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REVIEW

Cytotoxicity of Local Anesthetics on Bone, Joint, and Muscle Tissues: A Narrative Review of the Current Literature

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Background: Local anesthetics are commonly used in surgical procedures to control pain in patients. Whilst the cardiotoxicity and neurotoxicity of local anesthetics have received much attention, the cytotoxicity they exert against bone, joint, and muscle tissues has yet to be well recognized.

Objective: This review aimed to raise awareness regarding how local anesthetics may cause tissue damage and provide a deeper understanding of the mechanisms of local anesthetic-induced cytotoxicity. We summarized the latest progress on the cytotoxicity of local anesthetics and the underlying mechanisms and discussed potential strategies to reduce it.

Findings: We found that the toxic effects of local anesthetics on bone, joint, and muscle tissues were time- and concentration-dependent in vitro. Local anesthetics induced apoptosis, necrosis, and autophagy through specific cellular pathways. Altogether, this review indicates that toxicity of local anesthetics may be avoided by rationally selecting the appropriate anesthetic, limiting the total amount, and determining the lowest effective concentration and duration.

Keywords: local anesthetics, cytotoxicity, myotoxicity, chondrotoxicity, cell death mechanism

Introduction

Peripheral nerve blocks are an important component of multimodal postoperative pain management. They have been shown to decrease pain scores and opioid use in the immediate postoperative period.[1] Although this method is becoming increasingly safe, using local anesthetics still carries potential risks. Previous studies have focused on the cytotoxicity of local anesthetics in the nervous and cardiovascular systems. With the application of fascial plane blocks, such as transverse abdominis block, erector spinae plane block, and periarticular infiltration, the cytotoxicity of local anesthetics to muscles, bones, and joints has attracted much attention. In vitro studies have found that local anesthetics can be toxic to myocytes,[2–4] chondrocytes,[5–8] tendon cells,[9–11] intervertebral disc (IVD) cells,[12–14] and mesenchymal stem cells(MSCs),[15–17] leading to reduced cell metabolism and increased apoptosis, necrosis, and autophagic activity.

In this review, we would like to raise awareness regarding tissue damage caused by different local anesthetics and provide a deeper understanding of the mechanisms of local anesthetic-induced cytotoxicity. Although the cytotoxicity of local anesthetics is not common in clinical practice, to use the anesthetic more safely due to the variance in cytotoxicity among local anesthetics, the information provided here may help guide anesthesiologists in their medication selection.

Methods

A literature search was performed using PubMed, Embase, Cochrane Library, and Web of Science without any language restriction. The keywords "cytotoxicity", "toxicity", and "local anesthetics" were used to search. Studies from January 1, 2000, until October 28, 2022, and any referenced articles deemed significant were included. Randomized controlled

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trials, case reports, retrospective studies, meta-analyses and systematic reviews were included. The articles unrelated to the bone, joint and muscle were excluded. Articles were assessed for relevance, and data were qualitatively analyzed.

Local Anesthetics Induced Cytotoxicity in a Concentration- and Time-Dependent Manner

Sixteen studies using four different local anesthetics were included in this review (Table 1). The data showed that different local anesthetics might lead to varying degrees of decreased cell death. Lidocaine and bupivacaine were found to be more cytotoxic than ropivacaine and mepivacaine.[8,15] Studies showed significant cytotoxicity with high

Table 1 Studies on Local Anesthetic Cytotoxicity Affecting Bone, Joint, and Muscle Tissues

