could explain i.v. lidocaine prolonged antinociceptive effects in human sural nerve injury, which ameliorate the neuropathic pain well beyond the end of the exposure to lidocaine [35].

2.5 G protein-coupled receptors

The G protein-coupled receptors (GPCRs) consist of a large family of membrane proteins, which are of great importance for intra- and intercellular communication pathways [36]. After injury, their expression on sensory neurons for signaling pain changes considerably [37]. The Gq protein α-subunit ($G_{\alpha q}$) plays a significant role in pain modulation and inflammation [38, 39] and is a potential target for lidocaine antinociceptive and anti-inflammatory modulatory effects. Lidocaine binds with the $G_{\alpha q}$ in certain GPCRs, such as m1 and m3 muscarinic receptors, lysophosphatic acid (LPA), platelet-activating factor (PAF), and thromboxane A2 (TXA2) receptors [9 = E J Pain 2016 – самата статия] and inhibits their receptor signaling in a reversible and time-dependent manner [40]. Prolonged exposure to lidocaine increased the inhibitory potency on m1 and m3 receptors in a biphasic time-dependent manner, with initial inhibition followed by enhanced signaling [41]. However, the observed $G_{\alpha q}$ inhibition in experimental settings was at lidocaine concentrations much lower than those observed clinically [23]. Lidocaine inhibits LPA and PAF-mediated priming of human polymorphonuclear neutrophils (hPMN) and thus hPMN-mediated tissue injury on the site of inflammation in clinically relevant concentrations [42, 43], whereas TXA2 inhibitory concentrations are relatively high (IC_{50} of 1.1 mM) [44].

2.6 N-methyl-D-aspartate receptors

The N-methyl-D-aspartate (NMDA) receptors are heavily involved in excitatory neurotransmission and modulation of nociceptive signaling in the dorsal horn, contributing to the development of hyperalgesia and allodynia and spinal central sensitization [45–47]. Lidocaine inhibits the activation of NMDA receptors in a dose-dependent manner via an intracellular biding site. Therefore, higher lidocaine doses are needed for NMDA receptors blockade (IC_{50} of 0.8–1.2 mM) [9].

2.7 Glycinergic system

Glycine has a dual role in central nervous system neurotransmission. Depending on its extracellular levels, it can be both an obligate inhibitor and an excitatory co-agonist of NMDA receptors. The glycine levels are regulated by glycine transporter 1 (GlyT1) and glycine transporter 2 (GlyT2). GlyT1 removes glycine from the synaptic cleft, whereas GlyT2 reuptakes glycine into nerve terminals by reloading it into synaptic vesicles [48]. During the high-frequency abnormal neuronal activity, glycine released from inhibitory inter-neurons escapes from the synaptic cleft, reaches nearby NMDA receptors, and stimulates them as an excitatory NMDA receptor co-agonist [49]. Lidocaine modulates the glycinergic system in a dose-dependent manner. Low-dose lidocaine (10 μM) enhances, whereas high-dose lidocaine (1 mM) inhibits glycinergic signaling [50]. In addition, lidocaine metabolites monoethylglycinexylidide (MEGX) and N-ethylglicine (NEG), but not lidocaine itself, inhibit the GlyT1 in vitro in clinically relevant concentrations (55 μM) [51]. The i.v. lidocaine metabolites are glycine transporter's substrates that compete with endogenous and synaptically released glycine for reuptake and by blocking the reuptake lead to increased extracellular and synaptic glycine levels. Thus by facilitating the inhibitory neurotransmission, the systemic lidocaine and its metabolites may produce antihyperalgesia [52].

2.8 Analgesic and antihyperalgesic properties

The analgesic and antihyperalgesic effect of i.v. lidocaine infusion is obtained through inhibition of the VGSCs, VGCCs, various potassium channels, NMDA receptors, glycinergic system, and G protein pathways [9], the mechanism of action of which has already been discussed in detail above.

