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## CASE REPORT

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# Use of systemic lidocaine for postoperative acute pain management in single-lung transplantation: Case report

*Lidocaína sistémica para el tratamiento del dolor agudo posoperatorio en trasplante unipulmonar. Reporte de caso*

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## Abstract

**Introduction:** Lung transplantation is associated with severe pain, which can delay recovery. Systemic lidocaine has useful analgesic properties for managing acute pain; however, little is known on its use after lung transplantation. Due to pharmacological alterations during the postoperative period, the use of analgesics implies a demanding process to avoid toxicity, so lidocaine may play a role in this scenario. In this sense, the purpose of this case report is to present the use of systemic lidocaine as an option for acute pain management when other analgesics fail.

**Case presentation:** The following is the case of a male patient with acute pain in the postoperative period of single-lung transplantation. Opioids and non-opioid analgesics showed limited efficacy, so systematic lidocaine was administered. Systemic administration of lidocaine was effective for pain control, functional recovery, and opioid decrease during the postoperative period.

**Conclusions:** Systemic administration of lidocaine was a useful alternative for achieving optimal postoperative pain management in lung transplantation, since it allowed adequate analgesia and lung function recovery with decreased use of opioids. This drug may be a component of multimodal analgesia in selected patients when other options fail however, its routine use is not recommended.

**Keywords:** Acute Pain; Lung; Transplantation; Lidocaine; Metabolism (MeSH).

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## Resumen

**Introducción.** El trasplante pulmonar se asocia con dolor severo, lo que puede retrasar la recuperación del paciente. La lidocaína sistémica tiene propiedades analgésicas útiles para el manejo del dolor agudo; sin embargo, su uso después del trasplante pulmonar es poco conocido. Debido a las alteraciones farmacológicas durante el período posoperatorio, el uso de analgésicos es un proceso exigente para evitar toxicidad, por lo que la lidocaína puede tener un rol en ese contexto. En este sentido, el objetivo del presente reporte es describir el uso de lidocaína sistémica como una opción para el manejo del dolor cuando otros analgésicos han fallado.

**Presentación del caso.** Paciente masculino con dolor severo en el posoperatorio de un trasplante unipulmonar. El uso de opioides y de analgésicos no opioides mostró una eficacia limitada, por lo que se decidió aplicar lidocaína sistémica, la cual fue efectiva para el control del dolor, la recuperación funcional y la disminución de opioides durante el período posoperatorio.

**Conclusiones.** La lidocaína sistémica fue un fármaco útil para el manejo del dolor posoperatorio del trasplante de pulmón, ya que permitió una analgesia adecuada y una recuperación funcional pulmonar con menor uso de opioides. Este fármaco puede ser parte de la analgesia multimodal en pacientes seleccionados cuando otras opciones analgésicas han fallado; sin embargo, no se recomienda su uso rutinario.

**Palabras clave:** Dolor agudo; Pulmón; Trasplante; Lidocaína; Metabolismo (DeCS).

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Introduction

Pulmonary fibrosis is a low-incidence disease —97.3 cases per 100 000/year— that generates a heavy burden for patients, their families and society.<sup>1</sup> One of the treatment options for this progressive disease is lung transplantation (about 3 600 procedures are performed per year worldwide);<sup>2</sup> this procedure is classified as very painful during its acute period and acute pain is recognized as a risk factor for chronic postoperative pain.<sup>3,4</sup> In this scenario, effective acute pain control after lung transplantation is associated with better clinical outcomes, since at least 30% of patients will develop chronic postoperative pain.<sup>5-8</sup>

Uncontrolled acute pain also prevents early mobilization including walking, respiratory functions such as coughing and deep inspiration, thus favoring the occurrence of atelectasis and lung infections.<sup>9</sup> Given the mechanisms of pain, treating nociceptive and neuropathic pain after lung transplantation (i.e. pain affecting costo-vertebral joints, rib retractions, skin, muscles, pleural layers, intercostal nerves) using a single analgesic may be insufficient to achieve pain relief.<sup>10,11</sup> Several analgesic techniques could be effective (opioids, non-steroidal anti-inflammatory drugs, ketamine, neuroaxial and regional blocks) but serious side effects may occur, so a multimodal approach is usually recommended.<sup>12-15</sup>