Cytotoxicity	References	LAs	Concentration	Exposure Time	Main Evaluation Index	Conclusion
Myotoxicity	Hofmann et al[2]	Bupivacaine Ropivacaine	0.05%, 0.1%, 0.175%, 0.25%, and 0.5% 0.05%, 0.1%, 0.175%, 0.25%, and 0.5%	1or 2 h	Live/dead assay	Increasing concentrations of bupivacaine (>0.1%) led to a significant decrease in muscle cell survival. Ropivacaine caused no significant toxicity. Exposure time influenced cell survival.
	Metterlein et al[3]	Bupivacaine	0.05%, 0.1%, 0.175%, 0.25%, and 0.5%	1or 2 h	Propidium iodide staining, live/dead assay	Increasing concentrations of bupivacaine (>0.175%) led to a significant decrease in muscle cell survival. Exposure time, but not recovery time, influenced survival.
	Ling et al[4]	Lidocaine	0–25%	8 or 24 h	Caspase assay, live/dead assay	Cell viability of cultured myogenic precursor (C2C12) cells was inhibited by lidocaine in a concentration-dependent manner, with concentrations ≥0.08% dramatically reducing cell viability.
Chondrotoxicity	Piper et al[5]	Bupivacaine Ropivacaine	0.5% 0.5%	30 min	Live/dead assay, cytotoxicity assay, and CellTiter-Glo luminescent cell viability assay	Ropivacaine was significantly less toxic than bupivacaine in chondrocyte cell culture.
	Jacob et al[6]	Ropivacaine Bupivacaine Lidocaine	0.2% 0.5% 1% and 2%	30 min	Cell death examined by fluorescent microscopy, XTT ELISA assay	The count of vital chondrocytes was significantly decreased. Ropivacaine appeared to be the local anesthetic with the lowest toxic effect on human chondrocytes.
	Park et al[7]	Bupivacaine Lidocaine Mepivacaine	0.5% 0.5% 2%	30 or 60 min	Live/dead assay, MTT colorimetric assay	Bupivacaine and lidocaine exhibited a marked chondrotoxicity. Mepivacaine was less toxic than lidocaine.
	Adler et al[8]	Bupivacaine Mepivacaine Ropivacaine Lidocaine	0.0625%, 0.125%, and 0.25% 0.25%, 0.5%, and 1% 0.125%, 0.25%, and 0.5% 0.25%, 0.5%, and 1%	30 or 60 min	MTT colorimetric assay, lactate dehydrogenase assay, and trypan blue.	Clinically relevant concentrations of LAs were cytotoxic to chondrocytes in a time- and concentration-dependent manner in vitro. Ropivacaine was the least toxic at the clinically relevant concentration.
Tendon toxicity	Nuelle et al[9]	Lidocaine Bupivacaine	0.5% and 1% 0.0625%, 0.125%, and 0.25%	1 or 7 d	Live/dead assay	Significant decreases in cell viability were caused by 1% lidocaine. Treatment with 0.125% and 0.0625% bupivacaine did not affect cell viability or metabolism.
	Sung et al[10]	Ropivacaine Bupivacaine Lidocaine	0.2% and 0.75% 0.25% and 0.5% 1% and 2%	5–60 min and 2–72 h	Cell viability with double staining with annexin V and propidium iodide	Cytotoxicity of the anesthetics studied against tenofibroblasts depended on exposure time and concentration. Ropivacaine was the least toxic at the clinically relevant concentration.
	Zhang et al[11]	Ropivacaine Bupivacaine	0.125%, 0.25%, and 0.5% 0.5%, 0.25%, and 0.125%	30 min	Cell viability with double staining with annexin V and propidium iodide	Bupivacaine 0.5% and 0.25% showed necrosis-inducing effects. Ropivacaine caused no significant necrosis.

(*Continued*)

Table 1 (Continued).

