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NANOTECHNOLOGY IN THE IMPROVEMENT OF LOCAL ANESTHETICS

NANOTECNOLOGIA NO APRIMORAMENTO DE ANESTESICOS LOCAIS

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ABSTRACT

Local anesthetics are widely used in regional blocks during surgical procedures, in postoperative pain relief, acute or chronic pain management, and even oncological therapies. However, these conventional local anesthetic agents present several disadvantages, such as neurotoxicity, short duration of action, and uncontrolled release, which restrict their application in clinical practice. This literature review explored recent advances in using nano-structured topical anesthetics, highlighting the benefits of nanotechnology-based formulations. The methodology involved the analysis of scientific publications from the last ten years. Nanotechnology management strategies have advanced considerably, mainly due to their low systemic toxicity and the enhanced efficacy of unconventional local anesthetics. Different nanometric-scale materials, including polymers, lipids (such as solid lipid nanoparticles, nanostructured lipid carriers, and nanoemulsions), metallic nanoparticles, non-metallic inorganic nanoparticles, and hybrid nanoparticles, can be used to treat and control pain in a safe, localized way.

Keywords: Anesthesia; Blocking; Evolution; Pain; Topic.

RESUMO

Os anestésicos locais são amplamente utilizados em bloqueios regionais durante procedimentos cirúrgicos, no alívio da dor pós-operatória, no manejo da dor aguda ou crônica e até mesmo em terapias oncológicas. Entretanto, esses agentes anestésicos locais convencionais apresentam várias desvantagens, como neurotoxicidade, curta duração de ação e liberação não controlada, que restringem sua aplicação na prática clínica. Esta revisão da literatura explorou os avanços recentes no uso de anestésicos tópicos nanoestruturados, destacando os benefícios das formulações baseadas em nanotecnologia. A metodologia envolveu a análise de publicações científicas dos últimos dez anos. As estratégias de gerenciamento da nanotecnologia avançaram consideravelmente, principalmente devido à sua baixa toxicidade sistêmica e à eficácia aprimorada dos anestésicos locais não convencionais. Diversos materiais em escala nanométrica, como polímeros, lipídios (como nanopartículas lipídicas sólidas, carreadores lipídicos nanoestruturados e nanoemulsões), nanopartículas metálicas, nanopartículas inorgânicas não metálicas e nanopartículas híbridas, podem ser usadas para tratar e controlar a dor de forma segura e localizada.

Palavras-chave: *Anestesia; Bloqueio; Dor; Evolução; Tópico.*

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INTRODUCTION

Obtaining quality healthcare is, without a doubt, an individual's right. Health services must offer effective, efficient, and safe patient care to achieve this. Local anesthetics are medications widely used to control pain in clinical procedures in Medicine and Dentistry, as they act by blocking sodium channels, which prevents the transmission of electrical impulses to the central nervous system. There has been a significant increase in the demand and performance of procedures that frequently use these topical medications. This application allows for better pain control, providing greater comfort to the patient and ensuring more effective treatment results. (1)

Although local anesthetics have been widely used in clinical practice over the past century, two major challenges persist: neurotoxicity and short half-life, compromising its clinical efficacy significantly. An appropriate approach to administering local anesthesia can bring several benefits to the healthcare system, such as greater patient satisfaction, early hospital discharge, and reduced unscheduled hospital stays. (2)

There is still no topical anesthetic considered ideal. This drug should be effective in reducing pain, with immediate action, long duration, few side effects, ease of application and removal, and a pleasant aesthetic presentation. The choice of the appropriate topical anesthetic will depend on the properties of the drug, the vehicle used, and the type of surface to which it will be applied. (3)

