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Lidocaine infusion, basics and clinical issues

Lidocaína endovenosa, fundamentos y usos clínicos

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Abstract

Optimum pain management, minimizing chronic complications and ensuring a good safety profile, is growing in importance day by day. Lidocaine infusion has an adequate safety profile and several desirable characteristics in the clinical setting. This review describes the characteristics of this drug, as well as its potential indications. Moreover, it describes the basic concepts around lidocaine use, mechanisms of action and clinical applications, as well as the use of infusions in acute pain and repercussions in chronic pain. A review of the literature in English and Spanish was conducted in several databases, with no publication date limit. Articles considered relevant, without including the grey literature, were selected independently. Lidocaine infusion is an option for acute postoperative pain control in major surgery and contributes to opioid sparing and reduced length of stay, with ample evidence in abdominal surgery, rendering it an option to recommend in various protocols. It has an acceptable safety profile in special populations and it is considered useful to diminish the incidence of persistent, chronic and neuropathic pain related to the surgical procedure.

Keywords

Lidocaine intravenous; Pain; Adults; Children; Pregnant women.

Resumen

El manejo óptimo del dolor, minimizando las complicaciones crónicas y cumpliendo con un buen perfil de seguridad, cada día resulta más importante. La lidocaína en infusión tiene un perfil de seguridad adecuado con diversas propiedades deseables en el ámbito clínico. En la presente revisión se describen las características de este medicamento, así como sus potenciales indicaciones. Este artículo describe los conceptos básicos de la lidocaína, sus mecanismos de acción y utilidades clínicas, así como su uso en infusión en el dolor agudo y su repercusión en el dolor crónico. Se realizó una revisión de la literatura en varias bases de datos, sin fecha límite de publicación, en inglés y español. Se realizó la selección independiente de los artículos considerados relevantes, sin incluir literatura gris. La lidocaína en infusión es una alternativa para el control del dolor agudo postoperatorio en la cirugía mayor y contribuye a la disminución del consumo de opioides y la estancia hospitalaria, con amplia evidencia en cirugía abdominal que permite recomendarla en diversos protocolos. Tiene un perfil de seguridad aceptable en poblaciones especiales y se considera útil para disminuir la incidencia de dolor postoperatorio persistente, crónico y neuropático ligado al procedimiento quirúrgico.

Palabras clave

Lidocaína endovenoso; Dolor; Adultos; Niños; Embarazadas.

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INTRODUCTION

Optimum pain management to avoid long-term complications is increasingly important, with a view not only to achieve symptom relief but also to ensure the lowest risk of adverse events and their occurrence. The use of intravenous drugs in continuous infusion has become ever more relevant, lidocaine being one of the drugs shown to have analgesic, anti-inflammatory and antihyperalgesic properties; other effects, such as immune regulation, are also under study. This review describes the rationale for its use in some clinical acute settings, as well as the expected impact on chronic pain.

A review of the literature was conducted in several databases, including PubMed/Medline and ScienceDirect. The keywords "lidocaine," "continuous infusion," "intravenous," "analgesia," "pregnant women," "heart disease," "children," "pain", "postoperative," "neuropathic," "opioids" and "surgery" were used in the search. No limitations in terms of date of publication were applied, and the search included articles in English and Spanish. Articles considered most relevant were selected independently and included meta-analyses, systematic literature reviews, non-systematic reviews, clinical trials, observational studies, series and case reports. The grey literature was not included in the review. The selected studies are discussed below and presented as supplementary content (Annex 1).

RATIONALE

Systemic and local mechanism of action

Lidocaine is a local anesthetic of the amide type, synthesized for the first time between 1943 and 1946 by Nils Löfgren and Bengt Lundquist. It acts by blocking voltage-dependent sodium channels (VDSC) in the internal portion of the neuronal cell membrane, interrupting nerve transmission (1).

When administered intravenously (IV), the drug loses selectivity for sodium channels and its properties are enhanced, with action on peripheral receptors and central pain transmission, and the effects described below (2).

Analgesic

The effect is produced through diffusion of the drug from the bloodstream to the tissues, where nerve conduction of C fibers at the site of the lesion is interrupted. In the spinal cord, it dampens signaling, explaining its anti-hyperalgesic and anti-nociceptive effect, although the mechanism is not yet entirely clear (3).

