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NARRATIVE REVIEW

Lidocaine in oncological surgery: the role of blocking in voltage-gated sodium channels. A narrative review

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Metastasis;
Cancer recurrence

Abstract
Background: The current evidence suggests that oncological surgery, which is a therapy used in the treatment of solid tumors, increases the risk of metastasis. In this regard, a wide range of tumor cells express Voltage-Gated Sodium Channels (VGSC), whose biological roles are not related to the generation of action potentials. In epithelial tumor cells, VGSC are part of cellular structures named invadopodia, involved in cell proliferation, migration, and metastasis. Recent studies showed that lidocaine could decrease cancer recurrence through its direct effects on tumor cells and immunomodulatory properties on the stress response.
Objective: The aim of this narrative review is to highlight the role of VGSC in tumor cells, and to describe the potential antiproliferative effect of lidocaine during the pathogenesis of metastasis.
Contents: A critical review of literature from April 2017 to April 2019 was performed. Articles found on PubMed (2000–2019) were considered. A free text and MeSH-lidocaine; voltage-gated sodium channels; tumor cells; invadopodia; surgical stress; cell proliferation; metastasis; cancer recurrence – for articles in English, Spanish and Portuguese language – was used. A total of 62 were selected.
Conclusion: In animal studies, lidocaine acts by blocking VGSC and other receptors, decreasing migration, invasion, and metastasis. These studies need to be replicated in humans in the context of oncological surgery.

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PALAVRAS-CHAVE
Lidocaína;
Canais de sódio dependentes de voltagem;
Células tumorais;
Invadópodes;
Estresse cirúrgico;
Proliferação celular;
Metástase;
Recorrência do câncer

Lidocaína em cirurgia oncológica: o papel do bloqueio dos canais de sódio dependentes de voltagem. Revisão narrativa

Resumo
Justificativa: As evidências atuais sugerem que a cirurgia oncológica, usada no tratamento de tumores sólidos, aumenta o risco de metástase. Nesse sentido, uma ampla gama de células tumorais expressa Canais de Sódio Dependentes de Voltagem (CSDV), cujos papéis biológicos não estão relacionados à produção de potencial de ação. Nas células epiteliais tumorais, o CSDV é parte integrante de estruturas celulares denominadas invadópodes, que participam da proliferação, migração e metástase celular. Estudos recentes mostraram que a lidocaína pode diminuir a recorrência do câncer por meio de efeitos diretos nas células tumorais e de propriedades imunomoduladoras na resposta ao estresse.
Objetivo: O objetivo desta revisão narrativa é analisar o papel do CSDV nas células tumorais e descrever o possível efeito antiproliferativo da lidocaína na patogênese das metástases.
Conteúdo: Foi realizada uma revisão crítica da literatura de Abril de 2017 a Abril de 2019. Os artigos encontrados no PubMed (2000–2019) foram analisados. Pesquisamos textos de linguagem livre e descritores MeSH-lidocaína; canais de sódio dependentes de voltagem; células tumorais; invadópodes; estresse cirúrgico; proliferação celular; metástase; recorrência do cancer – em artigos publicados em inglês, espanhol e português. Foram selecionadas 62 publicações.
Conclusão: Em estudos empregando animais, a lidocaína atua bloqueando o CSDV e outros receptores, diminuindo a migração, invasão e metástase. Esses estudos precisam ser replicados em humanos submetidos a cirurgia oncológica.