Cytotoxicity	References	LAs	Concentration	Exposure Time	Main Evaluation Index	Conclusion
IVD toxicity	Iwasaki et al[12]	Bupivacaine Lidocaine	0.25% and 0.5% 1% and 2%	2 h	Cell viability and apoptosis measured by confocal microscopy and flow cytometry	The number of apoptotic cells doubled when lidocaine increased from 1% to 2% (23% and 42% apoptotic cells, respectively) and bupivacaine from 0.25% to 0.50% (25% and 48% apoptotic cells, respectively).
	Cai et al[13]	Ropivacaine Bupivacaine Lidocaine	0.125%, 0.25%, and 0.5% 0.125%, 0.25%, and 0.5% 0.5%, 1%, and 2%	1 h	Live/dead assay using flow cytometry	There was no significant difference in IVD viability after treatment with different doses of ropivacaine. The cytotoxicity of ropivacaine was lower than that of lidocaine and bupivacaine.
	Quero et al[14]	Bupivacaine	0.75%	2 or 18 h	Cell viability and proliferation, MTT colorimetric assay	After 18 hours, bupivacaine exhibited either a cytotoxic or a proliferative effect on human IVD cells. Similar but lower effects could be observed after 2 hours.
MSCs toxicity	Dregalla et al[15]	Bupivacaine Mepivacaine Ropivacaine Lidocaine	0.5% 2% 0.5% 1%	40 min, 120 min, 360 min, and 24 h.	Live/dead assay, apoptotic assay, and delayed adherence on cell viability	Ropivacaine did not induce significant apoptosis. Others induce MSC apoptosis in a time-dependent manner.
	Rahnama et al[16]	Ropivacaine Bupivacaine Lidocaine	0.2% and 0.5% 0.25% and 0.5% 1% and 2%	1 h	Live cell counts, ATP content	Bupivacaine had limited toxicity in human MSCs. Lidocaine (>1%) significantly decreased MSC viability.
	Breu et al[17]	Bupivacaine Ropivacaine Mepivacaine	0.5% 0.75% 2%	1 h	Live/dead assay and caspase staining	Bupivacaine analyzed caused cytotoxicity to MSCs undergoing chondrogenesis, especially in superficial layers.

Abbreviations: ELISA, enzyme-linked immunosorbent assay; IVD, intervertebral disc; LAs, local anesthetics; MSCs, mesenchymal stem cells; MTT assay, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay; XTT assay, 2.3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide assay.

concentrations of bupivacaine (>0.175%) and lidocaine (>1%);[3,12] the number of dead cells increased in a concentration- and time-dependent manner, whereby cell death obviously increased after exposure of >1 h.[10] In contrast, ropivacaine was the least toxic at clinically used concentrations, with no significant dead cells after treatment with varying concentrations.[6] These findings, however, were limited to in vitro situations. Whether local anesthetics induce cytotoxicity in a concentration- and time-dependent manner in vivo remains to be explored.

Cytotoxicity of Local Anesthetics in Research Studies

Myotoxicity

Local anesthetics may induce myotoxicity; the higher the concentrations and the longer the duration of exposure to local anesthetics, the greater the damage to the muscles.[2–4] Clinically relevant local anesthetics concerning myotoxicity included lidocaine, ropivacaine, and bupivacaine, in increasing order of toxicity. The addition of epinephrine to local anesthetics may also increase myotoxicity.[18,19] The histological changes in muscle injury caused by different local anesthetics were similar, whereby a few minutes after local injection, the damage was the most obvious in the area close to the muscle fibers; a few hours after local injection, the sarcoplasmic reticulum dissolved and degenerated, and the myocytes showed oedema and necrosis. However, the basal layer, vascular system, neurons, and connective tissue structures remained intact. Characteristic fiber damage and eosinophils appeared in the adjacent areas.[20] Nevertheless, muscle injury caused by local anesthetics is entirely reversible: regeneration is complete within three to four weeks.[18]

Although many animal studies have confirmed the myotoxicity of local anesthetics, few clinical reports exist.[21] Studies have shown that approximately 0.53% and 0.11% of patients with ophthalmic blocks and adductor canal blocks experience myotoxicity symptoms.[18] The actual rate of myotoxicity may be higher as local pain at the injection site often causes anesthesiologists to ignore damage to the muscle. Most myotoxicity is missed due to rapid and complete recovery.[21] Additionally, the acute inflammatory response associated with surgery and acute-onset flaccid limb weakness may mask myotoxicity. Therefore, most cases of local anesthetic-induced myotoxicity are clinically overlooked.

