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REVIEW

A review and new insights to antimicrobial action of local anesthetics

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Abstract

Local anesthetics (LAs) are medications which can provide analgesia in distinct body regions through the blockade of voltage-gated sodium channels. Besides pain management, the supplemental role of LAs as antimicrobial agents has been documented in several studies. Different databases including PubMed, Scopus, and Web of Science with the name of different local anesthetics and related names for antimicrobial keywords were searched without time limitation. This review summarized different in vitro and in vivo studies regarding antimicrobial effects of different LAs with focuses on antimicrobial applications of most studied LAs, interaction with different agents which combined with LAs, and mechanisms of action and structural dependence of LAs antibacterial effects. Among different LAs, lidocaine is the most studied preparation. Reduction of the incidence of endophthalmitis after intravitreal injection, prophylaxis for surgical wound infections, prevention of the incidence of catheter-associated infections, oral biofilm reduction on the buccal mucosa, and prevention against bacteria that produced nosocomial infection are some examples of lidocaine antimicrobial application. Studies showed that different factors including structure, concentration, duration of exposure, type of microorganism tested, and temperature affect the degree of LA antimicrobial activity. In addition, various agents such as antibiotics, preservatives, opioids, epinephrine, and propofol can combine with LAs and affect their antimicrobial properties through synergistic or antagonistic action. Due to antibacterial activities, LAs could be applied in a clinic for prophylaxis of surgical site infection. In the application of LAs prior to diagnostic procedures caution should be needed; otherwise, when culturing the specimen, they could lead to false negative results.

Keywords Local anesthetic · Antibacterial · Antifungal · Bactericidal · Lidocaine · Bupivacaine · Ropivacaine · Tetracaine

Introduction

Local anesthetics (LAs) are medications which can provide effective analgesia in distinct regions of the body through the blockade of voltage-gated sodium channels. The chemical structure of most LAs composed of a lipophilic aromatic group linked to a hydrophilic amine group by an intermediate ester or amide chain. LAs are classified according to this chain [1]. Besides pain management, documented data indicated the additional role of LAs as antimicrobial agents against a wide spectrum of microorganisms [2]. There are many studies reporting in vitro and in vivo antimicrobial effects of LAs. Among them, lidocaine is the most studied preparation and its antimicrobial properties are largely evaluated in vitro [3] and in vivo [4]. Reduction the incidence of endophthalmitis after intravitreal injection [5], prophylaxis for surgical wound infections [6], prevention the incidence of catheter-associated infections [7], oral biofilm reduction on buccal mucosa [8], and prevention against bacteria that produced nosocomial infection [9] are some examples of lidocaine antimicrobial usage. Studies showed that various LAs exhibited different degrees of the antimicrobial effect that may be due to several factors including different structures [10], concentrations [11], duration of exposure [12], type of microorganism tested [13], and different conditions of exposure such as temperature [14].

Although the underlying mechanisms of antimicrobial effects of LAs are not fully elucidated, according to documents, proposed mechanisms for the inhibitory effects of LAs on bacteria might be mediated via disruption of bacterial

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cell membrane, inhibition of cell wall synthesis, dysfunction of cellular respiration, alteration in DNA synthesis, lysis of protoplasts, alteration in permeability, and leakage of intracellular components, ultrastructural changes, and inhibition of membrane-bound enzymatic activities [8, 15–18]. Some studies indicated that LAs that combined with some antibiotics do not interfere with their antimicrobial activity [19]. Moreover, a combination of LAs with other agents such as preservatives [20], opioids [21], and epinephrine [22] may affect their antimicrobial activity through synergistic or antagonistic action.

Supplemental role of LAs as antimicrobial agents results in their application in a clinic for different purposes such as prophylaxis of surgical site infection [4]. In the microbial evaluation of tissue biopsies [20], ophthalmic culture swabs and bronchial fluid samples [23], physicians should be alerted that they could lead to false negative results or suboptimal culture yields.

In this review article, we summarized different in vitro and in vivo studies regarding antimicrobial effects of different LAs with focuses on the antimicrobial applications of most studied LAs, interaction with different agents which combine with LAs, and mechanisms of action and structural dependence of LAs antibacterial effects.

Materials and methods

Different databases such as PubMed, Scopus, and Web of Science with keywords of antimicrobial, antibacterial, antifungal, bactericidal, fungicidal, local anesthetic, lidocaine (lignocaine), bupivacaine, prilocaine, mepivacaine, ropivacaine, articaine, procaine, tetracaine (amethocaine), dibucaine (cinchocaine), and benzocaine have been included in this search without publication time limitation. The most relevant articles were selected for this review.

Antibacterial activity of different LAs

Lidocaine (Xylocaine®, lignocaine)

Lidocaine is a systemic antiarrhythmic agent, as well as an amide LA. Its onset of action is rapid and it has an intermediate duration of action. It is about 95% metabolized in the liver. It is usually used at a 2% concentration [24, 25]. It is a reference standard LA and used for local anesthesia through infiltration, nerve block, epidural, or spinal techniques [26]. There are many in vitro and in vivo studies investigating antibacterial activity of lidocaine. Among LAs, lidocaine is the most studied preparation and acted as a potent antibacterial agent (Fig. 1).

Lidocaine reduced the incidence of endophthalmitis after intravitreal injection

Endophthalmitis is the most severe problem after intravitreal injection. The incidence of this complication was reported ranging from 0.02 to 0.2% [27]. Causative organisms of endophthalmitis are *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Streptococcus viridians*. Lidocaine showed bactericidal effects against all these organisms. A reduction in colony-forming units (CFU) of 90%, 95%, and 92% for *S. aureus*, *S. epidermidis*, and *S. viridans*, respectively, has been observed after 10 min of exposure. Complete reduction in CFU for each organism obtained with increasing exposure time. Furthermore, zero cases of endophthalmitis of 6853 intravitreal injections performed with subconjunctival 2% lidocaine/0.1% methylparaben and eight cases of endophthalmitis of 8189 intravitreal injections performed with other methods of anesthesia have been observed. According to this study, subconjunctival 2% lidocaine/0.1% methylparaben for anesthesia decreased the incidence of endophthalmitis after intravitreal injection [5].