2.9 Anti-inflammatory properties

The neurogenic inflammation is involved into the development and maintenance of chronic pain by means of activation of numerous non-neuronal cells such as monocytes, leukocytes, macrophages, lymphocytes, and peripheral or central glial cells which play a key role in the release of multiple inflammatory mediators (such as pro-inflammatory IL-1β, IL-6, IL-8, and TNF-α or anti-inflammatory IL-1Ra and IL-10, etc.) [23]. Lidocaine can inhibit leukocytes activation, adhesion, and migration, as well as human peripheral polymorphonuclear neutrophils priming (contact of B or T cells with and an antigen) and phagocytosis [42, 43, 53]. Furthermore, it can reduce the release of inflammatory mediators, such as IL-1β, IL-6, IL-8, TNF-α, the expression of intercellular molecule-1 (ICAM-1), the release of prostanoids, thromboxanes, leukotrienes, and histamine release by human leukocytes, mastocytes, and basophils [53, 54]. Animal studies reveal that the anti-inflammatory effects of lidocaine are mediated by VGSC, GCPRs, and ATP-sensitive potassium channels [47 = IntechOpen pediatric i.v. lidocaine - самата статия]. However, just a few human studies demonstrate the anti-inflammatory properties of lidocaine in reducing the surgery-induced release of pro-inflammatory cytokines IL-1, IL-6, IL-8, and TNF-α [55–58], or the TNF-α production in lipopolysaccharide-activated human leukocytes [59].

2.10 Anticancer properties

Laboratory research suggests that perioperative i.v. lidocaine inhibits cancer cell behavior and exerts beneficial effects on components of the inflammatory and immune responses which are known to affect cancer biology [7]. It could be done by using multiple biological pathways, not just by blocking the VGSCs [60]. Several potential mechanisms of its antineoplastic properties are suggested (**Figure 1**). Lidocaine could attack directly the cancer cells via many pathways, such as the inhibition of nuclear factor-KB (NF-KB), epidermal growth factor receptor (EGRF), or Src (oncoprotein tyrosine kinase)-dependent signaling pathway. In addition, i.v. lidocaine could modulate the immune cells by enhancing NK cells cytotoxicity or by preserving Th1 predominance (from shifting Th1/Th2 balance toward a decrease of Th2-dominance, which Th2-dominance protect tumor cells from immune attack). Moreover, it could interfere with tumor angiogenesis by inhibiting the hypoxia-inducible factor (HIF) and the vascular endothelial growth factor (VEGF) signaling pathways. And last but not least, i.v. lidocaine possesses anti-inflammatory properties which may modulate the pro-cancer effects of surgery-induced stress response by inhibiting the expression of pro-inflammatory cytokines (IL-1, IL-6, IL-8, IL-10, TNF-α, and IFN-gamma) [7, 61]. In addition, the lidocaine TRPV6 receptor inhibition [62], the lidocaine dose- and time-dependent demethylation of DNA in different cancer cells [63], and the lidocaine VGSCs inhibition in cancer cells [64] are all involved in reducing tumor cell invasion and migration. In vitro studies are helpful in establishing a multitude of potential underlying mechanisms of i.v. lidocaine