Chondrotoxicity

In few clinical studies, applying intra-articular local anesthetics by pain pumps may contribute to joint and bone damage.[22] Hansen et al[23] found that 19 of 177 patients undergoing shoulder arthroscopic surgery received postoperative intra-articular analgesia, and 12 patients, all of which had pain pumps, developed post arthroscopic glenohumeral chondrolysis (PAGCL) 19 months after surgery. Other studies have shown that the risk of PAGCL is associated with flow rates since, as compared to low flow rates, it is prominently higher in patients with high.[24] Moreover, for shoulder arthroscopy, using subacromial rather than intra-articular pain pumps prevents the development of PAGCL.[23,25] Chondrolysis was also observed after arthroscopic surgery in the knee in a study in which 21 patients who received intra-articular bupivacaine with a low or high flow rate after knee surgery developed severe postoperative knee chondrolysis, causing pain in the knee during daily activities.[26]

Kreuz et al[24] showed that exposure to local anesthetics for >1 hour significantly affected cultured chondrocytes. The half-lives of lidocaine, mepivacaine, ropivacaine, and bupivacaine are 1.6, 1.9, 1.9, and 3.5 hours, respectively, which may account for the higher chondrotoxicity of bupivacaine. Local anesthetics have concentration- and time-dependent chondrotoxic effects in vitro (Table 1).[6–8] Although in vitro studies indicated potential chondrocyte toxicity for bupivacaine and lidocaine, it was not clear the true duration of contact from local anesthetics injection into a peripheral joint in vivo. However, given the variance in chondrotoxicity among local anesthetics, the studies we have included here could help guide anesthesiologists in their medication selection. As far as clinical selection is concerned, studies have shown that low concentrations of ropivacaine and mepivacaine are chosen over bupivacaine and lidocaine as they are less toxic for cartilage.[6,24]

Tendon Toxicity

Injections of local anesthetics around tendons are commonly used to treat pain. In a rotator cuff study, Nuelle et al[9] assessed the effect of local anesthetics on tendons. They exposed supraspinatus tendon cell explants to lidocaine (0.5% and 1%) and bupivacaine (0.0625%, 0.125%, and 0.25%) and cultured them for seven days; exposure to 1% lidocaine ($p < 0.001$), but not to 0.125% or 0.0625% bupivacaine, significantly decreased cell viability.

In addition, Sung et al[10] investigated the potential cytotoxic effects of bupivacaine, ropivacaine and lidocaine on cultured human rotator cuff tenofibroblasts and found that the survival rate of these cells decreased significantly with an increase in anesthetic concentration and exposure time. They further identified an increased generation of reactive oxygen species (ROS) and caspase activation as factors mediating tenofibroblast death and observed that 0.2% ropivacaine exerted the least toxic effects. These findings were corroborated by Zhang et al,[11] suggesting that appropriate concentrations and exposure times should be chosen carefully when using local anesthetics to avoid associated side effects.

IVD Toxicity

Intra-IVD injection of local anesthetics has been used in diagnosing or treating discogenic back pain. Currently, bupivacaine is often administered intraoperatively and postoperatively, which is the most commonly used intervention to reduce pain by local, spinal, or epidural injection. Due to its mechanism of inhibiting sensitization of nerve endings and reducing inflammation in degenerative IVDs, in the treatment of back pain, the efficacy of bupivacaine has been demonstrated during clinical practice.[12] However, specific adverse effects of bupivacaine have been reported, particularly concerning its cytotoxicity towards IVD cells in vitro.[12] This was first observed by Quero et al,[14] who found that the viability of these cells decreased when exposed to bupivacaine.

The higher the concentration of the local anesthetic, the worse the damage conferred to the IVD cells. Cai et al[13] exposed cultured IVD cells to lidocaine, bupivacaine, and ropivacaine and found that the cytotoxicity of ropivacaine was lower than that of both lidocaine and bupivacaine.

MSCs Toxicity

It is common to use allogenic or autologous human MSCs for tissue repair by local injection or surgical implantation.[15] In orthopedic cartilage repair surgery, intra-articular injection of human bone marrow MSCs can be performed preoperatively, intraoperatively, and postoperatively with local anesthetics.[16,27] However, in vitro data, suggest that the use of local anesthetics at the same concentration clinically as that used in vitro can have cytotoxic effects on human

MSCs.[11,17] There are differences in cytotoxicity among different local anesthetics: ropivacaine is significantly less toxic than bupivacaine and lidocaine, whilst they have the same anesthetic efficacy.[15,16,28–32]

