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Can local anesthetics help with the healing process of surgical wounds?

Podem os anestésicos locais ajudar no processo cicatricial das feridas cirúrgicas?

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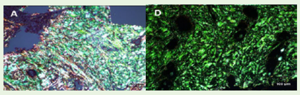
ABSTRACT
Introduction: Evaluating the scarring differences between areas previously anesthetized with different local anesthetics is interesting to verify whether the choice of anesthetic helps in surgical healing in relation to inflammation, neovascularization and collagen deposition.
Objectives: Review the existing literature with a focus on analyzing the role of local anesthetics in aiding the healing of surgical wounds.
Methods: Narrative review of literature selected from the SciELO – Scientific Electronic Library Online, Google Scholar, Pubmed and Scopus platforms. Initially, the review searched for keywords in the focus of the research, based on MESH/DeCS with the following terms: "local anesthetics, healing, neovascularization, collagen" with AND or OR search, considering the title and/or abstract. Next, only those that were most related to the topic were included, and the texts were read for inclusion.
Results: 73 articles were included, read and interpreted focusing on the role of anesthetics in healing, pain, side effects and the best that currently emerge in analgesia and scar potential.
Conclusion: No differences were observed between the anesthetics studied in terms of healing, inflammation and neovascularization. However, there was a significant difference in the production of collagens with an intensity of 6 to 12 times greater than collagen types I, II and III with the use of levobupivacaine.
KEYWORDS: Local anesthetics. Healing. Neovascularization. Collagen.

RESUMO
Introdução: Avaliar as diferenças cicatriciais entre áreas previamente anestesiadas com diferentes anestésicos locais é interessante para verificar se a escolha do anestésico auxilia na cicatrização cirúrgica em relação à inflamação, neovascularização e deposição de colágeno.
Objetivos: Revisar a literatura existente com foco de análise sobre o papel dos anestésicos locais no auxílio da cicatrização de feridas cirúrgicas.
Métodos: Revisão narrativa da literatura selecionada das plataformas SciELO – Scientific Electronic Library Online, Google Scholar, Pubmed e Scopus. Inicialmente a revisão realizou a busca por palavras-chave no foco da pesquisa, com base no MESH/DeCS com os seguintes termos: "anestésicos locais, cicatrização, neovascularização, colágeno" com busca AND ou OR, considerando o título e/ou resumo. A seguir, foram incluídos somente os que tinham maior relação ao tema, e realizada a leitura dos textos para inclusão.
Resultados: Foram incluídos, lidos e interpretados 73 artigos enfocando o papel dos anestésicos na cicatrização, dor, efeitos colaterais e os melhores que despontam na atualidade na analgesia e potencial cicatricial.
Conclusão: Não se observou diferenças entre anestésicos pesquisados quanto à cicatrização, inflamação e neovascularização. Contudo, verificou-se diferença significativa na produção de colágenos com intensidade de 6 a 12 vezes maior de colágenos tipos I, II e III com o uso da levobupivacaína.
PALAVRAS-CHAVE: Anestésicos locais. Cicatrização. Neovascularização. Colágeno.



D with the densest concentration of collagen: A) control group; D) levobupivacaine
Source: Carstens MG73

Central message
Evaluating the scarring differences between areas previously anesthetized with different local anesthetics is interesting to verify whether the choice of anesthetic helps in surgical healing in relation to inflammation, neovascularization, and collagen deposition. This study compared the most frequent local anesthetic solutions with controls to verify whether there are scarring differences between the different anesthetic solutions and the scarring result.

Perspective
The results indicated that the infiltration of local anesthetics into the surgical wound may play a role in the tissue repair process in humans. In the analysis of the influence of ropivacaine and levobupivacaine on the inflammatory phase of healing, no differences were observed between them in relation to scar areas, inflammation and neovascularization. However, there was a statistically significant difference in collagen production, with an intensity of 6 to 12 times higher for type I, II and III collagen in the levobupivacaine group, leading to the conclusion that it can play a positive role in the healing process of surgical wounds

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INTRODUCTION

Local anesthetics are substances that are widely used in superficial surgical procedures and work by blocking nerve signals in the area where they are applied.[1-3] The most common include: 1) lidocaine (the best known); 2) bupivacaine, generally used for longer procedures because it has a longer-lasting action compared to lidocaine; 3) most popular procaine (novocaine) in dentistry; 4) articaine, also more used in dentistry; and 5) mepivacaine, similar to lidocaine but less likely to cause vasodilation, making it useful in procedures requiring bleeding control. Ropivacaine and levobupivacaine are the ones in focus in this review.

