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Chapter

Local Anesthetics Infiltration and Wound Healing Process

João Abrão, Marcelo Antunes and Luis Vicente Garcia

Abstract

It is a good practice, nowadays, to infiltrate local anesthetics along the incision to prevent postoperative pain. This can reduce the use of opioids and the side effects they cause. It is known clearly that the surgical trauma causes inflammatory reaction, and this can be the beginning of a bad cicatrization or even a scar. The use of local anesthetics preventing the acute pain is a very simple technique and has proved to be useful. Nevertheless, the reaction that various anesthetics have over the tissues and the cicatrization process is yet controversial and deserves to be investigated deeply. The use of different formulations of these drugs has been stimulated. The duration and secureness have been the goals of many researches. Levobupivacaine, ropivacaine, and bupivacaine for their long action; lidocaine for less toxicity; and liposomal formulation for the longest duration ever seen, all of them have been indicated in the postoperative pain management. The aim of this chapter is to evaluate the role of long duration local anesthetics on the inflammatory reaction and consequently the collagen production and resistance of the tissue to traction.

Keywords: local anesthetics, pharmacology, ropivacaine, bupivacaine, tensile strength, wound healing, drug effects

1. Introduction (local anesthetics, general comments, classification regarding structure and duration)

Local anesthetics (LA) are widely used in clinical practice in anesthesiology. They possess the common property of transient interruption in the neural conduction, and in the fibers C and Aδ, they cause interruption of pain transmission. Pharmacologically, there is a selective blockade of Na^+ channels [1, 2]. The mechanism of action of LA is not related only to binding to the Na^+ channels. LA have an important role in other targets (channels and receptors); for example, in K^+ and Ca^{++} channels, they have an anti-inflammatory effect by bounding to G protein (inhibiting the adhesion of polymorphonuclear leukocytes, macrophages, and monocytes), increase the release of glutamate, as well as interfering in the activity of some intracellular signaling pathways [3, 4].

There are at least five applications for the use of LA in anesthesiology: local infiltration, regional intravenous anesthesia (Bier block), peripheral nerve block, central nervous system (CNS) blockade (spinal anesthesia, epidural, and caudal), and topical deposit (EMLA, eye drops in ophthalmology) [3]. In this chapter, we will discuss its application in the infiltration of the operative wound and its effects

in the inflammatory process, after a brief discussion about the pharmacological structure of LA.

2. Na^+ channel structure: the main target of conventional LA

The Na^+ channel is composed of one alpha subunit and one or two beta subunits, which can be present in three different states: resting, open, and inactivated (**Figure 1**). The AL binds to the Na^+ channel after crossing the plasma membrane, that is, they bind to an internal portion of the alpha subunit preventing its activation and consequent depolarization of the membrane (**Figure 2**). Thus, the impulse is not propagated through the neurons, which prevents the perception of nociceptive pain [5, 6].

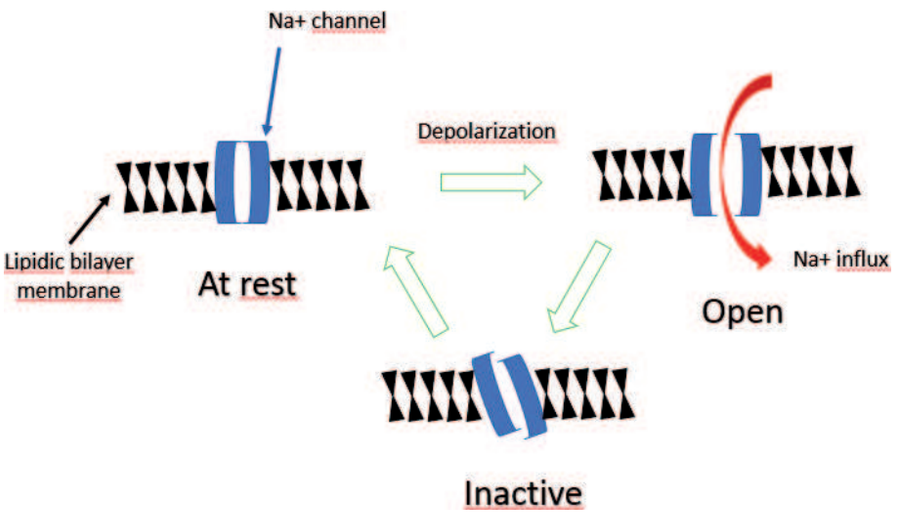

Figure 1.
Na^+ channels—it opens with the voltage changes (depolarization) propagated by the electrical impulse.