Lidocaine is used for prophylaxis of surgical and nosocomial wound infections

In vitro antibacterial effects of lidocaine (1–4%, clinical doses) on isolates of common bacterial pathogens which produced nosocomial wound infection including *Enterococcus faecalis*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *S. aureus* as well as a number of resistant strains of methicillin-resistant *S. aureus* and vancomycin-resistant *Enterococci* have been investigated. Results showed that a concentration-dependent inhibition of growth for all strains of bacteria has been observed. The most inhibitory effect of lidocaine was shown on *E. coli* and *P. aeruginosa* Gram-negative organisms. *S. aureus* was found to be least sensitive to lidocaine. The addition of epinephrine to lidocaine had no effect on the antimicrobial results obtained in this study [9].

Surgical wound infection is the most common postoperative problem which may prolong hospitalization, increase hospital costs, and cause morbidity [28]. *S. aureus* was reported to be an important pathogen in the etiology of surgical wound infection [4]. Lidocaine (2%) infusion induced a tenfold reduction in the number of colony-forming units of *S. aureus* (laboratory strain 259213) in surgically created wounds of BALB/c mice compared to the saline group, suggesting that lidocaine infusion may have a beneficial role in the prevention of surgical wound infections [6].

In another study, the effects of lidocaine (2%) with and without epinephrine on bacterial colonization in a wound infection model in a male Albino guinea pig have been evaluated. In this model, one of the two wounds of each animal was infiltrated with lidocaine and then inoculated with *S. aureus*

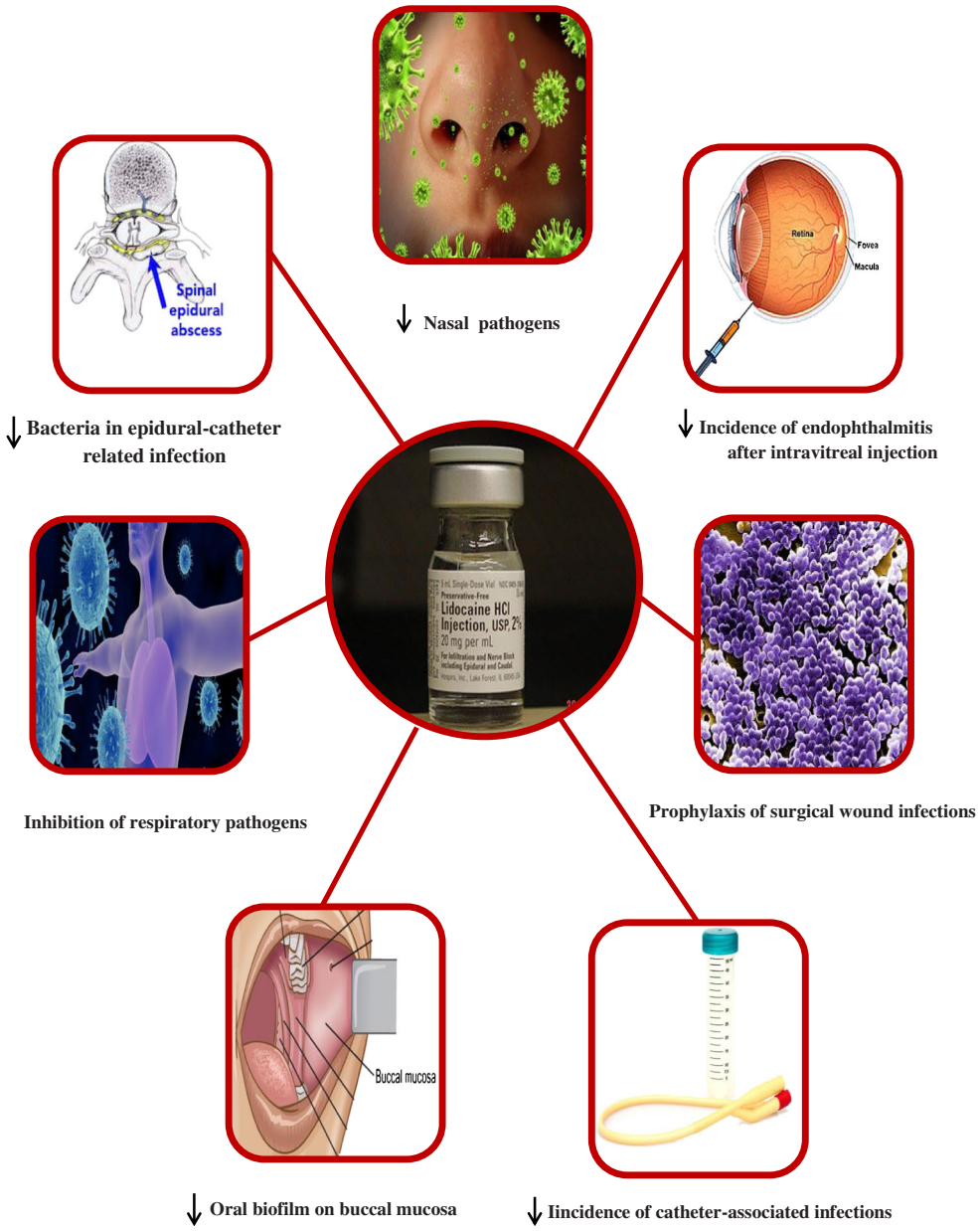

Fig. 1 The antimicrobial application of lidocaine

(laboratory strain 259213). The other wound was left untreated. Lidocaine alone caused a 70% decrease in the colony counts compared to the control group. The addition of epinephrine (1:100000) to lidocaine resulted in the greatly increased numbers of colony counts (20-fold) compared to the control indicating that the hypoxia results from vasoconstriction elevated the risk of surgical site infection [4].

