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Research Article

# Effects of Intravenous Lidocaine as an Analgesic Adjuvant in Oncological Pain

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## Abstract

**Objectives:** To verify that intravenous lidocaine is effective as an adjuvant analgesic in pain for hospitalized cancer patients at the National Institute of Cancerology, Mexico. **Methods:** Clinical records of patients hospitalized at the National Institute of Cancerology who received intravenous lidocaine infusion as an adjuvant to pain during the 4-year period from November 1, 2019, to October 31, 2023, were reviewed. Patients who met inclusion and exclusion criteria were included. A statistically significant measure was defined as a decrease equal to or greater than 4 points in the NRS value after lidocaine administration.

**Results:** A total of 179 patients were included; 46.4% were men, and 53.6% were women. The most common painful syndrome was somatic (54%). Patients with neuropathic pain received a higher lidocaine dose (mg/kg/hr) of 1.9 ± 0.79. Regarding adverse effects, 1.7% of patients experienced them. It was established that a reduction of 4 points with respect to the previous value on the numeric rating scale (NRS) would be considered statistically significant. A statistically significant association was found between patients under 38 years old and a higher risk of not achieving the objective (p 0.05, CI 0.95–1 OR 0.9). Patients who received lidocaine infusions for less than 4.63 days also had a risk of not reaching the goal (p 0.02, CI 0.7–0.9, OR 0.8).

**Conclusions:** This study demonstrated that the analgesic adjuvant use of intravenous lidocaine infusion is an effective and well-tolerated analgesic intervention for oncology patients.

**Keywords:** lidocaine**,** Neuropathic Pain, Somatic Pain, Visceral Pain, numeric rating scale.

## INTRODUCTION:

Cancer is the leading cause of death worldwide, attributing nearly 10 million deaths to this disease in 2020. The most common types of cancer are breast, lung, colon, rectum, and prostate cancers. Pain is highly prevalent in all cancer patients (30%–50%); it is particularly relevant for patients with advanced, metastatic, or terminal cancer, present in 70–90% of cases. [1]

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage."[2] This has negative repercussions on the quality of life and functionality of those suffering from any type of pain.

There are different types of pain based on their pathophysiology, such as neuropathic pain, defined as "pain caused by a lesion or disease of the somatosensory nervous system."[3] Regarding nociceptive pain, IASP defines it as "pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors." This term is designed to contrast with neuropathic pain.[4] Nociceptive pain can be further subdivided into somatic and visceral pain.

One proposed pathophysiological mechanism contributing to neuropathic pain is a constant state of hyperexcitability of primary afferents, overexpression of voltage-dependent sodium channels, leading to persistent sensitization, clinically manifested as spontaneous pain.[5] Lidocaine can modulate neuropathic pain by reducing the function of these sodium channels, reversing the effects of positive regulation of sodium channels.

Regarding visceral pain, it is suggested that pain associated with active obstruction activates mechanosensitive nociceptors in visceral afferents, releasing inflammatory mediators, including nerve growth factor (NGF), brain-derived neurotrophic factor, and prostaglandins. Voltage-gated sodium channels (VGSC), especially NaV1.7, NaV1.8, and NaV1.9, play a significant role in visceral pain perception.[6]

In a case report of two cancer patients with visceral pain, lidocaine infusion was an effective and safe intervention, allowing a reduction in opioid doses and their side effects.[7]

Somatic pain is typically well-localized and originates from the skin and musculoskeletal structures. Aδ and C fibers innervate somatic structures. The three main functional classes of nociceptors (mechanical, thermal, and polymodal) are widely distributed throughout their target tissues.[8]

A retrospective study of acute pain, including 394 patients who received intravenous lidocaine infusion for postoperative analgesia, demonstrated that 56.1% of patients experienced a decrease of more than 2 points in the pre-infusion NRS value or a change of ≥ 30% in pain intensity.[9]