Central sensitization occurs as a result of repeated painful stimulation through glycinergic pathways, increasing acetylcholine concentration in the cerebrospinal fluid (CSF). This results in an interaction with muscarinic and nicotinic receptors, with increased release of endogenous opioids (4). The lidocaine doses required to block glycine re-uptake in the spinal cord are known to be very high; however, the monoethylglycinexylidide (MEGX), glycinexylidide and N-ethylglycine metabolites produce this effect at lower than therapeutic doses (5).

In the spinal cord, lidocaine acts by reducing postsynaptic potentials of the N-methyl-D-aspartate (NMDA) and neurokinin receptors; additionally, it also inhibits protein kynase C and reduces hyperalgesia and opioid tolerance during the postoperative period (6). It appears to stimulate the serotoninergic pathways involved in acute and chronic pain control, given the observed reduction in the spinal sensory block effect when administered together with ondansetron (serotonin receptor inhibitor). However, no conclusive data have been found to date regarding this effect (7).

Anti-inflammatory

Starting at a dose of 1.5 mg/kg IV, lidocaine interferes with the initial steps of the systemic inflammatory response by modulating polymorphonuclear margination, adherence and diapedesis towards the site of the lesion. It also inhibits the production of reactive oxygen species as well as histamine release by blocking non-selective G-protein bound receptors, as supported by the fact that these cells do not possess VDSCs (3,6). Moreover, it has been found that tumor necrosis factor α (TNF-α) and interleukin 1, 6 and 8 levels are lower in these patients, demonstrating a clear dampening of the inflammatory cascade (6).

The anti-inflammatory effect of lidocaine is not a new observation. In fact, already in 1992, Eriksson et al. found significantly lower leukocyte counts in a wound following the local application of lidocaine. The same potential effect with the intravenous infusion has been under study since that time (8).

Antiarrhythmic

Plasma concentrations ranging between 1.5 and 6 µg/mL are required to produce this effect (Group IB), while doses greater than 8 µg/mL and 21 µg/mL, respectively, have been associated with neurological and cardiotoxic effects (2,3).

Other systemic effects

Lidocaine exerts antagonistic effects on M1 muscarinic receptors because of its action on acetylcholine and histamine-mediated bronchoconstriction, at doses between 0.5 and 1.5 mg/kg that suppress respiratory and cough reflexes, and attenuate laryngospasm, without significantly depressing respiratory drive (3).

The reduced incidence of ileus may be explained by various mechanisms, including pain reduction, which affects motility, as well as the lower need for opioids. Added to this are the anti-inflammatory effects, a drop in IL1, and attenuation of external reflexes on the enteric nervous system (3).

Thromboelastography studies suggest that there is delayed thrombus formation, while anti-aggregation properties have been attributed to the use of high-dose lidocaine. Likewise, some observational studies have described a reduction in gram-positive, gram-negative and fungal concentrations with the topical use of the drug during fiberoptic bronchoscopy. As far as viruses are concerned, the most significant impact has been observed for influenza and herpes type 1 concentrations (3,6).

Another finding from in vitro experiments is anti-tumor activity through stimulation of lectin-like receptors on natural killer (NK) leukocytes, which could be associated with slower metastasis progression. It has been considered to be beneficial in lessening delirium and perioperative cognitive dysfunction as it reduces the need for opioids and inhaled agents for analgesia maintenance (3,6).

CLINICAL APPLICATIONS

Perioperative management

Lidocaine use has been found to help with pain reduction in cases where propofol and other endothelial irritants are administered. A Cochrane meta-analysis documented this application which is independent from the dose and distal bloodstream occlusion (9). Associated benefits include dampening of the cough response during induction and attenuation of the catecholaminergic response to laryngoscopy; however, attributing an impact of lidocaine on hemodynamic outcomes is still controversial (3,10).

Recommendations for lidocaine use in continuous infusion have been increasing due to proven benefits that are applicable in several forms of surgery. A systematic review published in 2017 compared lidocaine versus placebo, according to the type of procedure. Results showed an impact on pain control, opioid sparing, early gastrointestinal function recovery and shorter length of stay, mainly in laparoscopic and open abdominal surgery (1,2). It also proposed a protocol for lidocaine administration intraoperatively, during the immediate recovery period, and over the first 48 hours postoperatively (10).