Lidocaine prevented the incidence of catheter-associated infections

Pretreatment of the catheter with antibacterial agents before fixation can prevent the incidence of infections induced by catheterization including urinary tract infections. Lidocaine was shown to be effective to reduce urinary tract infection induced by catheterization. In a study, lidocaine cream inhibited the growth of bacterial isolates from urine samples after a 10-min exposure in comparison with untreated samples [7].

Furthermore, a chlorhexidine-lidocaine jelly (Instillagel) decreased the number of urinary tract infections after instrumental procedures. This study conducted on 50 patients with urological diseases. Before and after the 10-min exposure to the jelly, urethral swabs were prepared. Results of this study indicated that prior to the application of the jelly, 46 of the 50 swabs resulted in pathogenic bacteria, while after the 10-min exposure, only 17 and 12 swabs contained pathogenic bacteria in the liquid and agar media [29].

Lidocaine reduced oral biofilm on buccal mucosa

The low incidence of local infections and injection abscesses in dentistry may be explained by using LA because of its antimicrobial effect. As, topical LA have shown antimicrobial effects [30, 31] and exhibited an important role in the prophylaxis of infection [7], most dentists use the topical LA to avoid the pain from needle injection.

An in vitro study showed that 10% lidocaine topical anesthetic spray exhibited the bactericidal activity against *E. coli*, *Streptococcus sanguinis*, and *Streptococcus salivarius* within 1 min but showed no effect against *S. aureus*, *Enterococcus faecalis*, and *Streptococcus pyogenes*. The antimicrobial effect was increased by increasing the exposure time from 1 to 3 min. In a clinical study, lidocaine spray application on buccal mucosa for 3 min caused 60–95% biofilm reduction. According to this study, due to the species, concentration, and exposure time, the effectiveness of lidocaine is different in each person [8].

In another study, antimicrobial effects of topical anesthetic liquid containing lidocaine (5%) against microorganisms commonly found in the oral cavity including *Streptococcus mutans, S. sanguinis, Streptococcus mitis, S. salivarius, Actinomyces viscosus*, and *Candida albicans* have been evaluated. Lidocaine liquid topical anesthetic caused 73–100% decrease in the microbial populations after a 1-min or 2-h exposure compared to controls without anesthetic [32]. As in dentistry, the usage of topical anesthetics just before the injection of LAs is common [33], therefore, the antimicrobial properties of topical anesthetics lead to a very low incidence of post-injection infections. Moreover, inhibitory effects of lidocaine solution (2%) with or without 1:100,000 epinephrine, used as a LA in dentistry, has been shown on the growth of different microorganisms including *P. aeruginosa*, *E. coli*, *Klebsiella pneumoniae*, *Neisseria*, *S. pyogenes*, *S. viridans*, *Streptococcus pneumoniae*, *Corynebacterium*, *S. aureus*, and *Proteus mirabilis*. Both solutions exhibited significant bactericidal activity compared to controls. The bactericidal activity of 2% xylocaine with epinephrine was significantly less than that of without epinephrine [34].

Lidocaine showed bactericidal activity against nasal pathogens

The antimicrobial activity of 4% lidocaine with phenylephrine on nasal pathogens including *Branhamella catarrhalis*, *Enterobacter sp.*, *Haemophilus influenzae*, *K. pneumoniae*, *P. aeruginosa*, *S. aureus*, and *S. pneumoniae* have been investigated. This topical anesthetic showed a weak bactericidal activity that can sometimes lead to false-negative results [35].

Lidocaine showed inhibitory effects on respiratory pathogens

The bactericidal effect of lidocaine 2% against *S. pneumoniae*, *Moraxella catarrhalis*, and *H. influenzae* has been shown without any inhibition of growth on *P. aeruginosa* and *C. albicans*. *S. pneumonia* was partially inhibited by lidocaine 1%. Lidocaine was commonly used prior to bronchoscopy and bronchoalveolar lavage (BAL) procedures. Due to the inhibitory effects of this agent on the growth of respiratory tract flora, especially *S. pneumonia* even at a concentration of 1%, this study suggested using of the lowest concentration possible of LA for bronchoscopy and BAL in order to get the most recovery of pathogens on culture media [23].

In another study, the effect of lidocaine, as well as lidocaine with methylparaben on BAL microorganisms, was evaluated and quantitative cultures were performed on aspirates at different time intervals. Reduction in the number of organisms isolated has been observed after 120 min by lidocaine solution (1%). The inhibitory effect of lidocaine plus methylparaben was more than lidocaine. According to this study, most pathogens of the lower respiratory tract in bronchoscopic aspirates except *Bacteroides melaninogenicus* were recovered at each sampling interval [36].

Effect of lidocaine on common pathogens isolated from spinal and epidural abscesses

Infections after epidural and spinal analgesia that are not common might be due to the antibacterial effect of LAs such as lidocaine [37].

The antibacterial effect of lidocaine 1 % and alkalinized lidocaine on three microorganisms (*S. aureus*, *E. coli*, and *P. aeruginosa*) which are isolated from spinal and epidural abscesses has been evaluated. Results indicated that lidocaine remarkably inhibited the growth of *S. aureus*, *E. coli*, and *P. aeruginosa* at baseline and 3 and 6 h after incubation, whereas, alkalinized lidocaine significantly inhibited the growth of *S. aureus* at baseline and 3 and 6 h and inhibited the growth of *E. coli* and *P. aeruginosa* only at 6 h. The inhibitory effect of lidocaine on the growth of *E. coli* was more than alkalinized lidocaine at 0 and 3 h. Therefore, alkalinization did not change the antibacterial effect of lidocaine 1% on *S. aureus*.