The safety of local anesthetics combined with bone marrow MSCs in intra-articular treatment has been widely studied. Dregalla et al[15] studied the effect of local anesthetics on MSCs viability and investigated the mechanism by which local anesthetics induce the death of these cells. They exposed cultured and expanded MSCs from three donors to ropivacaine, lidocaine, bupivacaine, and mepivacaine. They demonstrated that 24 hours of exposure significantly affected the viability and adhesion of MSCs, and all local anesthetics except ropivacaine caused cell death even after brief exposure.[15]

Mechanisms of Local Anesthetic-Induced Cytotoxicity

Cytotoxicity can develop within a few minutes of exposure to local anesthetics in vitro.[17] The underlying mechanisms responsible for these adverse effects include apoptosis, necrosis, and autophagy (Table 2, Figure 1).

Local Anesthetic-Induced Apoptosis

Fluorescence microscopic observations confirmed that the cytotoxicity observed in chondrocytes, IVD cells, and tenocytes was mainly caused by apoptosis after prolonged exposure to local anesthetics.[6] Local anesthetics could induce cell apoptosis by inhibiting mitochondrial energy metabolism,[33–39] which was based on a variety of mechanisms, such as mitochondrial uncoupling, reduction of the mitochondrial membrane potential, and reduction of the respiratory chain protein content.[34] All these phenomena could be observed during long-term local anesthetic exposure (>24 hours).[10,40] Grishko et al[36] analysed the chondrotoxicity of different local anesthetics in human chondrocyte cultures and found 1% and 2% lidocaine as well as 0.5% bupivacaine induced mitochondrial DNA damage, decreased mitochondrial protein levels, and enhanced mitochondrial membrane permeability; subsequently, caspases were activated, leading to cell apoptosis. Further studies showed that local anesthetics could induce various cellular changes, including DNA breakage, chromatin concentration, and apoptotic body formation,[15,24] all indicated apoptosis.

Local Anesthetic-Induced Necrosis

Whilst at low concentrations, local anesthetics could induce apoptosis in myocytes, higher concentrations predominantly cause necrosis in these cells.[40] Correspondingly, studies have shown that bupivacaine and ropivacaine mainly cause necrosis at high concentrations,[28] which was caused by lysosomal membrane permeabilization (LMP) mediated by ROS.[41–43] Treatment of IVD cells with bupivacaine produces ROS in a dose-dependent manner,[37] and ROS could quickly diffuse into lysosomes and interact with free iron. LMP was induced by lipid peroxidation of the lysosomal membrane through the Fenton reaction, which was followed by the release of the lysosomal content into the cytosol, subsequently leading to cell death.[37] Transmission electron microscopy revealed nuclear alterations, swollen organelles, rupture of the plasma membrane, and cytolysis following exposure to local anesthetics, which confirmed local anesthetic-induced cell necrosis.[44]

Local Anesthetic-Activated Autophagy

Local anesthetics could activate autophagy by inhibiting the PI3K/Akt/mTOR signaling pathway. Autophagy was important in regulating cell metabolism and was often associated with apoptosis in the cellular stress response.[45,46] The Beclin-1 expression level and LC3-II/I ratio were widely used as indicators of autophagy activation.[47–49] Clinically

Table 2 Mechanisms of Local Anesthetic-Induced Cytotoxicity

Cytotoxic Effects	Local Anesthetics
Mitochondrial-mediated caspase activation and apoptosis	Ropivacaine[34,37] Bupivacaine[33–37] Lidocaine[34,36] Tetracaine[39]
LMP mediated by ROS and necrosis	Bupivacaine[37,44]
PI3K/Akt/mTOR signaling pathway and autophagy	Bupivacaine[50–52]

Abbreviations: LMP, lysosomal membrane permeabilization; ROS, reactive oxygen species.

