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A clinical mini-review: Clinical use of Local anesthetics in cancer surgeries

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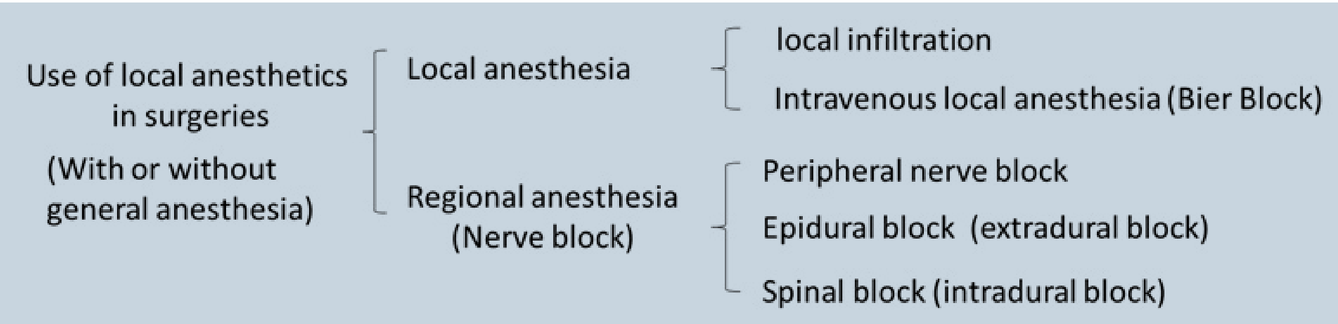
ABSTRACT

The application of local anesthetics is frequently involved in anesthesia in the surgical treatment of various cancers. It is used in addition to or instead of general anesthesia as a way to provide control of sensation and pain to specific regions or parts of the patients' bodies. They are thought to reduce the requirement for volatile anesthetics and opioids used in the surgery. This mini-review briefly summarized and commented on the frequent use of local anesthetics in cancer surgeries include local infiltration, intravenous local anesthesia, peripheral nerve blockade, epidural block, spinal anesthesia, etc. The potential pharmacological mechanisms of local anesthetics on cancer were also reviewed. This mini-review contributed to a better understanding and the optimization of the clinical use of local anesthetics in cancer surgeries.

GRAPH ABSTRACT



Introduction

A prescription of clinical local anesthetic usually includes the local anesthetic agent, the vehicle, the antioxidant, the preservative, and the buffer. The application of local anesthetics is frequently involved in anesthesia in the surgical treatment of various cancers. In those cases, local anesthesia is used in addition to or instead of general anesthesia as a way to provide control of sensation and pain to specific regions or parts of the patients' bodies. They are thought to reduce the requirement for inhaled general anesthetics (volatile anesthetics) and the dose of painkiller (opioids) and to control the stress response of neuroendocrine and immunosuppression caused by the surgery [1][2]. Local anesthetics anesthesia techniques frequently used in cancer surgeries include local infiltration, intravenous local anesthesia, peripheral nerve blockade, epidural block, spinal anesthesia, etc. This mini-review summarized and commented on the clinical use of Local anesthetics in cancer surgeries.

local infiltration in cancer surgery

Local infiltration is the injection of local anesthetics into the tissues near the surgical site which may be used alone or in combination with sedation or general anesthesia, depending on the size of the surgery, the time it will take, and the preferences of the patient. It is commonly applied in minor local surgeries like breast tumor biopsy or small melanoma resection. In local infiltrations, primary tumors directly exposed to local anesthetics during the surgery period. The peak concentrations of local anesthetics around the surgical site can reach an extremely high level and the anesthetics can also enter the circulation leading to a prolonged effect. Although a large part of the infiltrated area will be resected with the tumor, the remains of the primary tumor and the circulating tumor cells may be influenced by the local anesthetics. For example, after ropivacaine infiltration, the concentration of ropivacaine in circulation can remain around 3.5 to 3 μM after 24 hours [3]. Many *in vitro* and *in vivo* studies used 0.1 to 10 mM of local anesthetics to mimic local infiltration clinical conditions [4]. Clinically relevant concentrations of the several local anesthetics in blood and local tissues are presented in table 1.