Lidocaine, a local anesthetic and class Ib antiarrhythmic, is an aminoamide-based compound. It was first synthesized by Nils Lofgren in 1935 in the Stockholm laboratory of Professor Hans von Euler, where Lofgren began testing the compounds they had synthesized. Since then, lidocaine's use has expanded significantly in both surgical and nonsurgical applications, including antiarrhythmic therapy, suppression of airway reflexes, and acute pain management.[10-11-12]

Lidocaine, a type amide local anesthetic, achieves its pharmacological effects through non-selective blocking of voltage-gated sodium channels in nerve membranes. Lidocaine crosses the neuronal membrane and is converted to its non-ionized form by pH effects, binding to the S6 portion of the alpha subunit within the sodium channel. Lidocaine binding to these ionic channels reduces the maximum sodium current and accelerates the deactivation process of ionic channels. Lidocaine binds allosterically in the third or fourth domain of sodium channels, preferably in the open state, thereby preventing ionic flow. Intravenous lidocaine administration primarily affects the spinal cord and dorsal root ganglia (DRG).[13-14]

The usual dose is 1 mg/kg as an initial bolus, followed by a continuous infusion of 0.5–3 mg/kg/hr. The most used and well-described dose is a continuous infusion of 2 mg/kg/hr. When administered intravenously, lidocaine is distributed to highly vascularized organs such as the kidney, brain, and heart, then to less vascularized organs.[15]

Lidocaine has been associated with reduced opioid consumption, an earlier return of intestinal function, faster rehabilitation, and shorter hospital stays. 16 intravenous lidocaine infusions have shown anti-hyperalgesic effects in chronic central and peripheral neuropathic pain conditions in various studies.[17-18-19]

Regarding oncologic pain, a meta-analysis of data from 60 patients identifies potential benefits with lidocaine infusions of 4–5 mg/kg for 30–80 minutes compared to placebo for a >50% reduction in cancer pain NRS.[20]

## MATERIALS AND METHODS:

A cross-sectional, descriptive, retrospective observational study was designed, including patients in the inpatient area of the National Institute of Cancerology receiving intravenous lidocaine infusion as an adjuvant to oncologic pain over a 4-year period, from November 1, 2019, to October 31, 2023. Patients were identified through a database provided by the hospital's systems area, including those over 18 years old, men or women, with a complete medical record and a pre-lidocaine intravenous NRS equal to or greater than 4 points. Patients with incomplete records or a history of hemodynamic alterations before the lidocaine infusion were excluded. Sociodemographic characteristics, oncological diagnoses, pre- and post-lidocaine administration DN4 questionnaire, pre- and post-infusion NRS, lidocaine dose administered, total daily opioid amount converted to oral morphine (MEDD) before and after lidocaine administration, and any possible adverse effects during lidocaine administration were considered. The collected data were analyzed using SPSS version 25.

## RESULTS:

A total of 270 electronic records were reviewed, and 91 were excluded for not meeting the NRS criteria of equal to or greater than 4 points. Of the 179 patients, 46.4% were men, and 53.6% were women. Table 1 presents the general characteristics of the population. The mean age was 42.6 ± 14.7, with somatic pain being the most common syndrome (54% of patients), followed by visceral pain (29.6%). The most common oncological diagnosis was hematopoietic (22.9%), followed by gynecological (20.7%). Somatic pain was the most common syndrome in these cases (31% and 14.9%, respectively). Regarding lidocaine dose (mg/kg/hr), patients with neuropathic pain received a higher dose of 1.9 ± 0.79. In terms of the total dose received (mg), patients with neuropathic pain also received higher doses than those with somatic or visceral pain (259 ± 142).

Adverse effects were reported in 1.7% of the 179 cases in the study. All infusions were stopped once symptoms appeared. Two patients reported dizziness, while another reported anxiety, palpitations, and discomfort.