Because of the evidence in gastrointestinal surgery, it has been included as a recommendation in ERAS (Enhanced Recovery After Surgery) protocols since 2015, with clear guidance for use as part of multimodal pain management in order to reduce the use of opioids and their adverse effects (11-13).

The role of the modern anesthetist has migrated towards perioperative medicine, in an attempt at instituting measures to prevent outcomes associated with surgical stress, fasting and complications related to individual patient conditions, surgery and anesthesia. To that effect, regional techniques and analgesic drug infusions can be used, with multiple benefits (14).

These data are consistent with those derived from the meta-analysis by Vigneault et al. that included adult patients undergoing various emergent and non-emergent surgical procedures. The authors compared IV lidocaine versus placebo or the pre-established standard of care. Assessment included pain at 6, 24 and 48 hours at rest, during cough and ambulation, and rescue morphine requirement. The results described a significant benefit for pain control in the first 24 hours, plus significant opioid sparing, particularly in abdominal surgery (15).

Another meta-analysis included 45 studies with 1345 patients managed with lidocaine and 1407 controls, all of whom received general anesthesia for multiple surgery types. Controls could receive placebo or epidural analgesia. Results showed benefit in favor of IV lidocaine for pain control in the early (4 hours) and intermediate (24 hours) time period, postoperative ileus, time to the first flatus and return of bowel movements. Greater benefit in open and laparoscopic abdominal surgery was reaffirmed in terms of pain reduction, opioid requirements, and postoperative nausea and vomiting (16).

The most recent systematic review with meta-analysis is the study published by the Cochrane collaboration. It included 68 studies comparing IV lidocaine versus placebo or epidural analgesia in adult patients undergoing elective or urgent surgery in any part of the body, under general anesthesia. The results were significantly in favor of lidocaine for early and intermediate pain control (first 24 hours) in abdominal surgery, but no differences were found in extra-abdominal surgeries. Additional outcomes described were shorter length of stay in non-ambulatory surgery, reduced opioid use, shorter time to recovery of gastrointestinal function, less postoperative nausea and vomiting and improved patient-reported satisfaction (16).

Significant evidence in gastrointestinal surgery has opened the possibility of using lidocaine in other procedures. New research, including small clinical trials, has looked into its applicability in mastectomy, showing that the area of hyperalgesia as well as chronic postoperative pain improve with the use of the infusion compared to placebo (17,18).

There is also evidence in prostatectomy, with lower scores on the pain scales, opioid sparing and shorter length of stay in patients receiving intraoperative IV lidocaine bolus and infusion (10).

Opioid sparing

As acute postoperative pain is mostly described as very intense and up to 50% of patients arrive in pain at the postanesthetic care unit, opioid use has become the mainstay of management in that setting (6). The current trend of using multimodal analgesia focuses on reducing the use of these drugs, with the aim of optimizing early patient recovery outcomes (14).

Many patients have comorbidities or conditions that contraindicate the use of regional techniques or neuroaxial approaches, or limit the use of opioids. This is where the use of continuous lidocaine

infusion intraoperatively and during the first few hours is of greatest interest, in order to be able to reduce the need for opioids and halogenated agents and still achieve good analgesia with an acceptable safety profile (6).

As far as the ERAS protocols are concerned, the relevant clinical trial results show opioid sparing and pain control with bolus administration at the time of induction, at least 30 minutes before the start of the abdominal surgery, with comparable results to those obtained with epidural analgesia (12).

In the study by Ayala and Castromán (19), the use of morphine was implemented in patients undergoing open hysterectomy (n = 23). The authors reported lower opioid use in the group that received IV lidocaine in the form of an initial bolus of 1.5 mg/kg at the time of induction, followed by a continuous infusion of 1.5 mg/kg/h until the end of the procedure. Additional outcomes included lower pain scores on the numerical visual scale within the first 24 hours, and initiation of patient-controlled analgesia.

Calero et al. (20) described cutoff points for the opioid-sparing and analgesic effects of lidocaine, as well as toxicity values, as shown in Table 1. Based on this, they analyzed the use of lidocaine as part of balanced anesthesia. Results show a lower consumption of halogenated agents (sevoflurane) with no hemodynamic compromise; moreover, although the need for fentanyl rescue was lower, it was not significant. The regimen used was an initial bolus of 1.5 mg/kg followed by an infusion of 2 mg/kg/h during the entire procedure.