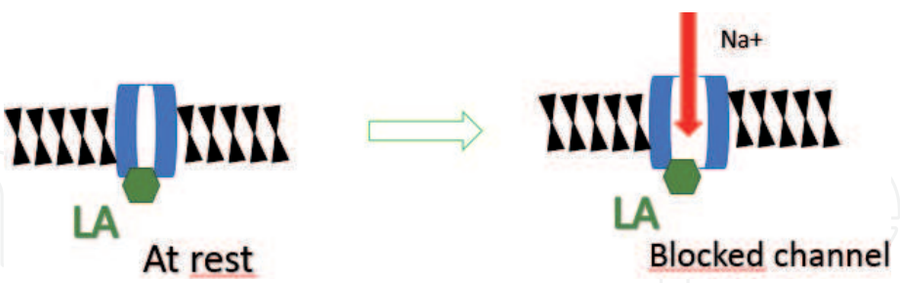

Figure 2.
The electric stimuli are not able to open the Na^+ channel because it is blocked by the LA.

3. Classification of AL (esters and amides and justify the use of each)

In its chemical structure, the LA are weak bases that possess in its molecule a lipophilic portion (aromatic ring) and another hydrophilic (tertiary amine) separated by an intermediate chain (hydrocarbon chain containing an ester or an amide group) (**Figure 3**) [7, 8].

The latter allows the classification of LA in amino-esters or amino-amides. These two groups differ in relation to its biotransformation site (the ester forms are metabolized by plasmatic esterases, while amide forms are degraded by hepatic enzymes) [9, 10].

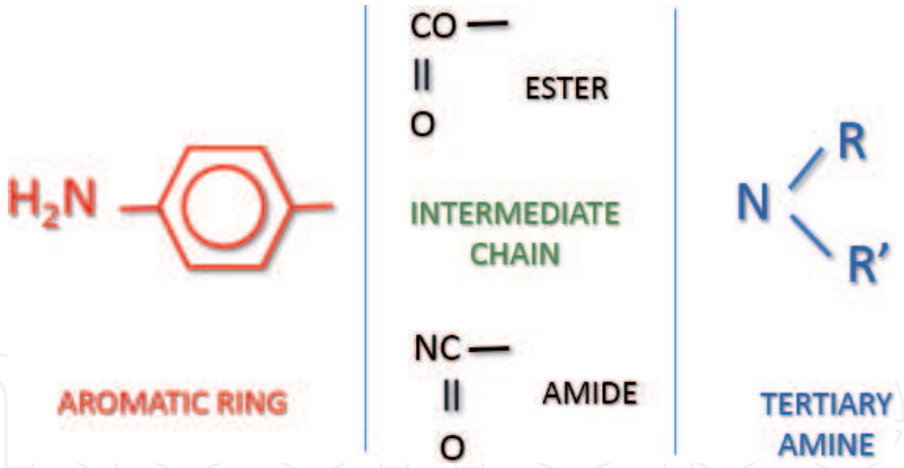

Figure 3.
LA generic structural formula.

Regarding the allergenic potential—the para amino benzoic acid (PABA) is an allergenic metabolite of the amino esters. Caution must be observed with some LA formulations, because methylparaben and metabisulfite are allergenic used as a preservative [11].

The size of the alkyl chain, in the amino group or aromatic ring, confers the LA molecule its hydrophobic character and its permeability in the lipid bilayer. So, the larger the nitrogenated radicals will be their potency and duration of LA blockades [12].