Alkalinized lidocaine significantly inhibited the growth of *E. coli* and *P. aeruginosa* only at 6 h [38]. In another investigation, the ability of different concentrations of lidocaine (1%, 1.5%, and 2%) to inhibit the growth of bacteria which involved in epidural-catheter-related infection has been determined. Lidocaine significantly inhibited bacterial growth at all concentrations. This growth inhibition reduced with decreasing the concentration of LA. Because the growth of common pathogens, especially *S. aureus*, is not inhibited at a low concentration of tested lidocaine, this LA may not prevent

epidural-catheter-related infection due to common pathogens [39].

Lidocaine 2.5% and prilocaine 2.5% (EMLA) ®

Prilocaine is an amide LA. It has a rapid onset similar to lidocaine with longer duration [40]. EMLA is a topical analgesic which is used for skin anesthesia before needle insertion and other invasive procedures [41]. Both in vitro and in vivo studies confirmed the antibacterial effect of the EMLA cream. It has bactericidal effect against *E. coli*, *P. aeruginosa*, *Micrococcus* spp., *S. aureus*, and methicillin-resistant *S. aureus* [42]. In another in vitro study, lidocaine plus prilocaine exhibited a rapid and potent antibacterial effect against common wound pathogenic bacteria including *S. aureus* (including methicillin-resistant *S. aureus*), *E. coli*, *P. aeruginosa*, and *S. pyogenes* [43]. Moreover, in vivo study indicated that lidocaine plus prilocaine cream (with no preservative) can reduce the number of bacteria on intact human skin. Lidocaine plus prilocaine cream showed longer bacteriostatic activity after an initial bactericidal effect compared to alcohol-based disinfectant [44].

Bupivacaine

Bupivacaine is an amide anesthetic. It has a slow onset and prolonged duration of action. It is usually used at a 0.5% concentration [24, 25]. It is applied for epidural infusions used for control of postoperative pain and labor analgesia [26]. Some studies related to the antimicrobial activity of bupivacaine are listed below.

The antimicrobial activity of bupivacaine (without any preservative) against coagulase-negative *Staphylococcus*, coagulase positive *Staphylococcus*, *E. coli, Klebsiella enterobacter*, and *Proteus* species has been evaluated. The most sensitive microorganisms were coagulase-positive *Staphylococcus* followed by coagulase-negative *Staphylococcus*, *K. enterobacter*, *E. coli*, and *Proteus* species [45].

Bupivacaine may be used for prophylaxis of catheter-associated infections

Bupivacaine at concentrations used in epidural anesthesia inhibited the growth of different microorganisms commonly colonizing the skin including *E. coli*, *S. aureus*, methicillin-resistant *S. aureus*, *S. epidermidis* (both sensitive and resistance), *S. pyogenes*, *E. faecalis* (formerly *Streptococcus faecalis*), and *S. pneumonia* suggesting that bupivacaine is able to reduce the occurrence of infection following repeated epidural injection via catheter. In this study, the antibacterial effect of bupivacaine compared to pethidine, another epidural drug. All the abovementioned pathogens except *S. aureus* and *E. faecalis* were inhibited by pethidine [46]. In another study, bupivacaine (0.25%) inhibited the growth of the sensitive *S. epidermidis* strain, *S. pneumoniae*, and *S. pyogenes,* while the growth of *E. coli*, *S. aureus*, resistant *S. epidermidis* strain, *E. faecalis*, *Bacillus cereus*, and *C. albicans* was inhibited by bupivacaine (0.5%). Only *P. aeruginosa* was not inhibited by bupivacaine. Morphine 0.2 and 2 mg/ml was not able to inhibit any of these pathogens [13]. *S. aureus* is responsible for about 60% of infections in catheter-related epidural abscesses. According to the study, 0.375% bupivacaine was able to inhibit three strains of *S. aureus* [11].

Bactericidal activity of bupivacaine on microorganisms in the human skin flora

The antibacterial effect of bupivacaine with and without preservative has been examined against two strains of MRSA, two strains of methicillin-susceptible *S. aureus* (MSSA), *S. epidermidis,* and *E. coli*. These pathogens were exposed to different concentrations of bupivacaine (0.125–0.75%) for 1–24 h at room and body temperatures. Increasing the concentration of bupivacaine decreased colony counts. The growth inhibition of the *S. aureus* by 0.5% bupivacaine was increased from 81.1 to 96% at 24 h without preservative and from 89.6 to 99.8% at 12 h with preservative. Moreover, by increasing temperature, the growth inhibition of *S. aureus* was increased from 21.7 to 34.1% without preservative and 24.2 to 74.1% with preservative at 1 h. The growth of *E. coli* was inhibited at 12 h. No *E. coli* and *S. epidermidis* growth was observed after 24 h at body temperature. Therefore, *E. coli* and *S. epidermidis* were more sensitive than *S. aureus* to the bactericidal activity of bupivacaine with and without preservative. Combination of preservatives (methyl para-oxybenzoate and propyl para-aminobenzoate) with bupivacaine showed more bactericidal activity than preservatives alone [12, 47].

Ropivacaine

Ropivacaine is another amide LA with a relatively slow onset of action and prolonged duration of action. It was introduced to the clinic as a replacement for bupivacaine (24). It is used for epidural infusions to control postoperative and labor pains [26]. It has been reported that although ropivacaine (2 mg/ml) supported the growth of *E. coli*, its higher concentration (10 mg/ml) inhibited the growth of both *E. coli* and *S. aureus* [48].

