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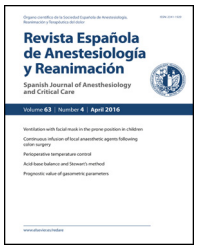

REVIEW

Intravenous lidocaine infusion☆,☆☆

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KEYWORDS
Intravenous lidocaine;
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Post-operative cognitive dysfunction;
Cancer recurrence

Abstract Systemic lidocaine used in continuous infusion during the peri-operative period has analgesic, anti-hyperalgesic, as well as anti-inflammatory properties. This makes it capable of reducing the use of opioids and inhalational anaesthetics, and the early return of bowel function, and patient hospital stay. The aim of this narrative review was to highlight the pharmacology and indications for clinical application, along with new and interesting research areas. The clinical applications of peri-operative lidocaine infusion have been reviewed in several recent systematic reviews and meta-analyses in patients undergoing open and laparoscopic abdominal procedures, ambulatory procedures, and other types of surgery. Peri-operative lidocaine infusion may be a useful analgesic adjunct in enhanced recovery protocols. Potential benefits of intravenous lidocaine in chronic post-surgical pain, post-operative cognitive dysfunction, and cancer recurrence are under investigation. Due to its immunomodulation properties over surgical stress, current evidence suggests that intravenous lidocaine could be used in the context of multimodal analgesia.

PALABRAS CLAVE
Lidocaína intravenosa;
Anestesia libre de opioides;
Hiperalgesia inducida por opioides;

Perfusión de lidocaína intravenosa

Resumen La perfusión perioperatoria de lidocaína intravenosa tiene propiedades analgésicas, antihiperalgésicas y antiinflamatorias, disminuyendo el consumo de opioides y agentes volátiles, brindando una rápida recuperación de la función intestinal y alta hospitalaria. Esta revisión narrativa tiene como objetivo exponer su farmacología e indicaciones para su aplicación en la clínica anestésica. Recientes revisiones sistemáticas y metaanálisis confirman su empleo en cirugía abdominal videolaparoscópica y abierta, como también en otros tipos de cirugía, destacándose su uso en protocolos de pronta recuperación. Potenciales beneficios en dolor crónico posoperatorio, disfunción cognitiva posoperatoria y

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Disfunción cognitiva posoperatoria; Recurrencia de cáncer

recurrencia de cáncer están siendo investigados. La evidencia actual avala su administración en el contexto de analgesia multimodal debido a sus propiedades inmunomoduladoras sobre el estrés quirúrgico, considerándose un fármaco necesario en la clínica perioperatoria moderna.

Introduction

Postoperative pain (POP) is a nociceptive stimulus produced by surgery-induced tissue damage, and results in emotional and cognitive experiences. Good pain management reduces morbidity, improves surgical outcomes, and reduces hospital costs. However, estimates suggest that more than 50% of patients undergoing surgical procedures experience moderate to severe pain.[1] Persistence of the painful stimulus can even change the plasticity of the nervous system, leading to chronic pain.[2] Inter-individual differences in pain thresholds and the use of inappropriate drugs are among the causes of POP.

Although opioids are frequently used in pain therapy, they can cause adverse effects, such as respiratory depression, postoperative nausea and vomiting, ileus, urinary retention, hyperalgesia and immune changes.[3] Intravenous (iv) perfusion of lidocaine, a drug whose analgesic, antihyperalgesic and anti-inflammatory properties modulate the inflammatory response produced by surgical stress, is an alternative to opioids in pain management.[4] Some studies have shown that lidocaine decreases POP and the need for opioids and volatile agents, and rapidly restores intestinal function.[5] The antihyperalgesic action of lidocaine reduces allodynia by acting on spinal cord neurons.[6] The anti-inflammatory action of the drug, which inhibits cytokine release and polymorphonuclear activation, has been demonstrated *in vitro* and *in vivo*.[7] The aim of this review is to describe the pharmacology of lidocaine, its indications for use in anaesthesia practice, and its effect on new fields of study, including chronic POP, postoperative cognitive dysfunction (PCD) and cancer recurrence.

Mechanisms of action

Lidocaine is an amide-type local anaesthetic that acts by blocking voltage-gated sodium channels (VGSC) in neuronal tissues, thus interrupting synaptic transmission.[8] VGSCs are composed of an α subunit (Nav1.5, 260 kDa) and 1 or more β subunits (Navβ1.1, Navβ1.1 a, Navβ3.1; 33–36 kDa). The α subunit is an integral heteromultimeric protein complex consisting of 4 homologous domains (D1–D4), each of which contains 6 α-helix transmembrane segments (S1–S6). The C- and N-terminus ends and P loops that bind the domains are intracytoplasmic. The S5–S6 segments and the P loop of each domain form the channel pore that penetrates the membrane. In mammals, VGSCs have 9 different α unit isotypes (Nav1.1 to 1.9), some of which are associated with neuropathic pain (Nav1.3, 1.7, 1.8 and 1.9) and others with inflammatory pain (Nav1.7, 1.8 and 1.9). Lidocaine passes through the neuron membrane and is converted to its non-ionised form by the effect of pH. It binds to the S6 portion of domain 4 of the α subunit inside the sodium channel. The affinity of lidocaine for VGSCs varies according to the status of the channel, being high when the channel is open and low when it is closed. Therefore, the greater the neural discharge, the greater the number of ionised lidocaine molecules entering the site of action, thus increasing the analgesic capacity of the drug.[9] The analgesic effect of intravenous administration is the result of increased acetylcholine levels in the cerebrospinal fluid, which cause downward inhibition, inhibition of glycine receptors, and increase the release of endogenous opioids. When lidocaine reaches the spinal cord, it reduces the post-synaptic depolarisation mediated by N-methyl-D-aspartate and neurokinin receptors, thus modifying the pain response.[10] N-methyl-D-aspartate blockade inhibits protein kinase C, thus reducing hyperalgesia and postoperative opioid tolerance. In animal models, lidocaine acts during the early stages of systemic inflammatory response, modulating the marginalisation, adherence and diapedesis of polymorphonuclear cells towards the site of the lesion, thus inhibiting the production of reactive oxygen species and the release of histamine. This immunomodulatory effect of the drug is achieved by blocking G protein-coupled receptors, since polymorphonuclear cells do not contain VGSCs.[11] Through G protein-coupled receptors, lidocaine inhibits inflammatory processes, such as the sensitisation and lysosomal degradation of neutrophils, the production of reactive oxygen species, and the secretion of cytokines in both macrophages and glial cells. On the other hand, it can also inhibit leukocyte adhesion and migration through the endothelium by inhibiting intercellular adhesion molecules, altering the cytoskeleton, or attenuating the release of chemotactic factors. Lidocaine blocks the release of interleukin (IL) 1, IL-1β, tumour necrosis factorα and IL-8 in polymorphonuclear cells. It also decreases circulating IL-6 and phospholipase A2 levels, both of which are involved in the disruption of the blood-brain barrier, inflammation and brain damage.[12] Lidocaine also inhibits the production of thromboxane B2 by inhibiting platelet aggregation, which reduces the risk of venous thrombosis. Finally, lidocaine has been shown to exhibit antioxidant properties by inhibiting the production of reactive oxygen species due to its interaction with phospholipid membranes and interference with mitochondrial radical formation.[13]