4. LA toxicity

Followed by the application of AL in the patient, a fraction will be absorbed by the bloodstream (plasma). Depending on the dose administered, the LA may reach higher or lesser degree the noble organs (e.g., brain and heart) producing physiological alterations in these tissues as well. The total dose used should comply with a maximum limit to try to avoid these undesirable effects, known as systemic LA toxicity [13]. Usually, in clinical practice, we must respect the maximum dose of each LA. Note that the CNS effects of lidocaine vary according to its plasma concentration (**Table 1**)—the higher the plasma concentration, the greater the risk to the patient, even develop a cardio-respiratory arrest. Thus, it is mandatory to observe the maximum allowable doses for each LA.

LA may also induce cardiac toxicity depending on the dose employed, acting directly in the heart (specialized conduction tissues) and decreasing the contractility of ventricular myocytes. Bupivacaine is more cardio depressor than lidocaine [14–16].

Plasma concentration (mcg/mL)	Effect
1–5	Analgesia
5–10	Numbness of tongue, tinnitus
10–15	Seizures
15–25	Coma, respiratory failure
>25	CV depression

Table 1.
CNS toxicity—lidocaine plasma concentrations and its effects [17].

5. Long-term local anesthetics: ropivacaine, bupivacaine, and levobupivacaine. (Pharmacological characteristics: concentration used in practice, toxic dose and care). Liposome formulations

The duration of action of LA is influenced by its effect on the vascular smooth muscle tone (vasoconstriction/vasodilatation) adjacent to the place where it is deposited. Other factors that determine its duration include the volume and concentration used, the approach itself (infiltrative versus regional peripheral nerve versus CNS blocks), the target tissue (fiber's diameter and myelin sheath), and the plasma protein binding (drug-specific affinity).

Long-term LA are the most used in clinical practice in anesthesiology at the following maximal allowed doses—bupivacaine (2 mg/kg), levobupivacaine (2 mg/kg), and ropivacaine (3 mg/kg).

5.1 Bupivacaine

Bupivacaine is presented as a racemic mixture of enantiomers R^+ and S^-. The optical isometry due to the presence of a chiral carbon (asymmetric) confers several possibilities in the formulation of the LA.

Bupivacaine promotes differential conduction blockade. As it produces more sensory than motor blockade, it plays an important role in the postoperative pain control. The use of epinephrine (5 μg/mL) gives a small increase in its duration of action (as opposed to lidocaine, which takes great advantage over this association). The use of large volumes for infiltration should be taken with cautious and done gradually and intermittently (3–5 mL at 5 min intervals). The patient should always be monitored to detect any unintentional intravascular injection of LA. Bupivacaine presents a higher risk of cardiac toxicity, when compared to levobupivacaine and ropivacaine. Every injection of this anesthetic should be done with the utmost care, always checking the positioning of the needle (by aspirating the syringe ensuring that the needle bevel is not intravascular).

5.2 Levobupivacaine

This anesthetic is the S-isomer of the bupivacaine, having the advantage of less neuro-cardio-toxicity due to lower affinity for these tissues. From a cardiac point of view, it causes a shorter prolongation of the QT interval and lower negative inotropism than racemic or R+ bupivacaine [18]. Its analgesic profile is similar to bupivacaine, because its duration of action is also long-lasting. Like ropivacaine, it has an intrinsic vasoconstrictor effect.

5.3 Ropivacaine

It is an anesthetic formulated by the pure enantiomer S of 1-propyl 2′-6′ pipecoloxylide [19]. As levobupivacaine, it has a safer profile than bupivacaine, because it has a lower toxicity in the CNS and heart. Its duration of action is long-lasting, like that of bupivacaine and levobupivacaine. It is widely used in infiltrative anesthesia and peripheral nerve blocks in anesthesiology. The same precautions should be taken with the use (intermittent and monitored injections). It is worth remembering that ropivacaine possesses intrinsic vasoconstrictor effect, which confers lower vascular absorption and increases its duration of action (levobupivacaine also owns this property).