Comparative studies related to the antimicrobial effects of different LAs

The antibacterial and antifungal effects of different LAs were compared in some studies. For example, according to a study, the antimicrobial effect of bupivacaine was more than ropivacaine and less than lidocaine and prilocaine against

E. coli, *S. aureus*, *P. aeruginosa*, and *C. albicans*. Ropivacaine did not inhibit the growth of these pathogens. Bupivacaine inhibited the growth of *P. aeruginosa* at 0.5 and 0.25% solutions. Prilocaine 2%, as well as lidocaine 5 and 2%, inhibited the growth of all microorganisms tested. The growth of *E. coli*, *S. aureus*, and *P. aeruginosa* was inhibited by prilocaine 1%, while, the growth of only *P. aeruginosa* was inhibited by lidocaine 1% [49]. The more antimicrobial activity of bupivacaine than ropivacaine has been shown in another study. At a clinically used concentration, bupivacaine showed stronger inhibitory effects on the growth of different microorganism tested such as *E. coli, P. aeruginosa, S. epidermidis, S. pyogenes*, and three strains of *S. aureus* compared to ropivacaine. No differences observed between the effects of these anesthetics on *K. pneumoniae.* The antibacterial activity of bupivacaine improved with increasing concentration [11]. In addition, the antibacterial effect of the bupivacaine isomers and levobupivacaine against *S. epidermidis*, *S. aureus*, and *E. faecalis* were compared. The minimum bactericidal concentration (MBC) of racemic bupivacaine and levobupivacaine was 0.25 and 0.5%, respectively. Therefore, racemic bupivacaine showed stronger antibacterial activity than levobupivacaine [50]. An in vitro study showed the inhibitory effects of four LAs (tetracaine, procaine, dibucaine, and lidocaine) on cell growth of standard strains of *E. coli, Bacillus megaterium, P. aeruginosa,* and *K. aerogenes*, with significant effect of tetracaine and dibucaine on cell viability and on the leakage of cellular constituents (10). In another study, the antimicrobial activity of lidocaine was compared to that of benzocaine (an ester LA) against microorganisms commonly found within the oral cavity for either 1 min or 2 h. Lidocaine 5% decreased the growth of the oral cavity microorganisms more than benzocaine in 1-min exposures to *S. mutans*, *A. viscosus,* and *S. salivarius* and with a 2-h exposure to *S. salivarius*. Lidocaine 5% was bactericidal or fungicidal to all microorganisms for both duration times, while benzocaine was bacteriostatic or fungistatic after 1-min exposures and bactericidal or fungicidal after 2 h [32]. The antimicrobial activity of some LAs and their active anesthetic components including Ultracaine D-S (articaine hydrochloride, an amide LA), Carbostesin (bupivacaine hydrochloride), Scandicaine (mepivacaine hydrochloride, an amide LA), Xylonest (prilocaine hydrochloride), xylocaine (lidocaine hydrochloride), hostacaine (butanilicaine phosphate, an amide LA), and novocaine (procaine hydrochloride, an ester LA) were compared against different pathogens of the oral, skin and intestinal flora. According to MIC and MBC values, Ultracaine D-S preparation showed the most antimicrobial activity. As the MIC values of Ultracaine D-S and its active substance, articaine hydrochloride, were the same, so, the antimicrobial activity is mainly related to the anesthetic component. Novocaine showed the lowest antimicrobial activity [51]. In another study, articaine 2% showed a bacteriostatic effect against *P. aeruginosa*, *S. aureus*, *E. coli*, *P. mirabilis,* and *Serratia marcescens*. Two of these five pathogens including *P. aeruginosa* and *S. aureus* were resistant to lidocaine 2% [16].

Antifungal activity of different LAs

Lidocaine

The antifungal activity of lidocaine against 20 *Candida* strains including *C. albicans* has been evaluated. This antifungal effect was concentration dependent. By increasing the concentration of lidocaine, fungistatic effect progressed to fungicidal property. The mechanisms of antifungal effects were metabolic impairment and damaging the cytoplasmic membrane for fungistatic and fungicidal, respectively [52]. In addition, lidocaine inhibited *C. albicans* germ tube formation due to calcium channel blockade [53]. Besides *Candida* spp., lidocaine was found to show antifungal activity against *Aspergillus* spp. Sub-inhibitory concentrations of the lidocaine inhibited the germination of *Aspergillus fumigatus*, *Aspergillus flavus,* and *Aspergillus niger*. Fungicidal activity against resting conidia due to cell membrane lesions was shown at higher concentrations of the lidocaine. Calcium chloride reversed the lidocaine inhibitory effect [54].

Other LAs

The inhibitory effects of bupivacaine (0.5%) on the growth of *C. albicans* [13], prilocaine (1–2%) [49], and benzocaine [32] have been shown in different studies.

Sporicidal activity of different LAs

The sporicidal effect of five LAs solution (1%) including tetracaine, procaine, and amylocaine (as ester LA), dibucaine, and lidocaine (as amide LA), as well as different preservatives (cetrimide, chlorocresol, chlorhexidine, phenoxyethanol, and phenylmercuric nitrate) alone or in combinations was evaluated against *Bacillus subtilis* and *A. niger* spores at different temperatures. Results indicated that the sporicidal activity was temperature dependent. The recorded temperatures for sporicidal (99% death) effects of different agents against *A. niger* in increasing order were the following: 30 °C for tetracaine, 43 °C for dibucaine, 45 °C for amylocaine, 48 °C for lidocaine, and 50 °C for procaine compared to 58 °C for saline control. The recorded temperatures for sporicidal effects of different agents against *B. subtilis* were higher than those of *A. niger*. Increasing order of temperatures was the following: 60 °C for dibucaine, 84 °C for amylocaine, 90 °C for tetracaine, and 100 °C for procaine, lidocaine, and saline control. Therefore, *A. niger* spores were more sensitive than *B. subtilis* spores to sporicidal effect of the LAs. Among the

preservatives tested, the combination of chlorocresol and LA showed the highest sporicidal effect [55].