Opioid sparing has also been described in thoracic surgery, open prostatectomy and major spine surgery, with good profile safety, although regimen variability continues to exist, with doses ranging between 1 and 4 mg/kg/h (21).

Table 1. IV lidocaine concentrations and effects.

Plasma concentration	Clinical effect
5 to 6 µg/mL	Analgesia
7 to 8 µg/mL	Prodromic symptoms: vertigo, tinnitus, metallic taste
Greater than 10 µg/mL	Neurologic symptoms: seizures, coma
Greater than 21 µg/mL	Cardiovascular symptoms: conduction disorders, atrio-ventricular block, QRS prolongation, bradycardia, arrest

Source: Authors, from Calero, et al (20).

Considerations in special populations

The benefits of using lidocaine have also been explored in children, in pregnant women and in adult patients with known heart disease, because they may not always be candidates for regional techniques and opioid use in these populations may be associated with complications.

Although lidocaine toxicity is infrequent, it has been associated with severe complications such as cardiovascular derangements, which might impair stability; hence, the recommendation is to avoid its intravenous use in patients with decompensated heart disease, atrioventricular conduction alteration, known branch blocks or prolonged QTc. Likewise, in patients with heart failure and liver disease, where a reduction of up to 40% in drug clearance has been observed, dose and infusion time are a concern, although there is no absolute contraindication (2,3).

There is a paucity of evidence in the pregnant population. In a study of 100 patients undergoing cesarean section under general anesthesia, IV lidocaine was administered intraoperatively in boluses of 1.5 mg/kg, with beneficial results in pain reduction during the first 24 hours and no adverse effects for the mother and baby. However, further evidence is required in order to determine usefulness and safety in these patients (22).

In the pediatric population, a relevant factor to consider as part of pain management is the reduction of complications such as postoperative delirium (23). Due to the high risk of toxicity, strong evidence regarding lidocaine use in this population is not available given that only studies with small sample sizes have been conducted. In 2013, a study by El-Deeb et al. assessed cortisol levels, ileus and length of stay using a continuous infusion of IV lidocaine at 1.5 mg/kg/h initiated 15 minutes before induction, and maintained for 6 hours. Results showed lower opioid consumption, shorter hospital stay and less ileus, without reaching toxic levels (24).

Persistent postoperative pain

Persistence of pain directly related with the surgical intervention is a matter of concern. It may be acute or chronic and, therefore, the impact of any strategies used to prevent it is high. The minimum duration of pain is two months in up to 45% of patients (17,25).

Lidocaine has been used as part of multimodal management in breast cancer surgery due to the higher incidence of this type of pain. In a study with 36 patients comparing lidocaine versus placebo, Grigoras et al. (17) found a reduction in persistent pain and hyperalgesia.

Later, Kendall et al., (25) in a sample of 148 patients, compared lidocaine versus placebo and found a significantly lower pain level at 6 months in the group that received lidocaine; however, standardization against persistent pain criteria was inadequate.

Postoperative neuropathic pain

Work in animal models has allowed to explore pharmacological options for pain control. A study by Batista et al. (26) in which the sciatic nerve was intervened in rodent models found that the use of lidocaine before the event was effective at reducing postoperative neuropathic pain.

In the study by Khan et al., (27) multimodal analgesia with lidocaine and pregabalin was used in 100 patients undergoing oncologic breast surgery, and it was shown that lidocaine improved neuropathic pain and reduced its incidence at 6 months; in contrast, no additional benefit was found with the use of pregabalin.

CONCLUSIONS

Intravenous lidocaine is an alternative for acute postoperative pain control in major surgery, resulting in opioid sparing and shorter hospital length of stay; in particular, evidence in abdominal surgery is highlighted, with reduced nausea and vomiting, and earlier return of gastrointestinal function. It can also be considered an alternative to epidural analgesia, with non-inferior performance in terms of these outcomes. Likewise, it is an option to reduce the incidence of surgery-related persistent, chronic and neuropathic postoperative pain. Doses for infusion applications are proposed based on the recommendations published in the management guidelines, such as the ERAS protocol, and on the information derived from this review (Table 2).

Further strong studies supporting its use in special groups are required. It has a good safety profile in patients with stable heart disease and pediatric patients undergoing major abdominal surgery.