6. Liposomal formulations

New methods of releasing the LA have been used in order to prolong the analgesia conferred by these anesthetic drugs. One of them is to produce liposomes spheres loaded with LA. This system allows LA deposit in the center of the liposomes, being involved by a double lipid layer. This setting allows a slower, controlled, and gradual release of LA, (72–96 h), consequently providing extended analgesic duration [20–23]. Liposomal bupivacaine (LB) has a decreased spread when compared with conventional bupivacaine. Therefore, several injections are needed and next to each other to obtain better results. In the infiltrative technique, it should be injected continuously from the fascia to the dermis. Unlike conventional formulations, which use bupivacaine HCl, the LB is produced only with its unprotonated basic form.

7. Infiltrative or transdermal techniques: practical recommendations

When the LA is used to infiltrate the operative wound, the anesthesiologist should seek a balance between the dose employed considering the size of the area to be anesthetized. In other words, it is sought to dilute the total dose used to cover most of the tissues operated. Thus, the same amount of LA used for infiltration on one side (e.g., right breast) needs to be diluted (doubling the volume) and to be employed bilaterally (e.g., right and left breast), always keep in mind that we must respect the maximum safety doses.

This approach allows an alternative to single dose injection of LA, namely the implantation of catheters for complementary use of the medication (continuous and/or in bolus, known as Patient Controlled Analgesia PCA) in order to prolong its therapeutic effect. In clinical practice, these resources increase costs because they need to be supervised, in addition to the increased risk of infection at the catheter implant site. New approaches are being investigated to optimize postoperative analgesia—use of newer drugs, innovative delivery systems (liposomal bupivacaine and ropivacaine), and the use of adjuvants along with LA.

8. Non-anesthetic drugs (adjuvants) injected together with LA (magnesium, epinephrine, clonidine, morphine, dexmedetomidine, and steroids). Is it worth?

With the advent of several approaches in the treatment of postoperative pain, the anesthesiologist can associate the use of various drugs and techniques aiming at greater efficacy in their control. The simultaneous use of several drugs (with pharmacological synergism) allows the anesthesiologist to decrease the total dose employed, when compared to the isolated use of each of them. This is one of the reasons for the use of adjuvants with the LA [24–26]. Another reason is to reduce opioid consumption in the post-operative period and associated collateral effects.

Usually, there is a consensus about the use of adjuvants in anesthesia, that is, the anesthesiologist must balance risks versus benefits and mainly the common sense. It is his/her responsibility to do the best choice in each case.

8.1 Magnesium

Magnesium sulfate antagonizes ionotropic N-methyl-D-aspartate (NMDA) glutamatergic receptor interfering in calcium homeostasis (membrane potential).

When injected together with LA in regional anesthesia, some evidence suggest that its use is beneficial [27]. Conversely, the use of magnesium sulfate intravenously is controversial [28, 29].

8.2 Dexmedetomidine

Dexmedetomidine (DMD) is a strong and highly selective α2-adrenoceptor agonist. When added to local anesthetics can enhance the analgesic efficacy of the peripheral regional nerve block [30]. DMD is eight times more selective than clonidine. It has analgesic, sedative, and antihypertensive effects, when used in systemic route. This substance has been associated with bupivacaine and lidocaine aiming prolonging the analgesic effect [31].

8.3 Epinephrine

Epinephrine has been used mixed to local anesthetics since a long time ago, and its recommended concentration is 5–10 μg/mL. It has, besides vasoconstrictive action that prolongates the local anesthesia, an analgesic effect mediated by alpha-2 adrenoceptor activation [32]. The vasoconstrictor effect of epinephrine can prevent inadvertent intravascular administration of local anesthetic solutions. Nowadays, the use of ultrasonography made such use largely redundant [33].

The onset time of local anesthesia after single injection was considered clinically significantly reduced when epinephrine was added to lidocaine or bupivacaine, when performing peripheral nerve blocks [34]. Current recommendations, however, allow the use of epinephrine in peripheral blocks only when ultrasonography is not available [35].