Introduction

Despite the advances in cancer therapies, cancer remains to be a major cause of morbidity and mortality globally.[1] The current evidence suggests that oncological surgery, which is a therapy used in the treatment of solid tumors, increases the risk of metastasis.[2–4] The surgical stress causes perioperative immunosuppression and a release of angiogenic factors which enables the spread of Circulating Tumor Cells (CTC) and the subsequent distance reimplantation.[5] The tumor cell escape, in combination with the impairment immunity in perioperative time, increases the susceptibility to recurrences, which is considered the ''perfect storm'' for cancer progression.[6–8] In this regard, a wide range of tumor cells express Voltage-Gated Sodium Channels (VGSC), whose biological roles are not related to the generation of action potentials.[9,10] In epithelial tumor cells, VGSC are part of cellular structures named invadopodia, involved in cell proliferation, migration, and metastasis.[10,11] Recent studies showed that lidocaine could decrease cancer recurrence through its direct effects on tumor cells and immunomodulatory properties on stress response.[12,13] Lidocaine acts by blocking VGSC and other receptors, and it is used in different scenarios in anesthetic practice, such as local infiltration, regional blocks (epidural, spinal, peripheral nerves), and intravenous infusion in the context of multimodal analgesia.[14] The aim of this narrative review is to highlight the role of VGSC in tumor cells and to describe the potential antiproliferative effect of lidocaine during the pathogenesis of metastasis.

Methodology

A critical review of the literature from April 2017 to April 2019 was performed. Articles found on PubMed (2000–2019) were considered. A free text and MeSH-lidocaine; voltage-gated sodium channels; tumor cells; invadopodia; surgical stress; cell proliferation; metastasis; cancer recurrence – for articles in English, Spanish and Portuguese language – was used. Additional studies from bibliographies of retrieved trials and previous reviews were recruited. Abstracts, case reports, and letters were excluded. Of the 156 articles screened, 96 were excluded. A total of 62 were selected, and these were reviewed with the propose to describe the role of VGSC in tumor cells and the different effects of lidocaine in cancer cells. In addition, we describe the clinical application of intravenous lidocaine.

Contents

Mechanisms of tumoral progression and metastasis

Both surgery and anesthesia stimulate the hypothalamic-pituitary axis and sympathetic nervous system, whose activation suppresses Cell-Mediated Immunity (CMI), releases catecholamines and prostaglandins, inducing perioperative immunosuppression.[5] Some of the mediators released during the inflammatory process included Interleukin 6 (IL-6), Interleukin-1β (IL-1β), Tumor Necrosis Factor-α (TNF-α), angiogenic factors such as Vascular Endothelial Growth

Factor (VEGF), reactive oxygen species, hypoxia-inducible factor-α and β (HIF-1α and HIF-2α), and factor NF-kB, which are directly or indirectly involved in the survival of tumor cells. The immune system plays a pivotal role in clearing new forming malignant cells and it does so by favoring anti-tumor mechanisms such as the production of cytokines. Th1 cells release IFN-γ, IL-2, and TNF-α; in contrast, Th2 cells secrete IL-4, IL-5, IL-10, and IL-13 cytokines. A shift towards Th1 polarization is the expected response against cancer. In contrast, surgical stress, volatile anesthetics, opioids, and blood transfusions are known to favor a Th2 response that manifests as immune suppression.[15] In this way, oncological surgery increases the risk of tumor dissemination, a complex process that involves the detachment of cancer cells from the primary tumor, local invasion, and their subsequent seeding in distant organs.[16,17] CTC carried in blood or lymph can reach distant tissues.[18] Cancer progression is linked to a subset of tumor cells known as ''cancer stem cells'' residing in a specific environment within the tumor microenvironment called the cancer stem cell niche. The niche plays a major role in maintaining cancer stem cell activity, protects the cell from the host defense mechanisms and facilitates metastasis.[19] The prevalence of escape mechanisms is greater in metastatic niche than in the primary tumor, indicating a higher selection pressure during the metastatic process. Taken together, the risk factors described above, which are all common in oncological surgery, occur simultaneously during the perioperative period.

Voltage-Gated Sodium Channels (VGSC)