Table 1. General characteristics of the population

| | Painful Syndrome | | | | |
|---|---|---|---|---|---|
| | Total N=179 (100%) | Somátic 87 (48.6 ) | Visceral 53 (29.6) | Neuropatico 39 (21.8) | P |
| Male Gender | 83 (46.4) | 47 (54.0) | 21 (39.6) | 15 (38.5) | 0.13 |
| Age ( Media ± DE) | 42.6 ± 14.7 | 43.5 ± 14.6 | 41.9 ± 14.3 | 41.3 ± 13.6 | 0.16 |
| Oncologyc Diagnosis | 37 (20.7) | 13 (14.9) | 20 (37.7) | 4 (10.3) | |
| Gynecological | 14 (7.8) | 7 (8) | 3 (5.7) | 4 (10.3) | |
| Breast | 19 (10.6) | 10 (11.5) | 9 (17) | 0 (0) | |
| Gastrointestinal | 35 (19.6) | 13 (14.9) | 13 (24.5) | 9 (23.1) | |
| Urological | 41 (22.9) | 27 (31) | 7 (13.2) | 7( 17.9) | 0.001 |
| Hematopoietic | 10 (5.6) | 6 (6.9) | 0 (0) | 4(10.3) | |
| Head and neck | 18 (10.1) | 8 (9.2) | 0(0) | 10 (25.6) | |

| | | | | | |
|---|---|---|---|---|---|
| Skin and soft tissues Lung and respiratory tract<br>Primary unknow | 4 (2.2)<br>1 (0.6) | 2 (2.3)<br>1 (1.1) | 1 (1.9)<br>0 (0) | 1 (2.6)<br>0 (0) | |
| Lidocaine Dose (mg/kg/h) | 1.75 ± 0.6 | 1.6 ± 0.56 | 1.7 ± 0.48 | 1.9 ± 0.79 | 0.014 |
| Lidocaine total dosis (mg) | 215 ± 99 | 211± 90 | 188 ± 59 | 259± 142 | 0.036 |
| Days of lidocaine administration | 5.2 ± 2.8 | 5.2 ± 3.02 | 5.3 ± 2.5 | 5.05 ± 2.7 | 0.1 |
| Adverse Effects<br>Bradycardia<br>Tachycardia<br>Hypotension<br>None<br>Others | <br>0<br>0<br>0<br>176 (98.3)<br>3 (1.7) | <br>0<br>0<br>0<br>84 (96.6)<br>3 (3.4) | <br>0<br>0<br>1 (0.4)<br>53 (100)<br>0 | <br>0<br>0<br>0<br>39 (100)<br>0 | <br><br>0.19 |
| ***Mean difference with Student's t-test, Proportion difference with $X^2$, p ≤ 0.05, 95% CI*** | | | | | |

In Table 2, the characteristics of pain indices are observed according to painful syndromes, where there is no difference in the NRS and MEDD before and after lidocaine administration. However, there is a difference in the DN4 for neuropathic pain since it is part of its diagnosis.

| Table 2. Pain indices by painful syndrome | | | | | |
|---|---|---|---|---|---|
| | Painful syndrome | | | | |
| | Total | Somátic<br>87 (48.6 ) | Visceral<br>53 (29.6) | Neuropathic<br>39 (21.8) | P |
| NRS pre-lidocaine | 6.31 ± 1.99 | 6.31 ± 1.92 | 6.17 ± 2.14 | 6.5 ± 1.96 | 0.2 |
| NRS post- lidocaine | 2.51 ± 2.40 | 2.44 ± 2.55 | 2.40 ± 2.39 | 2.8 ± 2.06 | 0.31 |
| DN4 pre- lidocaine | 3.49 ± 2.33 | 3.25 ± 2.04 | 2.1 ± 1.9 | 5.9 ± 1.5 | 0.02 |
| DN4 post lidocaine | 3.03 ±2.18 | 2.64 ± 1.92 | 1.97 ± 1.74 | 5.3 ± 1.5 | 0.01 |
| MEDD pre- lidocaine | 108.39 ± 74.9 | 101.36 ± 59.8 | 117.6± 83.58 | 11.4 ± 91.6 | 0.07 |
| MEDD post lidocaine | 135.55 ± 93.7 | 124.39 ± 79.5 | 148.4± 108.2 | 142.9 ± 101.1 | 0.21 |
| NRS reduction points | 3.92 ± 2.64 | 3.98 ± 2.73 | 3.9 ± 3 | 3.79 ± 1.7 | 0.16 |
| % NRS reduction | 60.68 ± 34.7 | 61.7 ± 37 | 60.6 ± 37 | 59.3 ± 25.3 | 0.14 |
| Mean difference with Student's t-test, Proportion difference with $X^2$, p ≤ 0.05, 95% CI | | | | | |