Advances in nanotechnology in healthcare, biomaterials, and biotechnology have created a new field of study called nanomedicine. Nanoparticles can be used for the controlled release of medicines, adhesion and resistance materials, coating implants, cancer treatment, the constitution of biomaterials, bone regeneration, and tissue biomimicry, among other purposes. These advances have overcome historical challenges in Medicine and Dentistry, improving existing techniques and driving the development of new methods and treatments. Delivery systems such as nanocapsules have been suggested in the hope of improving the availability and reducing the toxicity of drugs.(4)

To eliminate or minimize various side effects such as neurotoxicity, short life span, toxicity-induced neurological and cardiovascular manifestations, hypertension, and dysrhythmias, among other effects, several drug delivery systems (DDSs) encapsulating local anesthetic agents have been developed for continuous release, which ensures that drug release is considerably slower. Analgesia is maintained for a prolonged period with less associated neurotoxicity. (3)

Although the history of the discovery of local anesthesia is still not completely clear in many aspects, especially those of an authorial nature, it is known that its clinical use emerged 135 years ago, more than 6 decades after the beginning of general anesthesia (5). Progress in anesthetic pharmacology highlights its importance for medicine, especially in the context of human care. (6)

This article aims to review advances in transporting local anesthetics using nanotechnology-based carriers, highlighting the benefits identified in recent studies.

METHODOLOGY

A narrative review of the literature was conducted to identify the main local anesthetics currently used in clinical practice and the advances related to the application of nanotechnology in this context. The research for articles was conducted in the electronic databases Medline/PubMed, and the search for further technical information about the products was carried out in the BIREME platform and publications of the Brazilian Society of Anesthesiology (SBA), using the combination of the descriptors in English "local anesthetics" and "nanotechnology".

Articles published from 2003 to 2024 were included, primarily in indexed journals with a recognized impact factor. The search identified 32 articles in the PubMed Platform, with a significant concentration of content in the last 10 years.

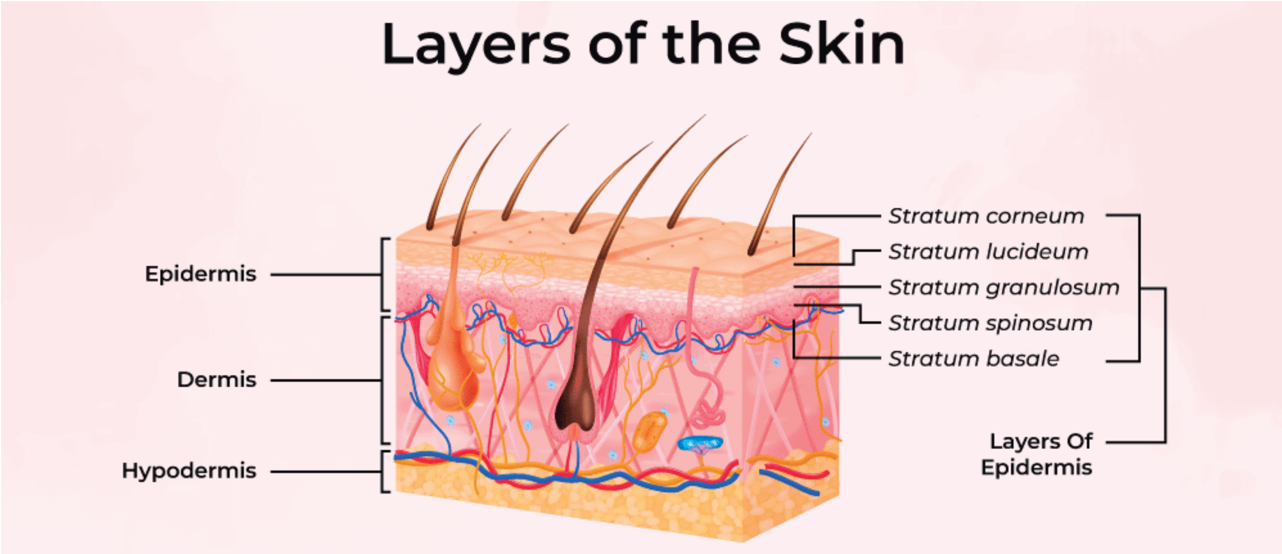
The inclusion criteria included studies that explored clinical and experimental applications of local anesthetics, with or without the use of nanotechnological systems, while studies without direct relevance to the topic or with insufficiently described methodology were excluded. In order to carry out this review, 16 articles (presented in Table 03) that address the proposed study object were selected. This approach allowed mapping the main trends and gaps in the use of nanotechnological carriers for local anesthetics.