Intravenous lidocaine has been proposed as an alternative therapy for treating postoperative pain following a number of surgical procedures<sup>16,17</sup> due to its mechanisms of action (sodium channel blocker, anti-inflammatory, reduction in the production of catecholamines and interleukins, and effects on the gastro-intestinal muscle), especially in gastrointestinal surgery, showing moderate level of evidence within 48 hours of use. The purpose of this report is to show the use of systemic lidocaine as an option to treat severe, uncontrolled postoperative pain in selected patients after lung transplantation, when other analgesic options have failed.

Case report

This is the case of a 30-year-old male patient, with a five-year history of idiopathic progressive pulmonary fibrosis; his main symptoms included dyspnea, even at rest, which required increasing doses of oxygen, persistent dry cough, fatigue, loss of weight, insomnia, incidental severe sharp pain in the limbs, and depressed mood. His pulmonary function tests showed a restrictive pattern, a forced vital capacity of 2 350 mL, a six-minute walk test (SMWT) of 383 meters, and oxygen saturation on exertion of 84%.

Since his overall condition worsened, he underwent single-lung transplantation under general anesthesia (midazolam, propofol, rocuronium, remifentanyl, nor-adrenaline, dexamethasone) uneventfully. Within the first 24 hours after the procedure, the patient required continuous intravenous sedation with fentanyl (up to 150 micrograms/hr) and dexmedetomidine (0.05-1.5 mcg/kg/hr IV) to facilitate mechanical ventilation; analgesia was initiated with hydromorphone (up to 1mg IV every 4 hours plus rescue doses), and then switched to morphine (4mg IV every 4 hours plus rescue doses); however, he experienced psycho-motor agitation, which was interpreted as uncontrolled pain.

On the second postoperative day, he developed tachypnea, tachycardia, diaphoresis and shallow breathing that did not allow adequate expansion of the thorax. According to the patient, pain was unbearable in the surgical wound (10/10) (Table 1). Consequently, he was administered multiple doses of opioids without adequate analgesic effect but with marked sedation, intermittent confusion and postoperative ileus.

The Pain Service started an analgesic management plan with a lidocaine bolus at 1mg/kg IV for 20 minutes plus continuous infusion at 0.5-1 mg/kg/hr, morphine-to-ketamine ratio (1:1) for patient-controlled analgesia, and intravenous paracetamol 1gm every 8 hours; opioids were considered as a second line of treatment because of their respiratory depressant, cognitive and gastrointestinal side effects. On the third postoperative day, the patient reported mild pain (3/10) on movement, showing improvements during respiratory therapy; he also started drinking fluids. Follow-up of inspiratory volume and expiratory time was performed and quantified with respiratory incentive, tolerance to percussion, arterial-blood gas test and vital signs during respiratory therapy, which showed evidence of improvement with each day of pharmacological treatment (Table 1).

Table 1. Patient postoperative follow-up.

|                                   | Days 0-2 | Day 3   | Day 4   | Day 5 |
|-----------------------------------|----------|---------|---------|-------|
| Lidocaine mg/kg/hr                | 0        | 0.5-1.0 | 1.0-2.0 | 0     |
| Morphine PCA (mg/24 hr)           | ≈30*     | ≈20*    | 13      | 5     |
| VAS on movement (0/10)            | 10       | 10      | 3       | 1     |
| Maximum RR during RT (breath/min) | n/a      | 24      | 22      | 20    |
| Maximum HR during RT (beat/min)   | 165      | 120     | 108     | 110   |
| Volume mobilized (mL)             | 400 †    | 600     | 1000    | 1200  |
| Time sustained (sec)              | n/a      | 1       | 2       | 3     |
| Vibration/percussion tolerance    | n/a      | -       | +       | ++    |
| Ability to walk                   | n/a      | ±       | +       | ++    |

PCA: patient-controlled analgesia; VAS: visual analogous scale; RR respiratory rate; RT: respiratory therapy; HR: heart rate; n/a: not applicable.  
\*Regular intravenous administration plus PRN doses.  
† Mechanical ventilation.  
Source: Own elaboration.