8.4 Clonidine

Clonidine applied at perineural sites, in doses up to 1.5 mcg/kg, acts as an adjuvant to local anesthetics prolonging analgesia and sensory/motor blocks [36]. It has intrinsic analgesic properties, inhibiting action potentials of C and Aδ fibers, as well as modulates the redistribution of local anesthetics through alpha1-receptors activation [37].

Side effects of this drug are dose dependent and include sedation, by decreasing sympathetic outflow (suppressing the release of norepinephrine in locus ceruleus (CNS) and substantia gelatinosa), hypotension, bradycardia, dry mouth, constipation, dizziness, and drowsiness [38].

Clonidine represents a good addition for the armamentarium of anesthesiologists because it prolongs the duration of analgesia, provides a faster onset of action, and improves the quality of nerve blocks (decreasing opioid consumption) [39, 40].

8.5 Morphine

Morphine is used by several routes and dosages (intrathecal: 100–200 mcg, epidural: 1–5 mg, peripheral nerve block: 75–100 mcg/kg, intravenous and intramuscular) [41]. Despite its use to prolong the analgesia, it is important to the anesthesiologist to pay attention at recommended doses to avoid the undesirable side effects (pruritus, nausea, vomiting, urinary retention, and respiratory failure). Always double check the vials before the administration of this medication because there are several vials currently in use (2, 4, 5, 8, and 10 mg/ml). All vital signals must be monitored at post-anesthetic care unit after the morphine use to early detect any cardiovascular or respiratory complications: bradycardia, hypotension, hypoxemia, and respiratory failure [42].

8.6 Steroids

Dexamethasone, a potent anti-inflammatory agent, has been investigated for its role as an adjuvant to local anesthetics in neuraxial as well as peripheral nerve blocks. This steroid has been used in intrathecal anesthesia (8 mg preservative free), in epidural analgesia (4–8 mg) and as an adjuvant in a variety of peripheral blocks, like brachial plexus, ankle block, and TAP block. A meta-analysis has found it to significantly prolong the duration of brachial plexus block when using conventional local anesthetics solutions [43]. Besides all the researches about the role of dexamethasone in neural block, one question has not been answered yet: is the better and prolonged analgesia caused by systemic effects of the steroid?

9. The four stages of wound healing

The wound healing is a continuous process, but for didactic understanding, it can be divided into four phases [44, 45]. The first phase occurs just after the incision or lesion of the skin, as soon as the blood leaks out of the body. There is a vasoconstriction, and the platelets stick together to initiate the coagulation. This phase is called the hemostasis phase. The platelet plug is reinforced by threads of fibrin. The hemostasis phase occurs very rapidly, in a question of seconds. As the fibrin mesh is formed, the blood is transformed from liquid to a gel state, that is, the pro-coagulant effect of prothrombin. This clot keeps the platelets and blood cells trapped in the wound area. Just after the injury of the skin, the epidermal tissue and the keratinocytes release the interleukin-1 (IL-1) pre-stored in these sites. The coagulation process activates the clotting cascade which is responsible to give the matrix for the influx of inflammatory cells. The degranulation of the platelets releases alpha granules, which secrete growth factors, like epidermal growth factor (EGF), platelet derived growth factor (PDGF), and transforming growth factor-beta (TGF-β). The PDGF and the IL-1 are responsible for attracting neutrophils to the wound site to remove bacteria [44]. The monocytes cells are converted to macrophages by influence of TGF-β, what has an important role in the initiation of the granulation tissue and a many proinflammatory cytokines (IL-1 and IL-6), besides other growth factors, like fibroblast growth factor (FGF), EGF, TGF-β, and PDGF. All these growth factors and the added endothelial cell proliferation ensues the angiogenesis beginning. During this hemostasis phase, the injured blood vessels leak transudate causing localized swelling and cell migrations to the site of wound. The damaged cells, pathogens, and bacteria are removed. White cells, growth factors, nutrients, and enzymes create the swelling, heat, pain, and redness, normally seen in the wound healing. This phase where all these signs appear is called the inflammatory phase. This phase is not a problem unless it is prolonged and excessive. After all the bacteria and debris are removed, the wound is rebuilt with a new tissue made up of collagen and extracellular matrix. This is the proliferative phase. In this phase, new blood vessels are formed, so that the granulation tissue can receive enough oxygen and nutrients. The myofibroblasts are responsible for the contraction of the wound, making the granulation tissue to take the ideal dimensions to the lesion. The granulation in this phase is pink or red. If there is a dark color is a sign of infection, ischemia or poor perfusion. At the end of this process the epitelial cells resurface the wound extension, what is called the maturation or remodelling phase. In this stage, it is wise to maintain the wound moist and hydrated to optimize the epithelialization [46]. Some authors consider that the wound healing has only three phases, and this is comprehensible as long as the hemostasis phase and the inflammatory phase are so concomitant, dynamic, and interactive, that they consider it just as an