Ropivacaine belongs to the group of aminoamides. It is used for surgical anesthesia and for the treatment of acute pain. It has several characteristics that distinguish it from other local anesthetics: 1) potency and duration, it is less potent and has a slightly shorter duration compared to bupivacaine; 2) selective blockade: tends to preferentially block sensory nerves over motor nerves, which can be beneficial in certain medical procedures where the preservation of muscle movement is important4; 3) safety profile, refers to its lower cardiotoxicity and lower potential for toxicity to the central nervous system. It provides effective local anesthesia and is a valuable option in the anesthesiologist's arsenal, especially in patients where motor function is desired or in those at higher risk of adverse reactions to other anesthetics5,6.

Levobuivacaine is also included in the group of aminoamides. It is the S-enantiomer of bupivacaine and is used similarly in regional anesthesia for local infiltration, peripheral nerve block, sympathetic block, and epidural and intrathecal anesthesia. Levobupicaine is known to have lower cardiotoxicity compared to bupivacaine, being a safer alternative in some cases. It works by blocking the generation and conduction of nerve impulses, effectively numbing the area where it is applied. The onset and duration of anaesthesia depend on the dose and specific use.

Side effects of local anesthetics can vary, but they are usually rare and mild when used correctly. They may include injection site reactions, dizziness, irregular heartbeat, and, in rare cases, severe allergic reactions.

Postoperative wound healing is a crucial step in the recovery process of patients undergoing surgical procedures. The use of local anesthetics has been associated with better pain control and faster recovery after the operation.[7-11] It is a complex process and involves several steps that the body takes to repair and close the wound.[12.13]

Nowadays there is a lot of talk about the auxiliary effect on wound healing that some local anesthetics have. It is a controversial topic that needs to be further researched.

The objective of this review, aiming to analyze the role of local anesthetics in postoperative wound healing and its clinical implications, is to update the existing research showing the possible effects of ropivacaine and levobupivacaine on superficial surgical wound healing.

METHOD

This study was done by researching information published in the period from January 2022 to August 2023. For analysis, the SciELO platforms – Scientific Electronic Library Online, Google Scholar, Pubmed and Scopus – were selected. Initially, the review searched for keywords in the focus of the search, based on the MESH/DeCS with the following words: "local anesthetics, healing, neovascularization, collagen" with AND or OR search, considering the title and/or abstract. Next, only those that were more related to the theme were included, and the texts were read, including 73 articles.

DISCUSSION

Cicatrization

Wound healing is a multifaceted, complex, and highly coordinated process aimed at restoring the integrity and functionality of the injured tissue. This process of repair is critical in all forms of life to sustain survival after injury from trauma, illness, or surgical procedures.[14]

Historically, wound healing has been studied by a variety of disciplines, and the current understanding is the result of input from fields as diverse as cell biology, immunology, genetics, tissue engineering, and many others.[15] This complex process is mediated by multiple cell types, chemical mediators, and extracellular matrix proteins, all working together to ensure that the injured tissue is repaired efficiently and effectively.[16]

Adequate response to wound healing is vital to maintaining the bodily barrier against the outside world, and failures in this response can result in significantly adverse outcomes. For example, slow or inadequate healing can lead to the formation of chronic ulcers, increasing the risk of infection and other complications.[17]

On the other hand, accelerated or excessive healing can result in excessive scar tissue formation, leading to hypertrophic scars or keloids. These are not only harmful, but can also be painful and limit functionality, depending on your location.[18]

Similarly, healing is an essential component of postoperative success. Complications in healing can lead to dehiscence of wounds with separation of their edges, infection, and eventually the need for additional surgical intervention. In addition, the quality of wound healing can also impact patient comfort and aesthetic satisfaction, particularly in plastic and reconstructive operations.[19]