VGSCs are typical of excitable cells, which are compound of one α subunit (Nav1.1-Nav1.9) and one or more β subunits (β1–β4).[20] The α subunit is an integral heteromultimeric protein complex consisting of four homologous domains (D1–D4), each containing six α-helical transmembrane segments (S1–S6).[21] Both terminus, C- and N-terminal, and ligand binding domains are intra cytoplasmic. S5 and S6 segments and a P-loop in each domain form the channel pore, penetrating the interior of the membrane. Seven of the voltage-gated sodium channels (Nav1.1–Nav1.3 and Nav1.6–Nav1.9) play major roles in electrogenesis in neurons, whereas Nav1.4 is the muscle sodium channel and Nav1.5 is the predominant cardiac myocyte channel. The canonical role of sodium channels in impulse electrogenesis and conduction in these excitable cells has been well established and is relatively well understood.[22] Lidocaine penetrates the neuronal membrane becoming in its not ionized form by the pH effect, joining the S6 portion of domain 4 α-subunit within the sodium channel. The analgesic and antihyperalgesic properties of lidocaine have been proven in vivo and in vitro studies.[12] The current evidence shows that VGSC are expressed in a wide range of non-excitable cells, such as astrocytes, oligodendrocytes, immune cells, dendritic cells, endothelial cells, macrophages, osteoblasts, odontoblasts, keratinocytes, and tumor cells.[22] In non-excitable cells, the VGSC function is different from the generation of action potential since they participate in cell survival, differentiation, proliferation, migration, endosome acidification, and phagocytosis. All these functions are known as non-canonical functions of VGSC.[22,23]

VGSC in tumor cells

Tumor cells use VGSC for migrating, invading and metastasizing.[24] The Epithelial-Mesenchymal Transition (EMT) program is a developmental cell-biological program in which tumor cell lose its epithelial morphology and turns into mesenchymal, acquiring invasiveness.[25–27] In the course of this process, tumor cells degrade the extracellular matrix (ECM) through invasive protrusions referred to as invadopodia[25] (Fig. 1). The role of invadopodia in the ECM degradation is to facilitate the invasion of adjacent tissues.[26] VGSCs are precisely located in invadopodia along with the Na^+/H^+ type 1 exchanger pump (NHE1) and the Na^+/Ca^{++} exchanger pump (NXC).[28] In a meticulously orchestrated process, the NHE1 releases H^+ by acidifying the medium while the NXC increases the intracellular Ca^{++} concentration. This leads to the acidification of the peri-invadopodia, cathepsins secreted by tumor cells, and the consistent degradation of ECM. Furthermore, VGSC action sustains enzyme Src kinase activity, promoting the polymerization of actin filaments. These results suggest that VGSC activity in cancer cells enhances both the formation and ECM degradative activity of invadopodia. One of the most VGSC studied in breast cancer in its neonatal splice variant is the VGSC 1.5.[29] In vitro studies have shown that VGSC 1.5 block with shRNA reduces cell invasion. On the contrary, VGSC activation with veratridine increases the ECM invasion, showing the importance of these channels during the invasion process. In vitro, VGSC activation has shown to increase the metastatic power due to greater motility and invasion. Therefore, tumor cells behave as ''electrically excitable cells'', becoming hyperactive and gaining aggressiveness, an event that is called CELEX, which represents a hypothesis of metastatic tumor progression.[30] Several drugs that block the VGSC are being investigated due to their antiproliferative actions on tumor cells, including phenytoin, carbamazepine, divalproex sodium, lamotrigine, gabapentin, and lidocaine.[31,32] Taken together, these results suggest that VGSCs and Src kinase have a critical role, both in invadopodia formation and in proteolytic activity, promoting the mesenchymal invasion. Both migration and invasion occur during the early stage of metastasis.

Direct effects of lidocaine on tumor cells

Lidocaine and other local anesthetics might have direct effects on tumor cells (Table 1). Tumor cells express VGSCs in a wide range of carcinomas, including breast, cervix, bowel, lung (small-cell, non-small-cell, and mesothelioma cancer), skin, ovarian and prostate cancer.[21] In vitro blocked of the neonatal splice variants in VGSC (Nvgsc 1.5) expressed in highly metastatic breast cancer cell lines (MDA-MB-231) was obtained with lidocaine, at clinical concentration.[33] In vitro and in vivo studies show that lidocaine inhibits the migration and reduces the viability in all breast cancer cell lines, including high malignant cells such as triple-negative and HER2 positive.[34] In this regard, Fraser et al. suggest that intra- and postoperative local anesthetics may reduce