inflammation phase. In fact, the phases do not have a predetermined duration, as Witte and Barbul showed in their article (**Figures 4** and **5**), the migration of cells to the wound site and the matrix formation [47].

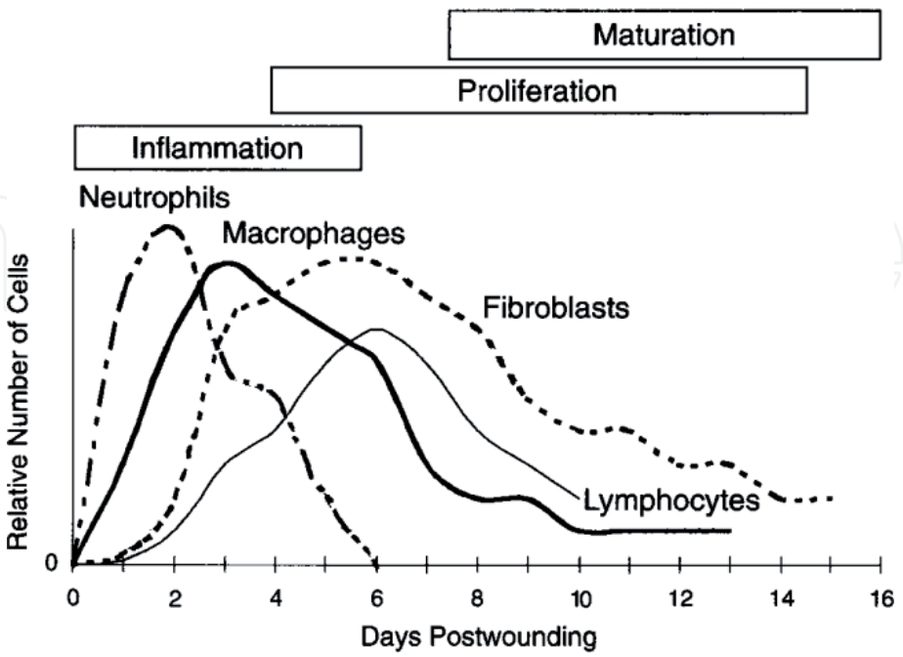

Figure 4.
The time course of different cells during healing process. Macrophages and neutrophils are predominant in inflammation phase, whereas lymphocytes peak somewhat later. In the proliferative phase, fibroblasts are more frequent [47].