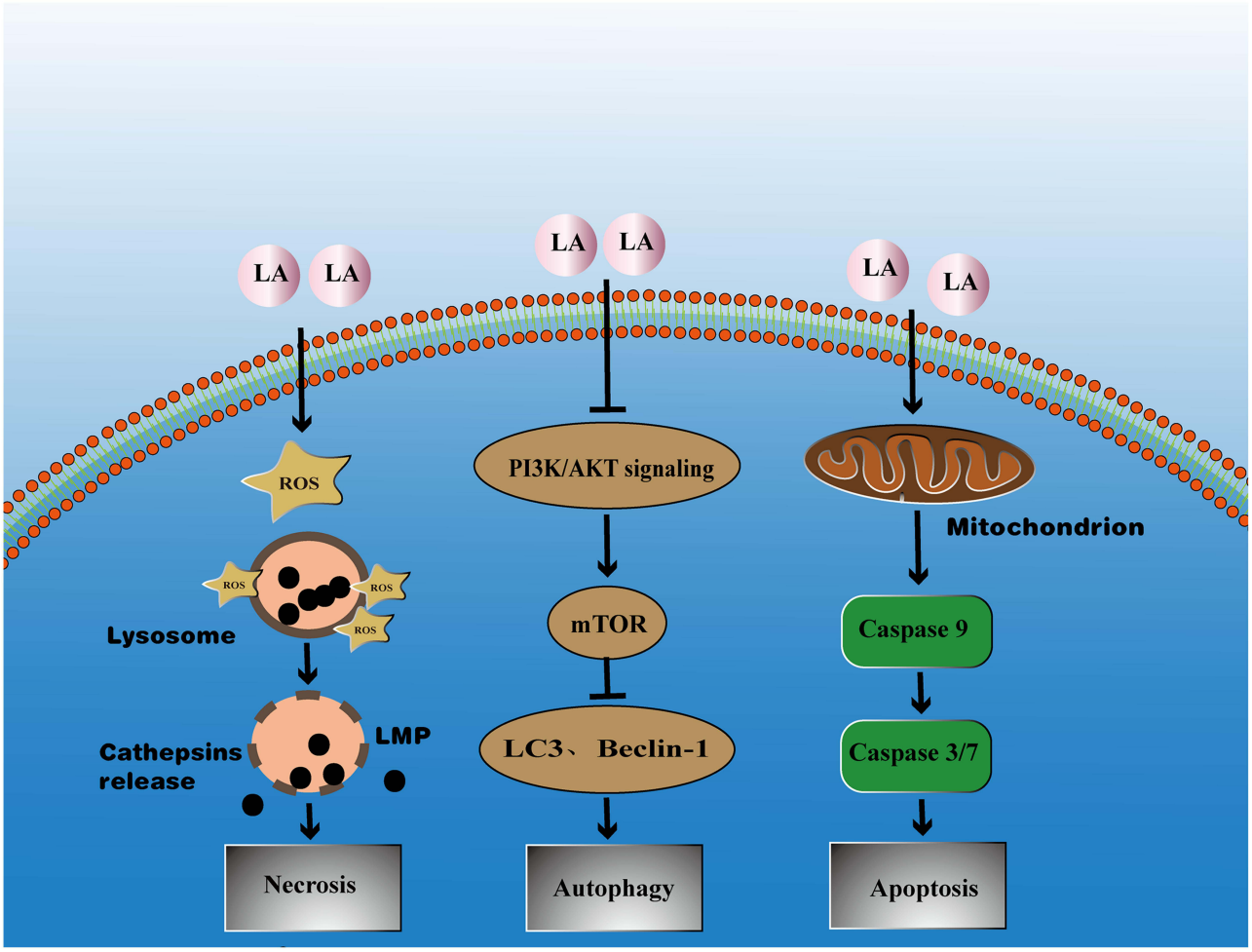

Figure 1 Local anesthetics are in contact with many targets leading the cell to death by autophagy, necrosis or apoptosis via different pathways. LA, local anesthetic; LMP, lysosomal membrane permeabilization; ROS, reactive oxygen species. LA stimulated cells to generate ROS, which could diffuse into lysosomes and induced lipid peroxidation of the lysosomal membrane with subsequent release of the lysosomal cathepsins into the cytosol leading to necrosis. The PI3K/Akt/mTOR pathway was a key regulator of cell survival; the mTOR was a serine/threonine kinase that integrates nutrients to execute cell growth and division regulated by PI3K followed by Akt. Autophagy was under the negative regulation of mTOR as assessed by LC3 and Beclin-1. LA could activate autophagy by inhibiting the PI3K/Akt/mTOR signaling pathway. Local anesthetics could inhibit mitochondrial energy metabolism, then a molecular cascade was triggered involving the activation of caspases, the vital proapoptotic proteases. In the caspase cascade, caspase 9 activated the effector caspase 3 and caspase 7 by proteolytic cleavage. Activated caspases then cleaved numerous cellular proteins, leading to apoptosis.