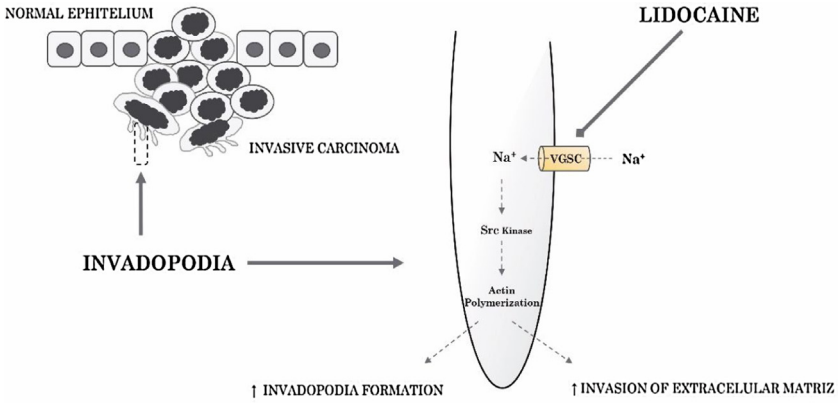

Figure 1 Voltage Gate-Sodium Channels (VGSC) in invadopodia of cancer cell. Blocking by lidocaine. The Epithelial-Mesenchymal Transition (EMT) program is a developmental cell-biological program in which tumor cell lose its epithelial morphology and turns into mesenchymal, acquiring invasiveness. VGSCs are precisely located in invadopodia. VGSC action sustains enzyme Src kinase activity, promoting the polymerization of actin filaments. VGSC activity enhances both the formation and ECM degradative activity of invadopodia. Adapted from Roger et al. Front Pharm, 2015.

Table 1 Direct effects of lidocaine on tumor cells.

Reference	Cancer cell line	Local anesthetics	Direct effects on tumor cells	Effect on tumor cell activity
Fraser[33]	Breast cancer	Lidocaine	VGSC blocking	Reduction cellular activation
Chamaraux[34]	Breast cancer	Lidocaine	VGSC blocking	Inhibition of cellular migration
Piegeler[36]	Lung cancer	Lidocaine, ropivacaine, chlorprocaine	Src kinase inhibition	Inhibition cellular activation
Chang[37]	Breast cancer	Lidocaine, bupivacaine	Induction of apoptosis	Induced cell death at clinically relevant levels
Wang[38]	Non-small cell lung cancer	Lidocaine, ropivacaine	Induction of apoptosis	Suppressed invasion and migration of tumor cells
Xing[39]	Hepatocellular carcinoma cells	Lidocaine	Induction of apoptosis	Suppresses tumor growth
Lirk[40]	Breast cancer	Lidocaine, procaine	DNA demethylation	Inhibition tumor growth
Sakaguchi[42]	Human tongue carcinoma	Lidocaine	Modulation of EGFR (Epidermal Growth Factor Receptor)	Altering mobility of tumor cells
Mammoto[43]	Human cancer (HT1080, HOS, and RPMI-7951) cells	Lidocaine	Modulation of HB-EGF (Heparin-binding epidermal growth factor)	Inhibition of cancer invasion
Jiang[44]	Breast, ovarian and prostate cancer	Lidocaine	Inhibition of TRPV-6	Inhibition of migration and invasion of tumor cells

the ability of tumor cells to metastasize by blocking VGSC and thus inhibiting their motility and invasiveness.[35] Independent actions of block of VGSC have been evidenced as possible antiproliferative properties. In vitro studies have shown that exposure to lidocaine inhibits Src protein tyrosine kinase in tumor cells, a protein involved in proliferation, migration, invasiveness and tumor metastasis.[36] Moreover, it has been shown that both lidocaine and ropivacaine inhibit tumor cells the expression of Intercellular Adhesion Molecules (ICAM-1), which are synthesized at once in the metastasis process. Another antiproliferative effect of lidocaine is the induction of apoptosis in a culture of different tumor cells.[37–39] A research conducted by Lirk et al. showed that lidocaine interferes with the process of genetic regulation by altering DNA methylation in cancer cell cultures. Methylation is catalyzed by the enzyme DNA Methyltransferase (DNMT1), whose role is crucial in the cancer pathogenesis inhibiting the tumor growth. It is speculated that lidocaine might alter the methylation by inhibiting DNMT1. This was an additive effect in chemotherapy that was also shown using ropivacaine but not bupivacaine.[40] It is important to mention that opioids have the opposite effect, being involved in DNA hypermethylation.[41] Also, lidocaine would act by modulating the receptor for Epidermal Growth Factor (EGFR), impeding the mobility of tumor cells.[42,43] Eventually, a recent evidence has shown that tumor cells use Ca^{++} to mobilize through transient receptors type V6 (Transient Receptor Potential Cation Channel Subfamily V Member