Interaction of LAs with different agents

The addition of different agents to LAs and the type of interaction were evaluated. Some important agents that combined with LAs include antibiotics, preservatives, opioids, propofol, and epinephrine.

Antibiotics

The antibacterial activity of minocycline hydrochloride alone or in combination with the lidocaine (2%) and prilocaine (2%), or the antiseptic chlorhexidine has been evaluated. Results showed that lidocaine/prilocaine does not interfere with minocycline HCl bacteriostatic effect. The additive antibacterial activity has been shown in a combination of lidocaine/prilocaine or chlorhexidine with minocycline HCl [19]. In another study, the reduction of antibacterial activity of some antibiotics including oxacillin, methicillin, cefalotin, cephaloridine, vancomycin, carbenicillin, and gentamycin against *S. aureus* or *P. aeruginosa* has not been observed when incubated with lidocaine hydrochloride [56].

Additionally, subinhibitory concentrations of the lidocaine and bupivacaine resulted in synergistic effect with the antifungal activity of amphotericin B, itraconazole, and caspofungin. This was due to the germination blockage of different *Aspergillus* spp., which is the invasive form of microorganism. However, at higher concentrations, because of impairment of the membrane, lidocaine exhibited antifungal activity. It is worth to mention that lidocaine and bupivacaine had an antagonistic effect when associated with voriconazole [54].

Preservatives

Studies showed that the presence of methylparaben with LAs agents resulted in greater antimicrobial activity. For example, results of the study on the antibacterial activity of lidocaine as well as lidocaine with methylparaben on bacteria isolated from dermal lesions indicated that greater antibacterial activity in the presence of methylparaben has been observed [20]. Moreover, in another study, the inhibitory effect of lidocaine plus methylparaben was more than lidocaine alone on BAL microorganisms [36]. In addition, the combination of preservatives (methyl para-oxybenzoate and propyl para-aminobenzoate) with bupivacaine showed more bactericidal activity against the human skin flora than preservatives alone [47].

Opioids

The interaction of some opioids including morphine, meperidine, fentanyl, and tramadol with antimicrobial activities of the ropivacaine and bupivacaine against *E. coli*, *P. aeruginosa*, *S. aureus*, *S. epidermidis*, *K. pneumonia, Proteus* spp., and *Enterococcus* spp. were assessed. In the absence of ropivacaine and bupivacaine, no antibacterial effect has been shown with the adjuvant agents. However, the combination of bupivacaine and fentanyl, as well as ropivacaine and meperidine, exhibited antibacterial activity against one of the *E. coli* strains. These opioids do not have a synergistic effect on the antimicrobial effects of ropivacaine and bupivacaine [21].

The effect of lidocaine and bupivacaine with fentanyl or sufentanil to inhibit the growth of bacteria which involved in epidural-catheter-related infection at clinical concentrations was investigated. No inhibition of bacterial growth was observed as a result of the addition of fentanyl or sufentanil [39]. Moreover, the combination of ropivacaine and sufentanil significantly inhibited the growth of *P. aeruginosa* and slowed the multiplication of *S. aureus* at room temperature [57].

In another study, the inhibitory effects on the growth of *E. coli* and *S. aureus* have been demonstrated by using bupivacaine and ropivacaine alone or in combination with sufentanil. Both bupivacaine and ropivacaine alone inhibited the growth of *E. coli* and *S. aureus*. These LAs do not affect the growth of *E. faecalis. E. faecalis* was partially sensitive to the combination of bupivacaine + sufentanil. Combination of sufentanil and bupivacaine showed a partial synergistic effect on bupivacaine antibacterial activity, while a partial antagonistic effect has been observed as a result of ropivacaine and sufentanil combination [58]. Combination of LA with opioids may prolong the duration of storage at room temperature. For example, a solution of levobupivacaine plus sufentanil may be used for 24 h at room temperature during local anesthesia without bacterial growth [59].

Propofol

Propofol is a drug which is commonly used in operative anesthesia. Extrinsic contamination of propofol is considered to be a source of postoperative sepsis and wound infection [60]. One method for preventing propofol-induced pain is to add lidocaine either before the propofol injection or mixing with propofol [61]. There are several studies investigating the antimicrobial activity of lidocaine in the presence of propofol. Most of these studies reported that the addition of lidocaine hydrochloride to propofol solutions may inhibit bacterial growth. For example, in a study, the antibacterial effect of different concentrations of lidocaine (0.005–2%) that is mixed with propofol against microorganisms that produced sepsis because of extrinsically contaminated propofol has been

evaluated. By increasing concentrations of lidocaine, bacterial colony counts were reduced and through inhibition, the growth of bacteria, lidocaine, at the doses used to prevent pain on injection, was able to reduce propofol bacterial contamination [60].

In another study, propofol increased the colony count of *E. coli* compared to that of the control, while the colony counts of *E. coli* were lower after exposure to lidocaine (1–4%) and lidocaine (0.25–4%) plus 1.0% propofol compared to that of propofol. Moreover, propofol decreased the growth rate of microorganism compared to lidocaine alone or lidocaine-propofol mixtures. Addition of lidocaine to propofol may reduce the consequences of an infection due to the extrinsic contamination of propofol [62]. In contrast to the abovementioned studies, in another study, the addition of 0.2 and 0.5% lidocaine to propofol could not prevent the growth of the *S. aureus*, *E. coli, P. aeruginosa,* and *C. albicans* which may be due to lower lidocaine concentrations used in this study [63]. According to another study which assessed the growth inhibition of *S. aureus* by propofol/lidocaine admixture, the mean colony count of *S. aureus* in lidocaine plus propofol solution was significantly less than that of propofol alone. The mechanism may be due to the activation of lidocaine by a higher pH as a result of the combination of lidocaine and propofol [64].