In recent years, there has been considerable interest in strategies to improve wound healing and minimize scar formation. This includes the investigation of a variety of growth factors, cytokines, and other chemical mediators, as well as the manipulation of the wound environment with occlusive or pressurenegative dressings.[20] There is also interest in understanding the potential role of various drugs, including local anesthetics, in wound healing and its phases.[21]

Inflammatory phase

It is the first stage of the healing process and begins immediately after the injury occurs. It forms a fibrin clot that serves as a provisional matrix for the migration of cells involved in tissue repair. In this context, platelets play a fundamental role, releasing a series of growth factors and cytokines that promote cell migration and proliferation.[22]

During inflammation, leukocytes, especially neutrophils and macrophages, are attracted to the site of injury. Neutrophils, which are the first to arrive, have as their main function the destruction of bacteria and the cleaning of debris from the wound through phagocytosis. However, their activity must be carefully regulated, as they can cause damage to healthy tissue if not properly controlled.[23] Macrophages, in turn, have double activity during the inflammatory phase. They participate in wound cleaning, just like neutrophils, but they also release growth factors, such as platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF), which are essential for the beginning of the proliferative phase of healing.[24] Blood vessels dilate, increasing vascular permeability, which allows immune cells and nutrients to reach the site of injury more easily. This results in the classic symptoms of inflammation: flushing, heat, edema, and pain.[25]

Although it is essential for the beginning of healing, the inflammatory phase must be transient and controlled. Chronic or dysregulated inflammation can lead to inadequate healing and the development of chronic wounds. Thus, understanding the details of the inflammatory phase of healing is essential for the therapeutic manipulation of this process in order to improve tissue repair.[26]

Proliferative phase

It is characterized by the reconstruction of tissue that has been damaged. This phase, which begins around the 3rd day after the injury and lasts up to 2 weeks; It involves various cells and cellular processes, such as neovascularization, granulation tissue formation, re-epithelialization, and collagen synthesis.[14]

Angiogenesis is a vital process for wound healing, in which new blood vessels form from existing ones. Fibroblasts are important for the formation of granulation tissue, which is essential for filling the wound. In addition, these cells are also responsible for production of collagen, a key protein that imparts strength and integrity to the skin and other tissues.[27]

Re-epithelialization is the process of restoring the epidermis, the outermost layer of the skin, over the wound. This process is crucial for protecting the wound from infection and fluid loss. It is performed by keratinocytes, the most prevalent cells in the epidermis, which migrate to the wound and proliferate to form a new layer of epidermis.[28]

In addition, the extracellular matrix plays a crucial role in the proliferative phase of healing, as it provides scaffolding for cell migration and proliferation. During this phase, the extracellular matrix is constantly remodeled by fibroblasts, which synthesize and degrade its components.[29]

The proliferative phase of healing is a highly regulated process, and any disturbance can lead to poor healing. For example, inadequate angiogenesis can result in insufficient granulation tissue, while excessive fibroblast proliferation leads to the formation of hypertrophic scars or keloids.[30]

Refurbishment phase

The remodeling phase is the final stage of the wound healing process, starting around 1 week after the injury and can last for more than 1 year. In this phase, collagen is reorganized and the extracellular matrix is remodeled, which increases wound resistance.[31]

Fibroblasts differentiate into myofibroblasts during remodeling, cells that have the ability to contract and promote wound closure.[32] The conversion of type III collagen, predominant in the proliferative phase, to type I collagen, which is more resistant, occurs during remodeling.[33]

A crucial process in the remodeling phase is apoptosis, or programmed cell death, of fibroblasts and inflammatory cells that are no longer needed.[34] In addition, the balance between collagen synthesis and degradation is maintained by matrix metalloproteinases and their tissue inhibitors. Dysregulation of this balance can result in abnormal scarring.[35]

Remodeling ends with the formation of the mature scar, which has fewer blood vessels, fewer cells, and more organized orientation of collagen fibers compared to granulation tissue.[36] The remodeling phase is a complex and highly regulated process, and its disturbance can lead to undesirable results, such as the formation of hypertrophic scars or keloids.[37]