Table 1: Clinically relevant concentrations of the commonly used local anesthetics [4]

Agents	Blood concentration (μM)	Local tissue concentration (μM)
Chloroprocaine	15	34,670 (1%)
Levobupivacaine	2.5	8667 (0.25%)
Bupivacaine	2.8	8667 (0.25%)
Mepivacaine	10	40,592 (1%)
Lidocaine	10	17,500 (0.5%)
Ropivacaine	3.5	7288 (0.2%)

Intravenous local anesthesia in cancer surgery

Intravenous local anesthesia, also named Bier's block, is an anesthetic technique on the body's extremities where a local anesthetic is injected intravenously and isolated from circulation in a target area. It had been occasionally applied in cancer surgeries for relatively short procedures on the distal upper extremity, but it is superseded by other anesthetics approaches since it will excessively increase the circulatory concentration of the local anesthetics and lead to severe intoxication.

Regional anesthesia in cancer surgery

Regional anesthesia (nerve blockage) is the injection of local anesthetics near specific nerves to decrease pain in a certain part of the body, type of which includes peripheral nerve blockage, epidural block, and spinal anesthesia. Peripheral nerve blockade is an injection of local anesthetic agents in proximity end of the limb to block signals traveling along a nerve for a regional surgery such as lung cancer surgeries or extremity bone cancer surgeries. Epidural block (extradural block) and Spinal blockage (spinal block, subarachnoid block, intradural block, and intrathecal block) are techniques that block the spinal nerves to achieve para-anesthetics for colon cancer surgeries or lower extremity bone cancer surgeries. An epidural block is an injection of local anesthetics into the epidural space around the spinal cord while the Spinal blockage is into the subarachnoid space inside the spinal cord. In nerve blockage, primary cancer cells do not directly expose to local anesthetics, but the agents are distributed in patients' circulation, which most metastatic cells journey through, thereby, in these cases, local anesthetics may affect the colonization and migration of cancer cells. The practical clinical approach for regional anesthesia is to give a bolus dose or a bolus dose followed by constant infusion, hence it will reach a peak circulation concentration. For example, after epidural anesthesia with lidocaine and bupivacaine, the peak circulation concentrations are around 40 μM and 10 μM respectively [5].

Pharmacological mechanisms of local anesthetics on cancer

Many preclinical studies also revealed the mechanism underlying the effects of local anesthetics on cancer cells [6]. Several pathways were reported to be involved in the effect of local anesthetics on cancer cells, including the Wnt/β-catenin pathway [7], the apoptosis pathway [8], the MAPK/ERK pathway [9,10], REDOX pathway [11], RhoA/ROCK/MLC pathway [12] and so on. Certain growth factors [13] or regulating molecular [14] were also through to be targeted by lidocaine. However, so far, no common mechanism of any local anesthetics has been discovered to be ubiquitous for all the cancer cells.

Some ion channel pathways were reported to mediate the effect of local anesthetics on cancer cells. In glioma cells, lidocaine causes cell cycle arrest and protective autophagy through interfering transient receptor potential cation channel subfamily M member 7 (TRPM7) and transient receptor potential cation channel subfamily V member 1 (TRPV1) [15][16]. TRPM7 was reported to be critical for breast cancer cells [17]. It was not surprising that lidocaine affects glioma cell lines because of the fact that glioma cells derived from brain tumors and the central nervous system where most cells are supposed to be affected by anesthetics. However, the mechanism of ion channel pathways might apply to many types of cancer cells other than glioma cells because lidocaine affects many commonly expressing ion channels some of which are thought to be overexpressed in highly active cancer cells [18]. Yuan Jiang et al. [19] linked the inhibition of lidocaine on cancer migration to the inhibition of lidocaine on the TRPV6 ion channel. They suggested that the inhibitory effect of lidocaine on TRPV6-expressing cancer cells was associated with a reduced rate of calcium influx, which partly results in less cancer cell invasion and migration, but the conclusion needs to be further validated.