Epinephrine

Epinephrine is commonly used in combination with LA to reduce the rate of vascular absorption of the LAs [65]. In a study, the antimicrobial effects of lidocaine (0.5 and 1%), epinephrine (1:200000), and lidocaine 1% plus epinephrine (1:200000) on different dermatologically important bacterial and fungal pathogens such as *S. aureus*, *P. aeruginosa*, *E coli.*, *Sporothrix schenckii*, *A. fumigates*, *C. albicans,* and *Trichophyton mentagrophytes* were evaluated. The growth of three pathogens including *S. aureus*, *E. coli,* and *T. mentagrophytes* were inhibited by lidocaine 0.5%, whereas, lidocaine 1% inhibited the growth of all pathogens except *A. fumigatus* ($p < 0.05$). Epinephrine alone inhibited the growth of *C. albicans* and *S. schenckii*. Combination of lidocaine and epinephrine resulted in a cidal activity more than that of lidocaine alone that may be due to the hydroxybenzoate, a preservative which often presented in the solution of lidocaine plus epinephrine [22]. In another study, lidocaine (2%) with or without 1:100,000 epinephrine exhibited significant bactericidal activity against *P. aeruginosa*, *E. coli*, *K. pneumoniae*, *Neisseria*, *S. pyogenes*, *S. viridans*, *S. pneumoniae*, *Corynebacterium*, *S. aureus,* and *P. mirabilis*. So that bactericidal activity of xylocaine with epinephrine was significantly less than that of without epinephrine [34]. The addition of epinephrine to lidocaine resulted in greatly increased numbers of colony counts of *S. aureus* compared to control in a wound infection model in guinea pig [4].

Sodium bicarbonate

The addition of sodium bicarbonate to LAs resulted in the improvement of the quality of anesthesia due to the increase in their nonionized form as a result of pH elevation. Alkalinization of LAs causes the onset of anesthesia at a lower serum concentration and prolongs the duration of anesthesia. Furthermore, the addition of sodium bicarbonate to LA reduces the pain associated with the injection [66]. In some studies, the effect of the addition of sodium bicarbonate on the antibacterial activity of LAs has been evaluated. According to a study, alkalinized lidocaine similar to the lidocaine 1% inhibited the growth of *S. aureus* at all study periods (baseline, 3 and 6 h after incubation). Although lidocaine significantly inhibited the growth of *S. aureus*, *E. coli,* and *P. aeruginosa* at all study periods, alkalinized lidocaine significantly inhibited the growth of *E. coli* and *P. aeruginosa* only 6 h after incubation [38].

Another study indicated that 1% lidocaine, as well as alkalinized lidocaine, displayed no antibacterial activity against *S. epidermidis*, *S. aureus,* or *E. coli*. Bupivacaine (0.25%) showed significant antibacterial activity, while the addition of bicarbonate did not change its antibacterial effect [67].

Additionally, bupivacaine (0.5%) was found to inhibit the growth of *S. aureus* and *E. coli* at all study periods (baseline, 3 and 6 h after incubation), but this LA inhibited the growth of *P. aeruginosa* only at 6 h. Alkalinized bupivacaine inhibited the growth of *S. aureus* at 0 h and *E. coli* at 0 and 6 h. Antibacterial effects of bupivacaine against *E. coli* was remarkably more than alkalinized bupivacaine at 6 h. Ropivacaine (0.2%) inhibited the growth of *S. aureus* at 0 and 3 h more than alkalinized form. Both ropivacaine and alkalinized ropivacaine inhibited the growth of *E. coli* at 3 and 6 h. Ropivacaine inhibited the growth of *E. coli* at 0 h. Ropivacaine and its alkalinized form inhibited the growth of *P. aeruginosa* at 3 h. This study suggested that alkalinization of bupivacaine does not change its antibacterial activity, while alkalinization of ropivacaine reduced its antibacterial effect. Moreover, the antibacterial activity of ropivacaine was less than bupivacaine [68]. Also, another study showed that sodium bicarbonate increases the bactericidal activity of lidocaine [69].

Structure activity relationship of LAs antibacterial effects

The antibacterial effect of hydrophobic LA is affected by the length of the alkyl chain. Thus, ropivacaine with shorter alkyl chain than bupivacaine exhibited less antibacterial activity. Moreover, among different LAs, dibucaine showed the most antibacterial activity followed by tetracaine, bupivacaine,

Table 1 Inhibitory effect of local anesthetics on different bacteria

Gram positive bacteria									
	Staphylococcus aureus	*Staphylococcus epidermidis*	*Streptococcus pyogenes*	*Streptococcus pneumoniae*	*Streptococcus mutans*	*Enterococcus faecalis*	*Streptococcus salivarius*	*Actinomyces viscosus*	Other
Lidocaine	+	+	+	+	+	+	+	+	*Streptococcus viridians, Streptococcus sanguinis, Streptococcus mitis Corynebacterium,* MRSA
Bupivacaine	+	+	+	+		+			MRSA MSSA
Ropivacaine	+								
Prilocaine	+								
Tetracaine									*Bacillus megaterium*
Dibucaine									*Bacillus megaterium*
Benzocaine					+		+	+	
Articaine	+								
Gram negative bacteria									
	Escherichia coli	*Pseudomonas aeruginosa*	*Proteus mirabilis*	*Klebsiella pneumonia*	*Haemophilus influenza*	*Serratia marcescens*	*Neisseria*		Other
Lidocaine	+	+	+	+	+	+	+		*Bacteroides melaninogenicus, Branhamella catarrhalis*
Bupivacaine	+		+						*Klebsiella enterobacter, Bacillus cereus*
Ropivacaine	+			+					
Prilocaine	+	+							
Tetracaine	+	+							*Klebsiella aerogenes*
Dibucaine	+	+							*Klebsiella aerogenes*
Benzocaine									
Articaine	+	+	+			+			