6, TRPV-6). Lidocaine blocks TRPV-6 channels, decreasing intracellular calcium levels and thus inhibiting migration and invasion in cancer cells.[44] These results, from different studies, have shown a multimolecular action of lidocaine on tumor cells, which could reduce the metastasis risk.[45]

Immunomodulatory effects of lidocaine

In the perioperative period, surgery induces immunosuppression, playing a critical role in the setting and growing of metastatic lesions.[5] Lidocaine has been shown to have analgesic, anti-inflammatory, and immunomodulatory properties, reducing neuroendocrine response caused by surgical stress.[46] These actions involve the blocking of several channels, including VGSC, K^+ channels, Ca^{++} channels, glycinergic system, G Protein-Coupled Receptors (GPCR) and N-Methyl-D-Aspartate receptors (NMDA).[47] The analgesic effect of intravenous administration is the result of increased acetylcholine levels in the cerebrospinal fluid, which causes downward inhibition, inhibition of glycine receptors, and increase the release of endogenous opioids. When lidocaine reaches the spinal cord, it reduces the post-synaptic depolarization mediated by NMDA and neurokinin receptors, thus modifying the pain response. NMDA blockade inhibits protein kinase C, thus reducing hyperalgesia and postoperative opioid tolerance. In animal models, lidocaine acts during the early stages of systemic inflammatory response, modulating the marginalization, adherence, and diapedesis of polymorphonuclear cells towards the site of the lesion, thus inhibiting the production of reactive oxygen species and the release of histamine. This immunomodulatory effect of the drug is achieved by blocking GPCR receptors since polymorphonuclear cells do not contain VGSCs. From an oncological point of view, lidocaine preserves the endothelial barrier function and cytotoxic function of NK cells.[44] Concerning to endothelial barrier function, it is mainly regulated by the protein Src tyrosine kinase. Src is activated by inflammatory cytokines released due to surgical stress, such as TNFα, enabling the synthesis of Intracellular Adhesion Molecules-1 (ICAM-1), and initiating neutrophil transmigration and adhesion. It is known that tumor cells can synthesize ICAM-1, allowing the binding to a neutrophil, which results in extravasation and transmigration. Studies have shown that lidocaine preserves the integrity of the endothelial barrier by modulating the endothelial protein Src tyrosine kinase, which prevents the spread of tumor cells to the systemic circulation, a necessary step for the manifestation of metastasis. In vitro studies analyzing lung microvascular endothelial cells, incubated with TNFα, lidocaine or ropivacaine, have suggested that both local anesthetics would block the Receptor for TNFα (RTNFα), impeding the Src activation and the synthesis of ICAM.[48] Concerning NK cells, they are part of CMI, having a vital role in detecting and removing Circulating Tumor Cells (CTC) that may develop into micrometastasis. Surgical stress, pain, opioids, and volatile agents are involved in the decrease of cytolytic activity of NK cells. On the contrary, a recent study has shown that lidocaine at low concentrations might preserve the cytotoxic function of NK cells.[49] Ramirez et al. observed that lidocaine, at concentrations lower than those typically found during intravenous infusion, enhanced the cytotoxicity of NK cells against three different types of leukemia cell lines. The same group of investigators has shown that lidocaine in vitro has strong stimulatory effects on the killing activity of NK cells against pancreatic, ovarian and osteosarcoma cells. Finally, Wang et al. have shown that IV lidocaine might also preserve the balance of Th1/Th2 after radical hysterectomy for cervical cancer.[50] Perioperative intravenous lidocaine had a beneficial effect on CMI, and this was associated with the preservation of lymphocyte proliferation and attenuation of apoptosis, maintenance of the balance of Th1/Th2 cells and the decreased production of cytokines. Collectively, the clinical data suggested an enhanced effect of lidocaine on immunity and might support its clinical use during the perioperative period.