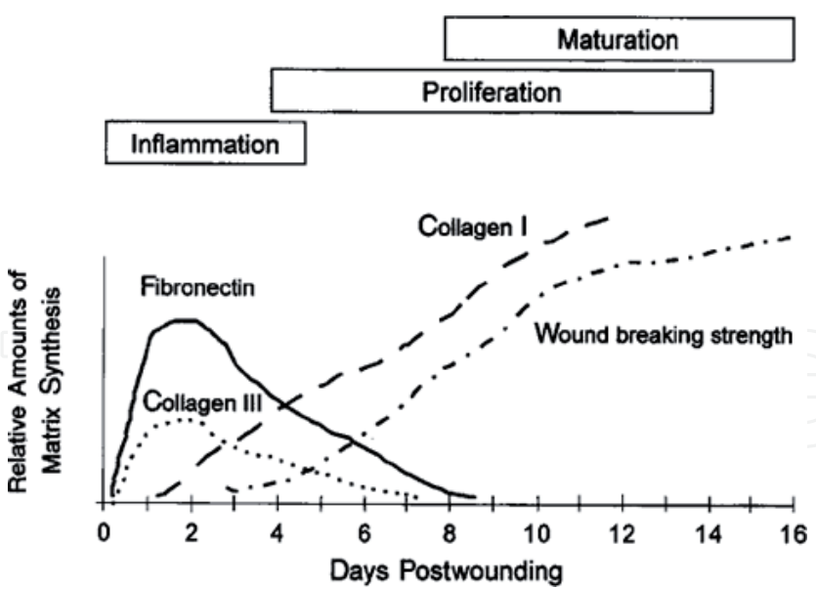

Figure 5.
Deposition of wound matrix components over time [47].

10. Local anesthetics can influence the process of wound healing?

When there is a rupture of vessels, there is an exposure of the subendothelial collagen to the platelets. This contact results in the aggregation and activation of the intrinsic factor of coagulation cascade. In the presence of thrombin, fibronectin, and their fragments, there is the release of cytokines and growth factors from platelets (PDGF), transforming growth factor-β (TGF-β), platelet-activating

factor (PAF), fibronectin, and serotonin. All this form the local fibrin clot that is the scaffolding for invading cells such as neutrophils, monocytes, fibroblasts, and endothelial cells. The neutrophils are the first cells to invade the wound, increasing the vascular permeability due to inflammation and release of prostaglandins. In the same time, chemotactic substances like complement factors, interleukin, tumor necrosis factor-α (TNF-α), TGF-β, platelet factor 4, and stimulate neutrophil migration [47–49]. The factors associated with wound healing can be seen in **Table 2**.

When analyzing the possible action of the LAs in the wound healing process, many aspects can take role. Injecting any substance in the surgery site, it is expected that it can have at least a pH influence, as the anesthetic has a pH different of the physiologic one. Many times, epinephrine is used to prolong the duration and lower the toxicity of the drug used [50, 51]. The influence of pain in the wound healing has been studied too [52–54]. The wound healing in the fetus has also been the object of research [55, 56]. And last, the LA probably can have a direct action in the eicosanoids or in the fibroblast formation and so in the cicatricial process [56].

These all are hypothesis that are discussed deeply, and many researches in human have to be done, unfortunately the majority of the manuscripts are in rats and they have a different immunologic system than humans.

The tissue injury caused by surgery produces directly and indirectly activation of nociceptors and higher expression of proinflammatory cytokines and cyclooxygenase-2 (COX-2), leading to peripheral and central sensitization with subsequent hyperalgesia. The pain and inflammation are maintained by abundant eicosanoids, like prostaglandin E_2, released after surgical trauma. The long-acting local anesthetics such as bupivacaine and ropivacaine are used to provide prolonged perioperative pain relief and to diminish the occurrence of postoperative sensitization that manifests with hyperalgesia after the anesthetic effect has dissipated. The occurrence of hyperalgesia is very common when high doses of anesthetic are used [57, 58]. The routine of infiltrating the surgical site reduces the postoperative pain and morbidity and accelerates the recovery. This can be explained by reducing the