ABSORPTION AND ACTION OF LOCAL ANESTHETICS

The history of the discovery of anesthesia still needs to be fully understood in several aspects, especially about authorship. However, it is known that the clinical use of local anesthesia began 135 years ago, more than 6 decades after the advent of general anesthesia. (5)

The skin is the main organ in contact with this topical medication. The epidermis plays a crucial role as a barrier to the penetration of topical medications, including anesthetics. It is an avascular layer of the skin, with a thickness varying between 0.12 and 0.7 mm, with the stratum corneum being the most superficial and effective portion of the skin barrier. The epidermis is mainly composed of water and lipids, which makes it difficult for the anesthetic to diffuse into the dermis. The intact stratum corneum is relatively impermeable to ionized molecules. Compounds with a higher concentration of neutral base (nonpolar) can better penetrate the stratum corneum, an important characteristic to consider when applying local anesthetics. These layers can be visualized in Figure 01 below. (7).

Figure 01 - Layers of the Skin.



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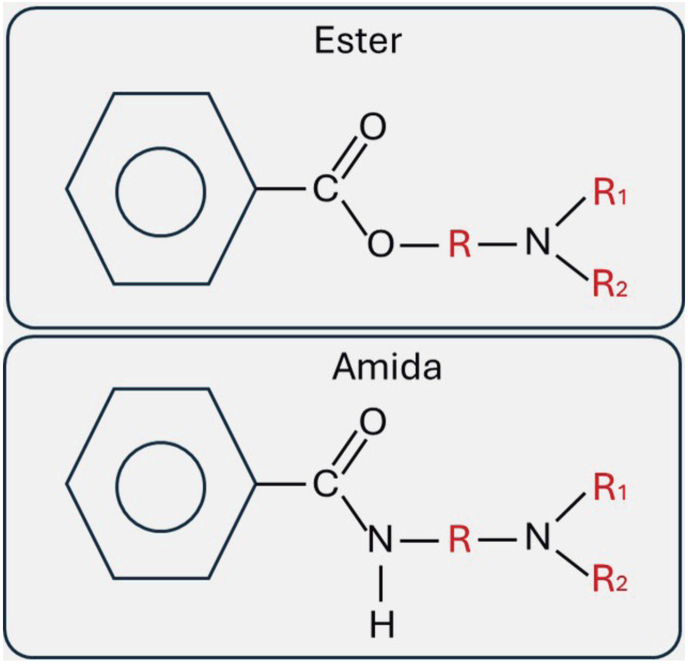
Local anesthetics act on neurons, promoting reversible blockade of neuronal signal conduction. More specifically, the anesthetic molecule acts directly on the neuron's cell membrane, binding non-permanently to a specific receptor in the pore of the sodium channels (8)(9).

The sensation of pain depends on the ability to transmit nerve impulses, which, in turn, depends on the propagation of the stimulus along the nerve fiber. This transmission is only possible due to the difference in the concentration of sodium and potassium in intra and extracellular fluids, which establishes an ionic gradient between the media maintained by the Na^+,K^+ -ATPase pump. (10)

Painful stimuli are transmitted by tiny unmyelinated nerve fibers, which are more sensitive to anesthetics than myelinated fibers that transmit other sensations. Consequently, patients may experience sensations of pressure and vibration while being numb to pain. (10)

Topical anesthetics, biochemically, are divided into two groups: esters and amides. Its basic structure consists of a lipophilic aromatic ring and a hydrophilic amine group connected by an intermediate chain. This chain is the basis for the classifying anesthetics into esters or amides, as shown in Figure 02. (11)

Figure 02 - Ester and Amide Molecular Structure.