Clinical application of lidocaine

Lidocaine can be used in different scenarios in the anesthetic practice, such as local infiltration, regional blocks (epidural, spinal, peripheral nerves), as well as an intravenous infusion (IV) in the context of multimodal analgesia.[14] Recently, Brown et al. introduced the concept of multimodal general anesthesia, combined different antinociceptive agents and monitoring continuously levels of antinociception and unconsciousness.[51] Regarding IV lidocaine infusion for multimodal analgesia, Chamaraux et al.[52] hypothesized that the administration in oncological surgery could be beneficial due to its antimetastatic effects on tumor cells. The IV lidocaine infusion decreases the exposure to opioids and volatile agents,[53] anesthetic drugs that suppress cell-mediated immunity, promote proliferation and angiogenesis.[54] Opioids are associated with immunosuppression by modulating the humoral and cell response, and direct actions on μ receptors expressed in tumor and endothelial cells.[55] Regarding volatile agents, some animal experiments indicate that both the number and the incidence of metastasis in cancer experimental models are increased[56] because of the stimulation of the Hypoxia-Inducible Factor α (HIF-α),[57] which provides cryoprotection and a greater survival to the tumor cell.[58] Volatile agents modify the immune response during the perioperative period in vitro and animal models,[59,60] mainly affecting the cytokines release. IV lidocaine infusion (bolus of 1.5 $mg.kg^{-1}$ followed by 2 $mg.kg^{-1}.h^{-1}$) is the most widely used and best-described dosage. When lidocaine is administered at this range of infusion, plasma concentrations of approximately 2 $ug.mL^{-1}$ are obtained. Plasma concentrations of more than 5 $ug.mL^{-1}$ are considered toxic. However, adverse effects and toxicity are extremely rare in controlled infusions.[46] In a recent study, Greenwood et al measured the plasma lidocaine concentration of 32 patients at 30 minutes, 6 hours and 12 hours after starting IV lidocaine infusion for analgesia after major colorectal surgery. Patients received a bolus of 1.5 $mg.kg^{-1}$ followed by a continuous infusion of lidocaine at 3 $mL.hr^{1}$ (60 $mg.hr^{-1}$) or 6 $mL.hr^{-1}$ (120 $mg.hr^{-1}$). The overall mean plasma lidocaine concentration was 4.0 $\mu g.mL^{-1}$ (range 0.6–12.3 $\mu g.mL^{-1}$). There were no adverse events or reports of symptoms of local anesthetic toxicity.[61] Although there is strong evidence from in vitro studies suggesting a protective effect on cancer recurrence, further preclinical and clinical stud-

ies are needed to support its role in oncological surgery. Consensus guidelines have recently recommended the use of standardized endpoints in investigation of the perioperative management of cancer patients to develop future clinical recommendations.[62]

Conclusion

Functionally active VGSCs are expressed in many metastatic cancer cells. In epithelial tumor cells, VGSCs are part of cellular structures named invadopodia, involved in cancer progression. This functional expression is an integral element of the metastatic process in many different solid tumors. For this reason, VGSCs can be targeted to decrease migration, invasion and metastasis. Lidocaine acts by blocking VGSCs and other receptors, and it is used in different scenarios in anesthetic practice, including anesthesia. IV lidocaine as part of the perioperative anesthesia regimen would be of major interest for anesthesiologists, as it might bear the potential to reduce the risk of cancer recurrence or progression patients undergoing cancer surgery. Despite these encouraging studies, they need to be replicated in humans, in the context of oncological surgery. While the concept that anesthetic or analgesic techniques might affect cancer outcomes, there is currently insufficient evidence to support any change in clinical practice.

Conflicts of interest

The authors declare no conflicts of interest.

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