Factors that can influence healing

Healing in a complex process can be influenced by several factors, both intrinsic and extrinsic. Intrinsic factors include age, nutritional status, comorbidities such as diabetes mellitus and peripheral vascular diseases, as well as genetic factors.[38] Nutritional status, especially, plays a crucial role in healing, as specific proteins, vitamins, and minerals are necessary for collagen synthesis and cell proliferation.[39] Among the extrinsic factors, smoking stands out, which impairs blood circulation and, consequently, the supply of oxygen and nutrients to the wound, delaying healing.[40] Additionally, medications such as corticosteroids and nonsteroidal anti-inflammatory drugs can also affect healing, as they interfere with the body's inflammatory and immune responses.[41] Mechanical factors such as strain and pressure on the wound can also impair healing. Excessive pressure can compromise the blood perfusion of the area, while tension leads to separation of the wound edges.[42] In addition, the presence of foreign bodies or contamination of the wound by microorganisms can cause infections that prolong the inflammatory process, impairing healing.[43]

Understanding these factors and how they affect wound healing is essential for effective wound management and for optimizing healing outcomes.

Local anesthetics

Local anesthetics (LAs) are substances that induce reversible loss of sensation in a specific region of the body, without causing loss of consciousness.[44] When administered directly to the target tissue, LAs transiently block the conduction of nerve impulses, providing pain relief. They work by blocking voltage-gated sodium channels in the membranes of neurons. When these channels are blocked, there is a decrease in the rate of depolarization of the neuronal membrane, which leads to the blockade of the generation and conduction of the nerve impulse.[46]

LAs are widely used in surgical, dental, diagnostic, and therapeutic procedures for pain management.[45] They have also been used for postoperative pain relief, through direct application to surgical wounds, as local infiltration or topical application.[47] However, while the efficacy of LAs in pain management has been well documented, the potential implications on wound healing are still being investigated.

Types of local anesthetics

LAs can be categorized in a variety of ways, although the most common classification is based on their chemical structure. Mostly, they fall into 2 categories: esters and amides.[48]

Ester types include procaine, tetracaine, and benzocaine. They are metabolised primarily by plasma esterases and have a relatively short half-life compared to amide-type anaesthetics.[49] They are also more likely to cause allergic reactions compared to amide-type anesthetics, although such reactions are generally rare.[50]

Amide-type local anesthetics include lidocaine, mepivacaine, prilocaine, bupivacaine, ropivacaine, and levobupivacaine. They are metabolized in the liver and have a longer half-life compared to those of the ester type.[49] Lidocaine is one of the most commonly used local anesthetics due to its relatively rapid onset of action and moderate duration of action.[51]

Use of LAs in surgical procedures

LAs in operations is a widely accepted and well-established practice, with multiple techniques and modalities used depending on the type of procedure and the individual patient's need.[52] One of its most common uses is regional anesthesia, where it is injected near a set of nerves to numb area of the body. This includes epidural and spinal anesthesia, brachial plexus anesthesia, and peripheral nerve anesthesia.[53] Administering LAs in this way can provide good pain control while minimizing the systemic side effects of opioid analgesics. They are also often used in topical anesthesia for minor procedures, such as skin sutures and eye procedures, and in infiltrative anesthesia, where the anesthetic is injected directly into the tissue being operated on.[5] LAs can also be used in a field block, which is similar to infiltrative anesthesia but is used to numb a larger area of tissue. They may also play an important role in postoperative analgesia. For example, ultrasound-guided administration of LAs (peripheral nerve anesthesia) has been shown to be effective in reducing postoperative pain, providing lower opioid use and early discharge after surgical procedures.[54]

Current criteria for choosing the LA to be used

They are multidimensional and involve considerations of the nature of the operation, the duration of the desired action, the potency of LA, pharmacokinetic properties, possible side effects, the patient's overall health, and possible drug interactions.[55]

Regarding the type of operation, the LA chosen should be appropriate to the duration of the operation and the type of pain expected after the procedure. For example, bupivacaine, which has a longer duration of action, may be preferred for more prolonged procedures or for postoperative pain management.[56]

The potency of the LAs is also an important consideration. Lidocaine and mepivacaine are less potent but have faster onset of action, while bupivacaine and ropivacaine are more potent but slower onset.[57]