On the fourth postoperative day, the patient achieved lung rehabilitation goals and adequate pain control at rest (0/10), which increased to up to 3/10 during respiratory therapy. The infusion of lidocaine was reduced progressively over the next two days. The patient was satisfied with the analgesic treatment and no side effects associated with systemic lidocaine administration were reported.

Discussion

This case report illustrates the use of systemic lidocaine as a co-adjutant rescue analgesic treatment after lung

transplantation when other analgesic modalities have failed. Basic and clinical research support the analgesic, anti-inflammatory and anti-hyperalgesic action of intravenous lidocaine infusion,<sup>18</sup> especially during the postoperative period of abdominal surgery, since it reduces opioid consumption and has fewer gastrointestinal side effects (nausea, vomiting, ileus).<sup>19</sup> Some of these findings may be helpful after lung transplantation.

The intravenous mechanism of action of lidocaine has not been clearly established, although it is concerned with its blocking effect on voltage-gated sodium channels, decreasing pain transmission from the site of injury.<sup>19</sup> Its use as part of analgesia for lung transplantation has not been reported in the relevant literature, but it is important to point out the pharmacokinetic and pharmacodynamic characteristics of this drug and the potential benefits it may have for these patients.

Lidocaine (C<sub>14</sub>H<sub>22</sub>N<sub>2</sub>O) is an amide-type local anesthetic and a class 1b antiarrhythmic agent. Its action reversibly blocks voltage-gated sodium channels, joining to the S6 segment of domain IV of the  $\alpha$  subunit and generating a conformational change in the sodium channel receptor with depolarization and subsequent decrease of nerve impulse propagation. It also has other action mechanisms such the blocking of presynaptic muscarinic, dopamine and NMDA receptors, and the reduction of substance P, which decreases neuronal activity and spreads the painful stimulus to the spinal cord.<sup>20,21</sup>

The anti-inflammatory properties of lidocaine have been described<sup>20</sup>, while a direct effect has been found *in vitro* on granulocytes, macrophages and polymorphonuclear cells function, as well as a decrease in the release of inflammatory mediators such as Leukotriene B<sub>4</sub>, an inducer of tissue edema in inflammatory processes, and Interleukin-1, which acts as a phagocytosis, degranulation and chemotaxis activator.<sup>20</sup> When used *in vivo*, it has been reported that lidocaine has an effect on the release of thromboxane B<sub>2</sub> with decreased activity on platelet aggregation and reduction of histamine release by mast cells, as well as on the inhibition of oxygen free radical formation because of its interference at the mitochondrial level, facilitated by its ability to interact with proteins and membrane phospholipids.<sup>20</sup>

Lidocaine plasma peak is independent of the route of administration and occurs within 20-30 minutes.<sup>20</sup> Its volume of distribution is 0.6-4.5 L/kg. The literature reports a rapid onset for intravenous boluses of 50-100 mg, with a half-life of 10 to 20 minutes, reaching stable plasma concentrations in 30-60 minutes with continuous intravenous infusion and an elimination half-life of 96 to 108 minutes. Plasma clearance is 10-20 mL/min per kilogram for infusions of less than 12 hours or bolus administration. When pharmacokinetics is linear, lidocaine has a half-life of 100 minutes and, in case of intravenous infusions it is longer than 12; when it behaves in a non-linear or time-dependent manner, its elimination half-life may be higher than 4 hours, and higher than 48 in case it is administered via infusions.