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DIFFERENT LOCAL ANESTHETICS

Examples of aminoamides include lidocaine, ropivacaine, bupivacaine, and prilocaine. Some examples of aminoesters are procaine, benzocaine, tetracaine, chloroprocaine, cocaine, and others. These anesthetics are sold as salts, consisting of weak bases with a pH close to physiological, and are hydrophobic, as shown in **Table 01**. (12)

Table 01 - Potency of drugs.

Drugs	Potency
Procaine	Low
Lidocaine, Prilocaine, Mepivacaine	Intermediate
Bupivacaine, Ropivacaine, Tetracaine	High

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Epinephrine is a drug closely associated with local anesthetics, whether esters or amides, which works as a vasoconstrictor. These are defined as chemical substances associated with anesthetic salts whose function is to slowly absorb this salt, reduce its toxicity, increase the duration of anestesia, and increase the effectiveness of the anesthetic block. It reduces the speed of systemic absorption and, consequently, the toxicity of the anesthetic through the vasoconstriction mechanism. This relationship is safe for short- and medium-acting local anesthetics such as lidocaine and prilocaine, which increase the drug’s duration of action. The classification and duration of local anesthetics can be seen in Table 02. (13)

Table 02 - Classification and Duration of Local Anesthetics.

Classification and Duration of Local Anesthetics		
Drug	**Classification**	**Duration**
Procaine	Ester	Short
Tetracaine	Ester	Intermediate to Long
Lidocaine	Amida	Intermediate
Mepivacaine	Amida	Intermediate
Prilocaine	Amida	Intermediate
Bupivacaine	Amida	Long
Ripovacaine	Amida	Long

Font: Author's Construction.

STUDIES OF SYSTEMS FOR THE ADMINISTRATION OF LOCAL ANESTHETICS BASED ON NANOTECHNOLOGY

The main objective of clinically applying technological innovations in DDSs (anesthetic administration systems) is to improve the drug's therapeutic index. The proposed formulations are designed to decrease the dosage of the anesthetic drug while increasing its absorption and permeability, maintaining the anesthetic at the target site for a long duration, and reducing its clearance (14).

Encapsulation of these drugs in advanced DDSs, such as nano- and microparticles, should facilitate improved retention time in the body and prolonged rates of drug release at the target site (15).

Studies involving the administration of these medicines using nanoparticles for transport are divided into three large study groups: polymeric, lipid, and inorganic. Table 03 highlights the main results in relation to this article's proposal and highlights the main advances in the use of nanotechnology in the application of topical anesthetics.

Table 03 - Nanotechnology studies and local anesthetics.

Drug Delivery System (DDSs)	Conveyor	Transported Droug	Main Effects	Font
Polymeric nanoparticles	Alginate nanoparticles, chitosan nanoparticles, polymeric nanocapsules, PLGA-coated chitosan nanoparticles, PLGA nanoparticles, and nanofiber-structured peptides	Bupivacaine Benzocaine, Ropivacaine	Prolongation of drug action, sensory blocks, prolongation of local anesthesia, alteration of pharmacokinetics, improvement of biodegradability, improved biocompatibility, reduction of toxicity, improvement of drug stability, prolongation of nerve block, improved efficacy and efficiency	(26), (27), (28), (29)