In addition, the pharmacokinetic properties of LA, such as how quickly it is absorbed and eliminated by the body, should also be considered. For example, lidocaine is quickly absorbed and eliminated, while bupivacaine is absorbed and eliminated more slowly.[58]

Side effects and toxicity are another important consideration. LAs have a risk of systemic toxicity, which can be mitigated by appropriate dose administration and careful patient monitoring.[59]

The patient's health status and potential drug interactions should also be considered when choosing an LA. For example, patients with liver or kidney disease, or who are taking other medications that may interact with LAs, may require adjustments in the choice or dose administered.[60]

LAs and healing

The relationship between LAs and postoperative wound healing is a growing field of interest, but conclusive evidence is still lacking. Several studies have examined the potential impact of LAs on wound healing, focusing on their ability to mitigate the inflammatory response, promote the proliferative phase, and modulate the remodeling phase.[61]

One aspect that has been highlighted in studies is their role in inflammation. Inflammation is a necessary response to tissue injury, but it is also the source of much postoperative pain. LAs have the potential to mitigate this inflammatory response, potentially reducing both pain and the deleterious effects of prolonged inflammation.[62]

The administration of LAs has also been suggested to affect the proliferative phase of healing. For example, administration of bupivacaine has been shown to increase fibroblast proliferation in vitro, which could potentially accelerate healing.[63]

Wound remodeling, the final phase of healing, is another process that can be influenced by LAs. Bupivacaine, for example, has been shown in animal studies to have the ability to promote collagen remodeling and wound maturation, which could have implications for the strength and appearance of the final scar.[64]

Modulation of type I, II and III collagens by local anesthetics

The main stages of the wound healing process, such as hemostasis, inflammation, and angiogenesis, are influenced by the extracellular matrix (ECM), collagen, and its compounds. In response to injury, collagen induces platelet activation and aggregation, resulting in the deposition of a fibrin clot at the site of injury. In the inflammatory phase of wound healing, activation of immune cells stimulates the secretion of pro-inflammatory cytokines that influence the migration of fibroblasts, epithelial cells, and endothelial cells. Fibroblasts contribute to collagen deposition. Simultaneously, collagen degradation releases fragments that promote fibroblast proliferation and the synthesis of growth factors that lead to angiogenesis and re-epithelialization.

Type I, II, and III collagens play key roles in the healing process and are known for their abundance in different tissues of the body. Type I collagen is the most abundant and is predominantly found in skin, tendons, and bones, providing mechanical strength to tissues.[65,66] Type II collagen is the main component of cartilage and is crucial for the support and flexibility of the cartilage matrix.[67] Type III is associated with type I collagen and is commonly found in soft tissues such as muscles and organs.[68]

In the context of healing, type I collagen is often the first to be deposited, contributing to the strength and integrity of scar tissue.[69,70] On the other hand, type III collagen is expressed in the initial phases of healing, but is eventually replaced by type I, since the latter is more resistant.[71.72]

In the context of studies with local anesthetics, the literature indicates that such substances can influence the deposition of collagen. Certain anesthetics, such as bupivacaine, have been shown to negatively interfere with type I collagen synthesis.[73.74.] This effect can slow healing and compromise the strength of the repaired tissue.

Type II collagen has minor relevance in the context of skin healing, but it has implications in orthopedic operations and in the treatment of cartilaginous lesions. The presence of this type of collagen in the extracellular matrix is critical for the regeneration of cartilage tissues.[75]

Understanding how local anesthetics affect the neovascularization and deposition of these types of collagen is essential, not only for the optimization of surgical procedures, but also for the improvement of results in scarring processes.[76]

In the analysis of the influence of ropivacaine and levobupivacaine on the inflammatory phase of healing, on the 5th day of circular incisions, Carstens MG77 did not observe significant differences between the groups in the measurements of scar areas and in relation to inflammation and neovascularization. However, they found a statistically significant difference in collagen production with an intensity of 6 to 12 times greater than types I, II and III with levobupivacaine77

CONCLUSIONS

This review analyzed findings from previous studies, and presented more current research, which highlighted the anti-inflammatory potential of LAs. Other publications have shown a comprehensive view of the molecular and cellular mechanisms of wound repair influenced by LAs. Thus, once again, the potential auxiliary role of LAs in the healing process of surgical wounds is raised.

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