relevant concentrations of Local anesthetics induced upregulation of autophagic activity by inhibiting PI3K/Akt/mTOR signalling.[50–52] Activation of this pathway negatively regulated autophagy and inhibiting autophagy activation might be a protective mechanism against bupivacaine cytotoxicity.

Discussion

With the popularization of ultrasound visualization technology, peripheral nerve block technology has been widely used, and the related local anesthetic toxicity has aroused the concern of anesthesiologists. Any complications that must be detected in time. Timely detection and effective treatment can significantly improve the clinical prognosis. It is also the key for the peripheral nerve block technique to be widely promoted. Therefore, we should pay close attention to the cytotoxicity caused by local anesthetics, even though the related clinical reports are not much.

This review summarized the findings on the cytotoxicity of local anesthetics to different cells. We found that treatment with ropivacaine resulted in less cell death than bupivacaine. Furthermore, the toxicity effect of local anesthetics was time- and concentration-dependent. The above was based on in vitro studies reviewed here, and these effects remained to be established in clinical cohorts. In clinical practice, the anesthesiologist can determine the minimum effective concentration of the peripheral block, the optimal duration of the protocol for the peripheral block, and the

precise delivery of the injection to the target site.[53] The use of ultrasound-guided peripheral nerve block may help to reduce the dose of local anesthetics using ultrasound-guided peripheral nerve block to avoid potential risks.[33]

Pichiorri et al reported a clinical spinal cord infarction due to cocaine use.[54] The mechanisms might include vasoconstriction and disruption of blood flow autoregulation in the nervous system.[55] However, the effects of local anesthetics administered spinally were debatable. Although lidocaine was claimed to cause vasoconstriction at low doses and vasodilation at high concentrations in the peripheral circulation,[56] the spinal administration of lidocaine has been observed to raise, maintain, or decrease spinal cord blood flow in diverse ways.[55]

Although some anesthetics are similarly used "off-label", lidocaine is still not permitted for intravenous usage as an analgesic with potential risks. 2.5–3.5 mcg/mL of lidocaine is the therapeutic plasma level. In the central neurological and cardiovascular systems, plasma concentrations higher than 5 mcg/mL are thought to result in an increased sodium channel blockage and local anesthetic systemic toxicity (LAST).[57] Seizures, myocardial depression, and severe cardiac arrhythmias are the symptoms which may result in cardiac arrest. Despite its extremely low incidence—less than 100 instances reported in the previous 30 years— LAST can develop after using any local anesthetic, while bupivacaine use is more frequently linked to cardiotoxicity.[57]

Wound infiltration with local anesthetics has recently been shown to minimize postoperative discomfort following various surgical procedures successfully. The possible toxicity of local anesthetics brought on by their high plasma concentrations is one of the most critical barriers to the widespread adoption of this technique.[58] Systemic absorption may be increased by significant surgical incisions and soft-tissue dissection, usually during major orthopedic surgery.[59] Given that toxicity varies among local anesthetics, to prevent the occurrence of toxic effects, it is necessary to raise awareness regarding how local anesthetics may cause tissue damage. We found that local anesthetics caused cell death through oxidative stress, mitochondrial and lysosomal dysfunction, and autophagy pathways. Local anesthetic cytotoxicity-induced tissue damage and metabolic changes should be kept to a minimum.[12]

The specific form of cell death caused by local anesthetics seems to be related to the duration of exposure, the concentration and the type of local anesthetics. Studies indicated that bupivacaine mainly caused necrosis, whereas lidocaine predominantly induced apoptosis.[17,28] At low concentrations, local anesthetics induced apoptosis in myocytes, whereas higher concentrations mainly caused necrosis of these cells.[28] Fluorescence microscopy confirmed that the short-term toxicity of local anesthetics on chondrocytes, IVD cells, and tenocytes was driven primarily by necrosis rather than apoptosis.[11] However, after prolonged exposure to local anesthetics for more than 24 hours, the number of apoptotic cells significantly increased.[6]

In addition, the identification of the underlying signaling pathways, as well as the development of protective agents that could reduce local anesthetic-induced cytotoxicity, require further research. Potential protective agents include mitochondrial fission inhibitors,[36] caspase activity modulators,[12] scavengers of ROS,[44] and autophagy inhibitors.[50] Mitochondria should be among the primary targets of such protective agents and may contribute to protecting tissues exposed to local anesthetics.