Another interesting explanation for cancer suppression of local anesthetics is the emerging theory of cancer stem cells [20]. Evidence has indicated a subpopulation of stem-like cells within tumors, which contribute to cancer proliferation [21]. Amide-linked local anesthetics, lidocaine, ropivacaine, and bupivacaine, have been proved to preferentially inhibit colony formation and self-renewal of cancer stem cells [7], but, so far, the theory of cancer stem cell itself is still controversial.

A non-classic used of local anesthetics on cancer treatment

Local anesthetics might never be developed as an independent anticarcinogen, but some studies suggested that they can be a part of cancer combined medication. In an *in vivo* study, lidocaine was reported to enhance the therapeutic effect of other anticarcinoma drugs like mitomycin C, pirarubicin, and Su Funing lotion [22]. Moreover, a recent study further provided evidence that lidocaine can alleviate cytotoxicity-resistance in cancer cells [14]. Interestingly, lidocaine was also showed to increase thermal damage in cancer cells [23]. These facts implied that lidocaine may trigger the potential disadvantageous targets for cancer cells which only make a difference if lidocaine treatment is along with other antitumor factors. Therefore, the exploration of combination and internal interaction of lidocaine and other cancer treatment might be a promising field for further study and it will be significant for clinical use of local anesthetics in cancer treatments.

Summary

In general, local anesthetics anesthesia techniques frequently used in cancer surgeries include local infiltration, intravenous local anesthesia, peripheral nerve blockade, epidural block, and spinal anesthesia. The local infiltration provides the highest concentration for cancer microenvironment in cancer surgery, but other local anesthesia methods also potentially affect cancer by their blood concentration. So far, no common mechanism of any local anesthetics has been discovered to be ubiquitous for all the cancer cells, but the use of local anesthetics as a part of cancer combined medication is promising in the future. This mini-review contributed to a better understanding and the optimization of the clinical use of local anesthetics in cancer surgeries.

Declaration of Competing Interest

The author declares that there are no conflicts of interest.

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Biography: Hengrui Liu studied Chinese pharmacology, Chinese materia medical, and biochemistry at Guangzhou University of Chinese Medicine (Guangzhou, China), Jinan University (Guangzhou, China), and the University of Cambridge (UK) respectively. He worked in the Department of Anesthesiology, Stony Brook Medicine (NY, US) as a Research Scholar and is currently studying in the Department of Biochemistry, University of Cambridge. He received the *Excellent Exam-free Graduate School Recommendation* and *Undergraduate Scholarship* from the Guangzhou University of Chinese Medicine, *First-class Graduate Scholarship* from the Jinan University, and *Academic Progress Award* from the Anesthesia and Cancer Laboratory (Stony Brook Medicine). He is an editorial board member of the *Chronicles of Complementary, Alternative Integrative Medicine* (GRF Publishers), *Cell Biology* (Science Publishing Group), and *Journal of Medicine and Biology* (TRIDHA Society of Biology & Medicine). He is a reviewer board member of the *International Journal of Molecular Sciences* (MDPI, IF 4.2), *Experimental and Therapeutic Medicine* (Spandidos Publicatio, IF 1.5), *Archives of Surgery and Clinical Case Reports* (Gavin publisher) and *Archives of Cancer* (Gavin publisher). He has published papers in *Pharmacology and Therapeutics* (IF 11.1), *Cancers* (IF 6.2), *Journal of Ethnopharmacology* (IF 3.4), *Biomedicine & Pharmacotherapy* (IF 3.7), etc. During his early career, he studied the potential mechanism underlying the effect of Chinese traditional medicine on osteoporosis. Later on, in stony brook, his work has contributed to the understanding of the role of ion channel and anesthetics in cancer progression. His current study is focusing on the function and structure of voltage-gated sodium channels and the development of subtype-specific ion channel antibodies for pharmacological application.