Pharmacokinetic studies on this drug report a dose range between 0.5-5.0 mcg/mL,<sup>20</sup> which is correlated with a bolus of 1-2 mg/kg, followed by the infusion of 0.5-3 mg/kg/h for perioperative analgesia.<sup>21</sup> Animal studies report median effective doses (ED<sub>50</sub>) of 19.5 mg/kg (95%CI:17.7-21.3) and 21 mg/kg (95%CI:19.0-23.4) for central nervous system toxicity and cardiac

toxicity, respectively. It has been established that toxicity may begin at plasma concentrations greater than 5 mcg/mL, which is a narrow therapeutic range.

Lidocaine undergoes hepatic metabolism through the cytochrome P450 3A4 isoenzyme by oxidative N-dealkylation, producing monoethylglycinexylidide (MEGX) and subsequently glycine xylidide (GX), which are active metabolites with pharmacological activity comparable to lidocaine. This metabolism depends on the hepatic blood flow, and elimination is renal considering that less than 10% of the drug is excreted in a non-metabolized form.<sup>20,22,23</sup> It is worth noting that lungs contribute to its metabolism, since about 40% of the lidocaine administered is subject to pulmonary extraction; this is an efficient mechanism because the total cardiac output goes through pulmonary circulation, and pulmonary pH is lower than plasmatic pH, which facilitates its passage.<sup>22</sup>

Studies conducted in rat models have showed pulmonary metabolism by CYP3A4, the main enzyme that transforms lidocaine in the liver. Another enzyme involved in this process is CYP2B1, responsible for N-demethylation by rat lung microsomes, which suggests that CYP2D is also involved in its metabolism,<sup>23</sup> configuring a first-pass pulmonary metabolism. Also, a bronchial smooth muscle relaxant effect has been reported. Lidocaine also prevents hyperresponsiveness induced by remifentanyl when administered through the trachea.<sup>24</sup>

In murine models, nebulized lidocaine reduces bronchial hyperreactivity and has an anti-inflammatory effect, evident in the decrease of lymphocytes, neutrophils and eosinophils in bronchoalveolar lavage.<sup>23</sup> Likewise, it has been associated with lower subepithelial fibrosis, reduction in collagen and mucus content, lower matrix metalloproteinase-9 activity, and reduced levels of IL-4, IL-5, IL-13 and eotaxin-1.<sup>25</sup> *In vivo* studies suggest a beneficial role in ischemia-reperfusion syndrome due to decreased inflammatory response.<sup>26</sup> By maintaining plasma concentrations from 3 to 4 mcg/mL in canine lung allografts, a statistically significant reduction of the polymorphonuclear count in bronchoalveolar lavage has been observed. A reduction in the activity of myeloperoxidase (a free radical-forming enzyme) has also been described, particularly in the expression of CD11b (a polymorphonuclear adhesion mediator molecule) and in the production of free radicals.<sup>26</sup> Furthermore, in porcine models of lung surgery, lidocaine infusions (1.5 mg/kg/hr) using a bolus (1.5 mg/kg) has been associated with reduced TNF- $\alpha$ <sup>27</sup> and with inflammatory and apoptotic changes related to one lung ventilation.<sup>27</sup>

Finally, it should be noted that lidocaine must be used with caution in patients with heart blocks and arrhythmias and in those with renal dysfunction and shock, because of the risk of systemic toxicity. The limitations of this case report include the few days of follow-up, the use of multi drug-therapy for analgesia and the limited evidence on the use of systemic lidocaine for analgesia currently available in the relevant literature.

## Conclusion

Systemic administration of lidocaine (1mg/kg bolus plus infusion of 1 mg/kg/hr) for 48 hours was a useful alternative for achieving an adequate postoperative pain management in lung transplantation, since it allowed adequate analgesia and lung function recovery

with decreased use of opioids. This drug may be a component of multimodal analgesia in selected patients when other options fail; however, its routine use is not recommended.

## Ethical considerations

The patient gave his informed written consent to report and publish this information.

## Conflicts of interest

None stated by the authors.

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