	Function
Hemostatic factors	
Fibrin, plasma fibronectin	Coagulation, chemo attraction Structure for cell migration
Factor XIII (fibrin-stabilizing factor) Circulatory growth factors	Chemo attraction and adhesion Modulation of chemo attraction, mitogenesis, fibroplasia
Complement	Antimicrobial activity, chemo attraction
Platelet-derived factors	
Cytokines, growth factors	Regulation of chemo attraction, mitogenesis, fibroplasia
Fibronectin	Early matrix, ligand for platelet aggregation
Platelet-activating factor (PAF) Thromboxane A_2	Platelet aggregation Vasoconstriction, platelet aggregation, chemotaxis
Platelet factor IV	Chemotactic for fibroblasts and monocytes, neutralizes activity of heparin, inhibits collagenase
Serotonin	Induces vascular permeability, chemoattractant for neutrophils
Adenosine dinucleotide	Stimulates cell proliferation and migration, induces platelet aggregation

Table 2.
Hemostatic and platelet-derived factors associated with wound healing [47].

production of cytokines. Although LA action is to block the nerve conduction, they have other cellular targets that modulate the inflammation, suggesting that the LAs have an anti-inflammatory effect [59, 60]. Several studies have shown that LA dose-dependently inhibits leukocyte adhesion to synthetic material and to blood vessel walls. LA can induce the release of prostacyclin, and this causes the release of leukocytes previously firmly adherent to vascular endothelium. It is shown that the LA can in low concentration stimulate the phospholipase A_2 (PLA_2) while in higher concentrations inhibited this enzyme [61].

All these considerations are important, but what is important in clinical aspects are the fibroblast formation and the quality of the wound healing. The first question the patient formulates is when he will return to normal life activity. To answer this question, it is important to have not only histological analyzes of the wound but also mechanical testing to be sure that the tissue is ready to normal work. Vasseur and cols in 1984 studied the effects of local anesthetics on abdominal wounds of rabbits [62]; using mechanical testing device, they could demonstrate that the breaking strength in the groups infiltrated with lidocaine or bupivacaine, do not vary consistently from the tissues infiltrated with saline solution, and so they conclude that the local infiltration with lidocaine and bupivacaine does not alter substantially the healing of midline abdominal incisions in rabbits. Abrão and cols in 2014 made a similar work using rats and long-lasting anesthetics, bupivacaine, and ropivacaine [63]. They used a computerized universal testing machine, and they concluded that there were no significant differences among the groups with respect to tensile strength after 14 days. These results, however, are not the same than Hanci and cols in 2012, who found that lidocaine and bupivacaine reduce the collagen production and the wound breaking strength in Wistar rats [64]. To further augment the argument, Kesici and cols in 2018 studied the effect of bupivacaine, levobupivacaine, and procaine in the Sprague Dawley rats [65]. They found that bupivacaine and levobupivacaine affect negatively the wound healing, especially at the late period (21 days). The differences in these studies increase the uncertainty and discussion regarding the effects of local anesthetics. Many aspects must be considered like the animal gender, the use of other analgesic like paracetamol, the infiltration method, and the time of evaluation. Interestingly, there is no work done on humans, who certainly have a different response to pain. Probably, the reason is the difficulty to use the same methodology. All the researches in humans have only clinic evaluation, it is almost impossible to make mechanical tests. Uncertainties in this field only will be clarified with new studies. The clinical studies in human beings have a very subjective way to follow the wound healing. They constitute another subject that must be studied separately. The analogic scale of pain as the consume of opioids has been used as parameters to analyze the efficacy of the method. These studies conclude that ropivacaine (0.3%) can be used alone or with the addition of DMD (1 μg/kg), and there is no effect on wound healing [31, 66]. We must bear in mind that some authors only used a clinic evaluation, what can vary a lot from one researcher to another.

11. Conclusion

Nowadays, all the anesthesiologists are engaged in avoiding the excessive use of opioids for their side effects in the postoperative pain treatment. In fact, the μ-opioid receptors are impaired by the unrestricted use of morphine like drugs, besides there is an inhibition of the beta-endorphin release. Considering that the infiltration of LA in the surgical site does not produce, clinically any significant harm to the tissue cicatrization, and has the property of sparing opioid use, this

technique is an important tool in the control of the postoperative pain and must be recommended.

Conflict of interest

We declare that we do not have any conflict of interest.

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