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Lipid nanoparticles	Solid lipid nanoparticles, nanostructured and lipid-based lipid carriers (nanoemulsions)	Dibucaine, Benzocaine, Butambem, Lidocaine	Prolong release, reduce toxicity, improve intensity, improve anesthetic duration, improve anesthesia in tissue inflammation, improve efficiency, improve transdermal drug delivery property, reduce drug dose, achieve sustained release, and decrease immediate pain to the patient	(30), (31), (32), (33), (34), (35), (36)
Inorganic nanoparticles	Gold nanoparticles, silver nanoparticles, zinc oxide nanoparticles, magnesium oxide nanoparticles, gold coated magnetite nanoparticles, organosilica nanoparticles, silica nanoparticles	Procaine, Tetracaine, Dibucaine, Cetamine, Ropivacaine	To characterize the interaction of gold nanoparticles and anesthetized sites, to characterize the interaction of silver nanoparticles and anesthetized sites, to attenuate neurogenic and inflammatory pain, to induce analgesic and anti-inflammatory effects, to characterize and localize medications to specific sites, to get lasting pain relief, to increase nerve block.	(37), (38), (39), (40), (41)

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DISCUSSION

Although nanomedicine is rapidly growing, its application in administering local anesthetics still faces significant challenges, mainly due to the complexity of pain physiology and the difficulty in treating chronic pain. This highlights the need for innovative strategies to overcome limitations (17).

Nanotechnology, which involves studying and developing nanometer-scale structures, is critical in the administering local anesthetics due to the advantages of smaller-sized and more efficient drug carriers. (18) This strategy offers numerous benefits, especially for the targeted administration of anesthetic medications at the required dose without affecting adjacent tissues. As a classic example, local anesthetics encapsulated by liposomes bring great technical advances to achieve targeted administration. Furthermore, nanoparticles have shown efficacy in relieving postoperative pain, with fewer side effects, suggesting great potential as specific drug delivery systems (DDSs) for local anesthetics.(19)

Nanoparticles have multiple beneficial characteristics, including small size, customizable surface, enhanced solubility, and multifunctional ability. These properties are crucial for improving the stability and controlled release of drugs and expanding their biomedical applications. (20)

Over the years, researchers have gradually designed a series of nanoparticle-based carriers, most of which are combined with different anesthetics for more efficient and targeted drug delivery. The most recent literature focusing on nanoparticles for administering local anesthetics is classified into polymeric, lipid, and inorganic nanoparticles, as shown in Table 03.

As mentioned above, nanosized materials show high efficiency in releasing encapsulated drugs and significant value in patient pain control. (24)

Despite these advantages, nanoscale DDSs have limitations, such as the low structural stability of liposomes, the release of nanoparticles induced by the high surface-to-volume ratio, and the foreign body response of synthetic polymers. (22, 23)

These challenges have driven increasing efforts to optimize nanoscale DDSs further. This article presentes the most promising nanodrug delivery systems, including polymeric, lipid, inorganic non-metallic, metallic, and hybrid nanoparticles, as shown in Table 03.

Although many of these systems have been tested in cellular, animal models and, in some cases, humans, most research is still restricted to the preclinical stage. Therefore, future research should focus on the validation and clinical application of nanoscale DDSs, aiming to consolidate the benefits of these technologies and overcome existing limitations in administering local anesthetics.

CONCLUSION

Local anesthetics can be considered safe medications for dermatologists to use. Although some adverse effects are considered serious, such as systemic toxicity and other adverse reactions, they are rare. The correct way to use the medication, the appropriate application technique, and knowledge of adverse events and their specific treatment significantly minimize the risks associated with local anesthetics and make their application viable and safe in the office.

Developing new delivery systems for local anesthetics is essential to meeting their expectations. A desirable system with controllable and sustainable drug release performance for adequate analgesic effect is vital for comfortable and safe use. Safety concern is particularly important since effective delivery of anesthetic medications is essential to the patient.

Significant advances have been made in the controlled release of local anesthetics to achieve a longer duration of analgesic effects and improve the safety profile, enabling successful use in the clinical setting. The application of polymeric, lipid, and inorganic nanoparticles, and various hybrid nanoparticles provides a wide range of options for vehicle selection and optimization. These customized delivery systems offer an extended range and the opportunity to prolong the duration of action of each agent, consequently maximizing local anesthetic effects.

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