MRSA, methicillin-resistant *S. aureus*; *MSSA*, methicillin-susceptible *S. aureus*

prilocaine, lidocaine, and procaine [11]. In another study, among four LAs including tetracaine, procaine, dibucaine, and lidocaine, dibucaine and tetracaine showed bactericidal activity and induced leakage of intracellular materials. The order of bactericidal effect was dibucaine>tetracaine>lidocaine>procaine. The stronger antibacterial activity of tetracaine than procaine may be due to the presence of the NH-C_4H_9 substituent on the benzene ring in tetracaine instead of NH_2 in procaine. Presence of this large alkyl chain not only increased the lipophilicity of the tetracaine but also acted as an electron-donating group fulfilling both hydrophilic and lipophilic attachment requirements. Similar discussion may be suggested for lidocaine and dibucaine [10].

Mechanisms of antimicrobial action

In a study by the author, the growth inhibition of four LAs against *E. coli* with the concentrations below their MICs (tetracaine 0.9, dibucaine 0.8, procaine 28.3, and lidocaine 18.6 mg/ml) was reported to be partially due to the inhibition of respiration and reduction of a dehydrogenase activity [17]. While the bactericidal effect of tetracaine and dibucaine against *E. coli* was due to changes in membrane integrity and release of intracellular components (K^+, pentose, inorganic phosphate, and 260 nm materials). This effect was not observed by the lidocaine and procaine. This differences in the effectiveness were interpreted on the basis of their structure. The first two are more lipophilic than the others [17]. According to another study, lidocaine and procaine reduce the viability of *E. coli* cells through the inhibition of protein synthesis and alteration of DNA and protein production respectively. RNA synthesis may be inhibited at a higher concentration of procaine [18]. Moreover, lidocaine is considered to inhibit bacterial growth via its effects on the cell wall or cytoplasmic membrane. Through depolarization of the cytoplasmic membrane, lidocaine disrupts bacterial membrane potential [70]. In addition, tetracaine can damage the cell membrane of *P. aeruginosa* through different mechanisms including lysis, increased cell wall permeability, leakage of intracellular components, and reduction of dehydrogenase activity [71].

More information about the mechanism of action of compounds is prepared by the effect on growing and non-growing bacterial culture. If the LA does not effect on non-growing culture, it means it may not effect on biosynthetic processes involved in bacterial growth. A study report indicates that procaine and lidocaine at all concentration range of study had no effect on non-growing culture of *E. coli*. Tetracaine and dibucaine showed a curve with three distinct regions. Their low concentration (up to 5 mg/ml tetracaine and 2.5 mg/ml dibucaine, both sub-inhibitory concentration) had no effect on turbidity of culture. In the second part of the curve, a small change in the concentration induced significant changes in turbidity. This part of curve was followed by nearly a plateau part (for several hours) at higher concentrations of LAs (> 20 mg/ml tetracaine, > 10 mg/ml dibucaine) [72]. Such changes in bacterial cell suspension because of some other antimicrobial agents have been proposed to be due to changes in the refractive index of the bacterial cells following adsorption [73] and cell wall effect [74]. However, cell surface integrity is not necessarily to occur [72].

Taken together, according to documents, proposed mechanisms for inhibitory effects of LAs on bacteria might be mediated via disruption of bacterial cell membrane, dysfunction of cellular respiration, alteration in DNA synthesis, lysis of protoplasts, alteration in permeability and leakage of intracellular components, ultrastructural changes, and inhibition of membrane-bound enzymatic activities.

Conclusion

Considering numerous studies, in addition to pain control, LAs can be used as antimicrobial agents against a wide range of microorganisms (Table 1). The antimicrobial effects of various LAs have been tested on different microorganisms. According to several studies, the most studied bacteria are *E. coli*, *P. aeruginosa,* and *S. aureus*. Moreover, among different LAs, lidocaine is the most studied preparation. Due to antibacterial activities, LAs can be applied in clinic for prophylaxis of surgical site infection. In the application of LAs prior to diagnostic procedures including tissue biopsies, ophthalmic culture swabs, and bronchial fluid samples, caution should be needed, otherwise, they could lead to false negative results or suboptimal culture yields. In some study, the antibacterial effect of various LAs was compared. The observed differences may be due to several factors including different structure, concentrations, duration of exposure, type of microorganism tested, and different conditions such as temperature. For example, procaine and lidocaine showed lower antibacterial activity than tetracaine and dibucaine which explicated on the presence of the –NH-C_4H_9 substitution on the benzene ring in tetracaine in comparison with $–NH_2$ in procaine. Similarly, one can explain the difference between dibucaine and lidocaine. Also, ropivacaine showed poor antibacterial activity when compared to bupivacaine or lidocaine that may be related to a different structure. The antibacterial effects of LAs such as lidocaine and bupivacaine were concentration and temperature dependent. Besides antibacterial effects, LAs showed fungicidal and sporicidal properties as well. *C. albicans* is the most studied fungi. The addition of different agents including antibiotics, preservatives, opioids, propofol, and epinephrine to LAs and the type of interaction were evaluated in some studies. These agents may affect LA antimicrobial activity through synergistic or antagonistic action.

Although limited studies are available regarding the mechanisms of action of LA antimicrobial activity, some mechanisms including the disruption of bacterial cell membrane, inhibition of cell wall synthesis, dysfunction of cellular respiration, alteration in DNA synthesis, lysis of protoplasts, alteration in permeability and leakage of intracellular components, ultrastructural changes, and inhibition of membrane-bound enzymatic activities may be involved.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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