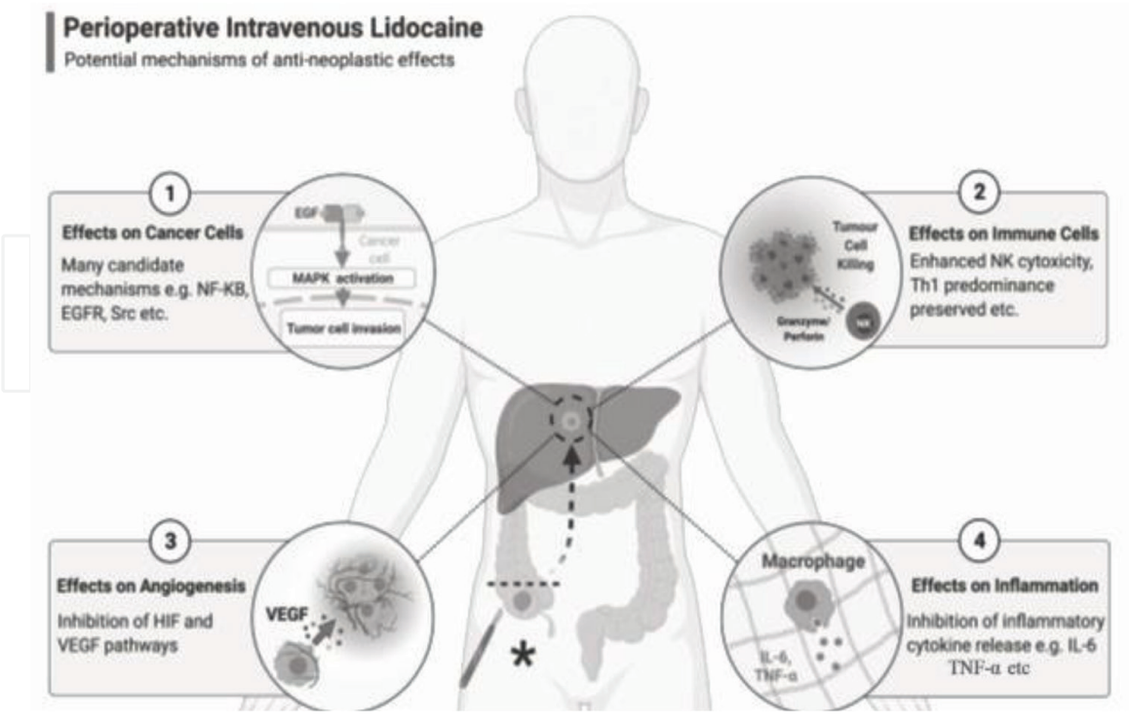

Figure 1.
Potential mechanisms of i.v. lidocaine antineoplastic effects (adapted from [7]).

anticancer effects, but their findings are not directly transferrable to in vivo settings. Preclinical studies usually use human-toxic lidocaine concentrations making their results inapplicable to the real clinical settings. In addition, the in vitro model could not replicate the tumor cells microenvironment with its complex interactions among cells, stroma, and cytokines [7]. Despite the accumulated evidence, different types of tumor cells are unique in their behavior, which further limits reaching a consensus on the exact anticancer mechanism of action of i.v. lidocaine [54].

3. Pharmacokinetics

I.v. lidocaine displays a rapid onset of action (45–90 seconds after i.v. injection), but a very short duration (10–20 min after 50 or 100 mg i.v. boluses) [2, 65]. When administered intravenously, lidocaine initially follows distribution in the highly vascularized organs of the body, such as the liver, heart, lung, and brain with a large volume of distribution of 0.6–4.5 L/kg. Lidocaine metabolism occurs rapidly by the cytochrome P450 system in the liver (90% hepatic biotransformation). It undergoes oxidative N-deakylation to the metabolites monoethylglycinexylidine (MEGX), glycinexylidide (GX), and N-ethylglycine (NEG), all of which possess a glycine moiety. MEGX and GX are active metabolites, whereas NEG is inactive. All lidocaine metabolites are excreted by the kidneys. About 10% of i.v. lidocaine is excreted unchanged by the kidneys as well [47]. Approximately 70% of i.v. lidocaine is bound to plasma proteins. Certain clinical conditions can modify the pharmacokinetics of lidocaine with impact on the lidocaine half-life, such as chronic hepatic diseases like liver cirrhosis where patients require lower doses due to decrease plasma clearance or cardiovascular disorders like congestive heart failure where the volume of distribution and clearance are reduced and patients may require smaller doses as well [8]. The

elimination of lidocaine usually follows a linear pharmacokinetic model with a half-life of approximately 1.5–2 hours after bolus or after infusion within 12-hour time frame. After 12-hour infusion, lidocaine exerts time-dependent rather than linear pharmacokinetic model of elimination and may have a half-life up to 4 hours [65].