It is worth highlighting that there is not enough evidence to demonstrate its antiaggregation, antithrombotic, antimicrobial or antitumor function. Moreover, its effect is unclear in outpatient surgery, pain control beyond 24 hours, intraoperative remifentanil consumption, or complications such as bleeding and postoperative infection.

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Authors' contributions

MPGO: Planning, data collection, data analysis, final drafting and approval of the manuscript.
MABL: Planning, data collection, interpretation, initial and final drafting, and approval of the final manuscript.
ACR and EVA: Planning, data collection, interpretation, initial and final drafting, and approval of the final manuscript.

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Conflict of interest

The authors have no disclosures to declare.

Presentations

None declared.

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Table 2. Proposed management regimens with lidocaine in the perioperative setting.

Dosis	Duration and frequency	Indication
0.2 mg/kg up 20 mg (bolus)	Single dose	Pain management with propofol injection
1 mg/kg (bolus) 0.5 to 1 mg/min (infusion)	Initial bolus plus infusion for up to 24 hours postoperatively	Perioperative acute pain management in abdominal and pelvic surgery, and as adjunct in breast and thoracic surgery.
1.5 mg/kg (bolus) 1.5 to 2 mg/kg/h (infusion)	Initial bolus plus intraoperative infusion	Reduced perioperative opioid use.
1.5 mg/kg	Single dose	Cesarean section: global pain control used intraoperatively.
1.5 mg/kg (bolus) 1.5 mg/kg/h (infusion)	Initial bolus plus infusion for up to 6 hours postoperatively	Major abdominal pediatric surgery: improved pain control and opioid sparing.
1.5 mg/kg (bolus) 1.5 mg/kg/h (infusion)	Initial bolus plus infusion for up to 1 hour postoperatively	Persistent postoperative pain: lower incidence rate.
1.5 mg/kg (bolus) 1.5 a 2 mg/kg/h (infusion)	Initial bolus plus infusion for up to 6 hours postoperatively	Postoperative neuropathic pain: lower incidence rate.

Source: Authors, from Scott, et al. (11) and Feldheiser, et al. (12).

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COMPLEMENTARY CONTENT

Annex 1. Studies analyzed on the use of IV lidocaine.

Author	Year	Design	Primary outcome	Secondary outcome	Drugs	Results
Euasobhon et al. (9)	2016	Systematic literature review and meta-analysis. N = 84 clinical trials, range: 36 to 464 patients.	Determine the incidence of severe pain on propofol injection.	Incidence of general pain. Patient satisfaction. Adverse events.	Lidocaine in higher or lower ranges with 20 mg or 0.2 mg/kg as baseline, in bolus application before propofol.	No significant differences in higher doses, adequate response with lower pain intensity at a dose of de 20 mg or 0.2 mg/kg.
Weibel et al. (16)	2016	Systematic literature review and meta-analysis. N = 45 clinical trials (2082 patients).	Pain assessment. Postoperative ileus. Gastrointestinal function recovery.	Length of stay. Surgical complications. Lidocaine-related adverse events. Postoperative nausea and vomiting. Opioid requirement. Patient satisfaction.	Perioperative intravenous lidocaine bolus (100 mg or 1-3 mg/kg) and infusion (1-5 mg/kg/h or 2-4 mg/min). Variable infusion length between studies.	Pain reduction within the first 4 hours and up to 24 hours postoperatively. Perioperative opioid sparing. Early return of gastrointestinal function, less ileus. Less nausea and vomiting.
Grigoras et al. (17)	2012	Randomized double-blind clinical trial. Patients scheduled for oncologic breast surgery. N= 36 patients.	Postoperative pain assessment and consumption of analgesics.	Persistent postoperative pain and secondary hyperalgesia.	Group 1: Intravenous lidocaine at 1.5 mg/kg (induction) followed by infusion 1.5 mg/kg/h, during surgery and 1 after surgical wound closure. Group 2: same placebo volume (0.9% NSS)	Pain scores and analgesic consumption similar in early postoperative period. Lower incidence of persistent postoperative pain and secondary hyperalgesia in lidocaine group.
Terkawi et al. (18)	2015	Randomized, double-blind clinical trial. Patients scheduled for mastectomy. N = 61 patients.	Assessment of chronic postoperative pain	-	L Group: intravenous lidocaine at 1.5 mg/kg (induction) followed by infusion 2 mg/kg/h, during surgery and up to 2 hours after the end of the procedure. P Group : same placebo volume administered (0.9% NSS)	Disminución de la incidencia de dolor crónico postoperatorio en el Group de lidocaína.
Ayala et al. (19)	2012	Randomized, double-blind, controlled clinical trial. Patients scheduled for hysterectomy. N= 23 patients.	Postoperative pain assessment.	Opioid consumption. Side-effects.	IVL Group: Intravenous lidocaine at 1.5 mg/kg (induction) followed by infusion 1.5 mg/kg/h, until skin closure. C Group: same placebo volume administered (0.9% NSS)	The lidocaine group had lower pain scores on the VAS on arrival at the recovery room, at 30 minutes and at 24 hours; shorter time to reach conditions for initiation of patient-controlled analgesia. Lower morphine consumption for pain control and in the first 24 hours.