Furthermore, the effects of adjuvants to local anesthetics on the tissue or cellular injury are mixed. It was thought that using epinephrine and local anesthetics simultaneously would increase myotoxicity.[60,61] Epinephrine has been demonstrated to increase significantly the skeletal muscle necrosis caused by lidocaine, even at low dosages where there is minimal damage on its own.[61] This potentiation was directly related to the drug's capacity to postpone local anesthetic absorption from the injection site.

On the other hand, Moser et al[62] found that the metabolic activity could be improved in human chondrocytes in vitro when local anesthetics and hyaluronic acid (HA) were administered simultaneously compared to local anesthetics alone. Ishida et al discovered that the surface marker CD44 on chondrocytes played a crucial role in anchoring the extracellular matrix components through binding HA. More significantly, the CD44-HA pathway stimulated various signals contributing to chondrocyte proliferation and matrix production.[63] Therefore, for patients with symptomatic knee osteoarthritis, co-administration of local anesthetics with hyaluronic acid may offer an alternative, less chondrotoxic approach. However, protective agents can only reduce the toxicity of anesthetic drugs at the cellular level; whether they are effective in vivo or clinically remains to be explored.

LAs may have anti-neoplastic actions within cancer cells, according to the evidence gathered from many laboratory investigations.[64–66] Along with their direct effects on cancer cells, LAs also have anti-inflammatory qualities that may be used to control the pro-cancer consequences of the stress response and maintain or improve immune cell function.[67] Although in vitro studies can help establish biological plausibility, their findings are not always transferable to in vivo settings, and clinical results in humans have been contradictory.[68] One retrospective study, for example, found that regional block during breast cancer surgery was associated with a lower risk of postoperative metastasis. Another study found that radical prostatectomy combined with epidural analgesia under general anesthesia significantly reduced recurrence.[69,70] Further research, however, revealed no benefit for colon or prostate cancer when patients underwent surgery with the general and epidural anesthetic.[71]

Data from cell cultures or animal models may not apply to human tissue. For clinicians, this requires follow-up on these findings in clinical research studies to find if a threshold dose and exposure time for a toxic effect might exist. Cell viability and tissue integrity can be affected by various personal factors, including body weight, the severity of a preexisting disease, or the test site. Such lesions are still difficult to diagnose in daily practice. Other local phenomena like pain and inflammation negate semiological signals of toxicity induced by LAs. MRI imaging in conjunction with other ambiguous symptoms may help in diagnosis.

Limitations

This review focused on the effects of local anesthetics. Most studies were done in vitro; thus, the in vivo effects still needed to be fully understood. In vitro results might have shown higher cell toxicity than in vivo examinations would show due to direct cell incubation. In vitro, local anesthetics did not have to pass various barriers such as the cartilage matrix or the synovial membrane. The other weakness of this review is that some results interpreted from data obtained in animals might not be transferrable to human tissue. Varying methods and protocols made it challenging to conduct general comparisons, which is a common problem within literature reviews such as this.

Conclusion

Toxic effects of local anesthetics were shown to be time- and concentration-dependent and ropivacaine showed the lowest cytotoxicity in vitro. Local anesthetics decreased cell viability by interacting with molecules in cell pathways leading to cell death by autophagy, necrosis, or apoptosis. Based on these results, clinical anesthesiologists could reduce local anesthetics-induced toxicity by rationally selecting local anesthetics, using limited total amounts, and determining the lowest effective concentration and duration.

Data Sharing Statement

All data relevant to this study can be obtained from the corresponding authors upon reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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