| Table 3. Differences among patients who achieved the post-infusion VAS target | | |
|---|---|---|
| | p | IC 95% |
| Gender | 0.2 | - 0.2 -0.08 |
| Age | 0.001 | 3-11.3 |
| Oncologic diagnosis | 0.43 | - 0.6-0.5 |
| Total lidocaine dosis | 0.79 | - 33 - 25 |
| Dose mg/kg/ hr | 0.3 | 0.09- 1.3 |
| Lidocaine administration time | 0.005 | 0.2-1.7 |
| Painful Syndrome<br>Neuropatic<br>Somatic<br>Visceral | <br>0.9<br>0.47<br>0.49 | <br>-0.1 – 0.1<br>- 0.1 – 0.1<br>- 0.1 – 0.15 |
| t de student o $X^2$, IC 95%, | | |

As for the NRS, a decrease of 4 points in the pre-NRS value was defined as statistically significant. In Table 3, factors associated with achieving the post-lidocaine infusion target are presented, with only age (p < 0.001, 95% CI 3 - 11.3) and lidocaine administration time (p 0.005, 95% CI 0.2 - 1.7) being statistically significant.

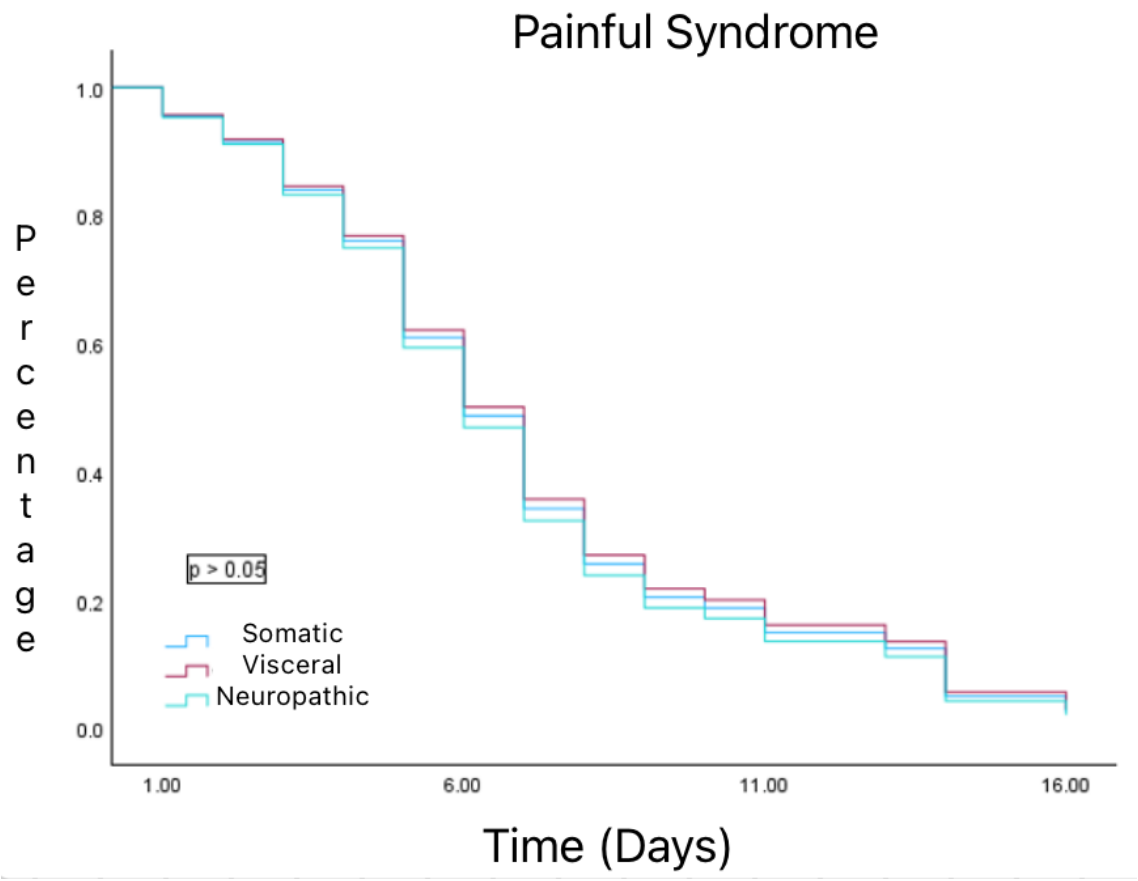
Table 4 analyzes the risk factors for not achieving the pain control objective. It was statistically significant that individuals under 38 years old have a higher risk of not meeting this objective (p 0.05, 95% CI 0.95–1 OR 0.9), as well as patients with oncological diagnoses such as breast cancer (p 0.009, 95% CI 1.3–9.2 OR 3.5) and lung cancer (p 0.05, 95% CI 0.95–1 OR 0.9). Patients who received lidocaine infusions for less than 4.63 days also have a risk of not achieving the objective (p 0.02, 95% CI 0.7–0.9 OR 0.8)