Author	Year	Design	Primary outcome	Secondary outcome	Drugs	Results
Calero et al. (20)	2016	Randomized clinical trial. Patients scheduled for videolaparoscopy. N= 32 patients.	Assessment of inhaled anesthetics and opioid consumption.	Adverse effects.	IVL Group: Intravenous lidocaine at 1.5 mg/kg (induction) followed by infusion 1.5 mg/kg/h, until skin closure. C Group: same placebo volume administered (0.9% NSS)	There was a lower consumption of sevoflurane in the lidocaine group (better hemodynamic stability) and a lower need for rescue fentanyl, albeit not significant.
Gholipour Baradari et al. (22)	2017	Randomized, double-blind, controlled clinical trial. Patients undergoing elective cesarean section under general anesthesia. N= 100 patients.	Assessment of postoperative pain and opioid consumption.	Satisfaction. APGAR. Adverse effects.	IVL Group: Intravenous lidocaine at 1.5 mg/kg (bolus induction). C Group: same placebo volume administered (0.9% NSS)	The lidocaine group had less pain in the first 24 hours postoperatively, with lower opioid consumption.
El-Deeb et al. (24)	2013	Randomized clinical trial. Pediatric patients undergoing elective major abdominal surgery. N= 80 patients.	effect on stress hormone levels, length of stay and bowel function.	Adverse effects.	IVL Group: Intravenous lidocaine at 1.5 mg/kg (induction) followed by infusion 1.5 mg/kg/h, up to 6 hours postoperatively. C Group: same placebo volume administered (0.9% NSS)	The lidocaine group had lower cortisol levels, less need for fentanyl boluses, shorter length of stay, earlier return of gastrointestinal function.
Kendall et al. (25)	2018	Double-blind, randomized, controlled clinical trial. Patients undergoing elective oncologic breast surgery. N=148 patients.	Frequency of persistent-chronic postoperative pain.	-	Group 1: Intravenous lidocaine at 1.5 mg/kg (induction) followed by infusion 2 mg/kg/h, up to 1 hour after surgery. C Group: same placebo volume administered (0.9% NSS)	The lidocaine group showed a lower incidence of persistent postoperative pain at 3 and 6 months of follow-up.
Batista et al. (26)	2009	Animal model experiment. Scheduled for surgical sciatic nerve compression. N=18 mice.	Assessment of effect on behavior on thermal stimulus.	-	Group 1: non-intervened control. Group 2: Sciatic intervention with no lidocaine use. Group 3: Sciatic nerve intervention and lidocaine use.	Rodents receiving preventive lidocaine exhibited less behavioral alterations and lower incidence of neuropathic pain.
Khan et al. (27)	2019	Randomized, controlled, multi-center clinical trial. Patients undergoing elective oncologic breast surgery. N= 100 patients.	Assessment of postoperative pain and postoperative neuropathic pain.	Adverse effects.	L Group: Intravenous lidocaine at 1.5 mg/kg (induction) followed by infusion of 2 mg/kg/h until surgical wound closure. Pr Group: Pregabalin 300 mg preoperatively and 75 mg every 12 h for 9 days. P Group: placebo in equivalent form to each of the two previous groups.	The lidocaine group had a lower incidence of neuropathic pain. Pregabalin did not have any significant impact.

Source: Authors.