4. Safety of i.v. lidocaine administration

The therapeutic plasma concentrations of i.v. lidocaine range from 1.5 to 5 μg/ml [2]. In normal adults without co-morbidities, a bolus dose of 100 mg i.v. lidocaine followed by an infusion at 1 mg/kg/h produces a plasma levels slightly above 1 μg/ml [66]. In mainstream clinical practice, the implemented i.v. lidocaine doses for pain management are in the range of 1–2 mg/kg/h. This rate of infusion reaches plasma levels less than 3–5 μg/ml. Even after a bolus administration of 2 mg/kg and a continuous infusion of 2–5 mg/kg/h, the i.v. lidocaine reaches plasma levels of 1–4 μg/ml. After exceeding the upper safety plasma level of 5 μg/ml, the awake patients may exhibit signs and symptoms of local anesthetic systemic toxicity (**Table 1**). Due to the short half-life of lidocaine, however, these symptoms of local anesthetic systemic toxicity are easily reversible by reducing the rate or stopping the infusion. In the presence of severe hepatic dysfunction and renal impairment (impaired lidocaine metabolism and clearance), severe hypoalbuminemia (impaired lidocaine protein binding), severe acidosis (increased lidocaine dissociation from plasma proteins), severe cardiac disease, heart block, or seizures, there are contraindications to i.v. lidocaine administration [2, 47].

Given the narrow therapeutic index of i.v. lidocaine leading to a high risk of reaching toxic plasma levels, the recently published international consensus in the field outlined some controversies regarding its intravenous use . The exact dose of i.v. lidocaine continues to be debated. The dose should be calculated based on the patient's ideal body weight. Systemic lidocaine should be avoided in patients weighing less than 40 kg. The maximum dose for any patients should not exceed 120 mg/h. The initial loading (bolus) dose should be a maximum of 1.5 mg/kg initially over 10 min,

System	Signs and symptoms
Central nervous system	Anxiety Dizziness or light-headed Confusion Euphoria Tinnitus Blurring of vision or diplopia Nausea and vomiting Twitching and tremors Seizures and coma
Cardiovascular	Bradycardia Hypotension Cardiovascular depression Cardiac arrest
Respiratory	Tachypnea Respiratory depression Respiratory arrest

Table 1.
Signs and symptoms of i.v. lidocaine systemic toxicity.

followed by a continuous infusion of 1.5 mg/kg/h under ECG, blood pressure, and pulse oximetry monitoring [68]. The most commonly reported i.v lidocaine doses in clinical settings still range from 1 to 2 mg/kg/h (which probably are too low as could be seen from preclinical research above). According to a Cochrane review subgroup meta-analysis, an early analgesic effect was only apparent with higher dose (≥ 2 mg/kg/h) infusion regimens [69]. The optimal i.v. dosage and postoperative duration continue to be unclear [70], pending the results of the ALLEGRO trial [71]. I.v. lidocaine should be postponed if other local anesthetic blocks are applied at the same time. It should not be used within 4 hours after implementing local anesthetic interventions (and vice versa). I.v. lidocaine should be administered after considering with the patient of its clear benefits over risks, not more than 24 hours and under a high dependency unit monitoring . However, according to the other authors, i.v. lidocaine could be used outside the high dependency unit setting as well. In the Ottawa hospital guidelines, a distinction was made between low-risk patients (American Society of Anesthesiology (ASA) class I and II) and high-risk patients (ASA III or above) in order to decide which ward for i.v. lidocaine infusion patients required [72]. In suitable patients, the postoperative lidocaine infusion could also be applied in surgical wards, as long as there is a well-established acute pain service and a clear protocol to follow [72].

5. Clinical effectiveness in the management of acute postsurgical pain

Until recently data suggest that i.v. lidocaine in the perioperative period results in less postoperative pain and opioid consumption, earlier return of gastro-intestinal tract function, and reduced hospital length of stay following abdominal procedures [69]. It could be a substitute to epidural for laparoscopic colorectal surgery within the ERAS pathways [73, 74]. Similar benefits have been observed after laparoscopic abdominal surgery when compared with systemic opioids, but not when compared to thoracic epidural analgesia, and especially in the absence of an ERAS program [69, 75, 76]. The latest revised Cochrane review concludes that the ERAS pathways benefits of perioperative i.v. lidocaine on reduction of pain, ileus, and PONV were uncertain due to limited quality of evidence [70]. Its conclusions are considered uncertain because of the existing heterogeneity of included trials as well. Thus, i.v. lidocaine may not always be beneficial in an individual setting given the variety of surgical interests. For example, the beneficial effects of i.v. lidocaine on postoperative recovery are of great interest to the colorectal surgeons, but probably of less interest to breast or spine surgeons [77]. Current evidence suggests that i.v. lidocaine alone may provide sufficient antinociceptive effect in patients undergoing abdominal surgery in addition to being an important component of perioperative multimodal analgesia [65]. In this context, the Enhanced Recovery After Surgery society guidelines for perioperative care in elective colorectal surgery (2019) make strong recommendations for lidocaine infusions during colorectal cancer surgery [78]. The following meta-analysis in elective colorectal surgery, however, reveals a statistically significant, but clinically irrelevant (the IASP criteria) reduction of pain after i.v. lidocaine infusion [79]. The less perioperative pain, the more difficult it will be to demonstrate the lidocaine's beneficial effects. This is supported by the results of a recent RCT which indicate that i.v. lidocaine has no significant benefits for patients undergoing robot-assisted colorectal surgery, including cumulated morphine consumption at 24 hours or 72 hours after the end of surgery [80]. To date, there appears to be limited evidence supporting

that lidocaine reduces opioid consumption intraoperatively and in the immediate postoperative period in breast and spine surgeries [65, 81]. The same applies to renal and orthopedic surgeries. As far as gynecological operations are concerned, there is some evidence that lidocaine may reduce intraoperative consumption in laparoscopic hysterectomy [82], but there is insufficient evidence to support improved postoperative pain control as a part of perioperative multimodal analgesia or alone [65].

6. Clinical effectiveness in the management of chronic postsurgical pain

Perioperative use of i.v. lidocaine can have a beneficial effect as a prophylactic measure to prevent the development of persistent/chronic postsurgical pain (CPSP). For breast cancer patients, the i.v. lidocaine infusion decreases the incidence and severity of CPSP at 3 months [83, 84] and mastectomy patients have 20 times less the relative risk of the occurrence of CPSP than their placebo controls [85]. Similar benefits of perioperative i.v. lidocaine are observed after complex spinal surgery [86] as well as before spinal surgery in patients with neuropathic radicular pain [87, 88]. According to a recent Cochrane review, there is moderate evidence that i.v. lidocaine may reduce the risk of developing persistent postsurgical pain 3 to 6 months after breast cancer surgery (NNT 3) [89]. Another systematic review and meta-analysis on the efficacy and safety of i.v. lidocaine for the prevention of CPSP concludes that perioperative lidocaine infusions may reduce the incidence of CPSP between 3 and 6 months after surgery. The effect size is considerable for both breast and nonbreast surgical procedures, indicating that for every five patients exposed to lidocaine, at least one will be spared the development of CPSP, an absolute risk reduction about 22% (OR 0.29, 95% CI 0.18-0.48) [90]. The authors described their meta-analysis as a hypothesis-generating project to stimulate future research [91]. The next systematic review corroborates that i.v. lidocaine seems to decrease the incidence of CPSP. However, given the limited evidence, more trials are necessary to define its efficacy and safety [92]. This gap for more strong evidence was partly filled by two recent randomized controlled trials. The first RCT reveals that perioperative lidocaine infusion reduces the incidence of CPSP at 3 months after radical gastrointestinal tumor surgery [93], whereas the second one confirms that intraoperative lidocaine infusion reduces the incidence of CPSP in breast cancer surgery at 3 and 6 months and is effective in relieving acute postoperative pain [94].

7. Clinical effectiveness in the prevention of postoperative cancer recurrence

As has been described above, lidocaine has promising anticancer properties. There is strong in vitro evidence of its protective effect on cancer recurrence. However, there are limited relevant clinical findings in the field. To date, only three recent retrospective clinical studies have shown an association between i.v. lidocaine infusion and improved outcomes after cancer surgery. The first covered 2239 patients who underwent resection of pancreatic carcinomas and found that those who received perioperative i.v. lidocaine had significantly better overall survival at 1 and 3 years, although disease-free survival was unaffected [95]. The second covered 144 patients who underwent radical cystectomy for bladder cancer and revealed that those who received intraoperative i.v. lidocaine (after the implementation of the specially

designed urological ERAS protocol) had significantly higher overall survival and lower incidence of cancer recurrence after 2-year follow-up compared to patients who did not received lidocaine [96]. The third covered 702 patients who underwent primary debulking surgery for ovarian cancer and showed that those who received intraoperative i.v. lidocaine had significantly prolonged overall survival and disease-free survival at 3 and 5 years after surgery [97]. Finally, focusing on the effect of implementation of ERAS protocol on 3-year survival after colorectal cancer surgery (with a strong recommendation, grade 1(+), for i.v. lidocaine as an integral part of the protocol [74]), the ERAS was associated with better 3-year survival and was identified as an independent protective factor with a 30% reduction in the risk of death (HR 0.70, 95% CI 0.55-090) [98]. It may be speculated that the strong modulation of the surgical stress response associated with the implemented ERAS protocol, rather than the adjuvant lidocaine therein, most likely led to the observed survival benefits.

8. Summary and future perspectives

Lidocaine is increasingly used by anesthesiologists as an intravenous adjunct to general anesthesia due to its anti-inflammatory, antinociceptive, and opioid-sparing characteristics [99]. Intraoperatively, it could be used as alternative of regional analgesia in the case of contraindication or failed epidural analgesia, in laparoscopic surgery or trauma with multiple significant injuries, and especially as a part of ERAS protocols. The application of i.v. lidocaine may also be continued postoperatively, usually up to 24 hours, in the setting of inadequate or failed epidural analgesia, in conversion from laparoscopic to open surgery, and for the prevention or treatment of postoperative ileus [72]. I.v. lidocaine is a useful option in the prevention and/or treatment of acute hyperalgesia, such as in surgery at a site of chronic pain (spine surgery, limb amputations) or in previous experience of poorly controlled pain, such as in patients who are already on high doses of opioids, intolerant of opioids, and those who are at high risk of chronic postoperative pain [67, 72]. Outside of the context of acute perioperative pain management, future research is needed to explore whether the anti-inflammatory and natural killer cell effects of i.v. lidocaine result in improved oncological outcomes [79]. The question of whether i.v. lidocaine has clinically relevant influence on postoperative cancer surgery outcomes can only be answered by well-designed RCTs. Two ongoing trials, VAPOR-C and ALLEGRO, have oncology outcomes included as primary, secondary, or tertiary end points, which when completed, would partially fill the gap [7, 71]. The upcoming role for intravenous lidocaine in oncosurgery might shift its place from a second-line non-opioid adjuvant to a first-line option in the context of improving oncological outcomes [100].

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Conflict of interest

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