Table 4. Risk Factors for Not Achieving Pain Control Objective (4-point decrease in NRS)

| Characteristics | OR | Confidence interval | p |
|---|---|---|---|
| Gender | 1.0 | 0.6-1.7 | 0.8 |
| Age | 0.9 | 0.95- 1 | 0.05 |
| Oncological Diagnosis | | | |
| Breast Cancer | 3.5 | 1.3 – 9.2 | 0.009 |
| Lung Cancer | 12 | 1.3 - 11 | 0.025 |
| Painful Syndrome | 0.9 | 0.7 – 1.2 | 0.7 |
| Neuropathic | 1.1 | 0.5 – 2.1 | 0.75 |
| Somatic | 0.9 | 0.4- 1.8 | 0.03 |
| Visceral | 1 | 0.6 – 1.6 | 0.07 |
| Pre-lidocaine NRS | 0.6 | 0.5-0.7 | <0.01 |
| Lidocaine Dosis mg/kg/h | 0.8 | 0.4-1.4 | 0.4 |
| Lidocaine time in days | 0.8 | 0.7-0.9 | 0.02 |

Bivariate logistic regression, OR: Odds Ratio

The survival curves did not show differences between the painful syndromes in achieving the objective.



## DISCUSSION:

Cancer incidence has been increasing globally, along with various associated painful syndromes, leading to poor outcomes such as increased analgesic requirements and reduced functional status. It is well known that the treatment relies on major opioids and some adjuvant drugs, with the risk of immediate and delayed adverse effects such as sedation, nausea, vomiting, hyperalgesia, constipation, and tolerance, among others.[21]

Lidocaine infusion provides clinically significant pain relief in patients with oncologic pain. In our study, a pain relief percentage of 61.7 ± 37, 60.6 ± 37, and 59.3 ± 25.3 was found for somatic, visceral, and neuropathic pain, respectively. The infusions are safe, and only 1.7% of patients reported side effects, none of which were severe or long-lasting.

Abouelmagd et al. demonstrated that lidocaine and duloxetine have a comparable effect on the incidence and severity of taxane-induced peripheral neuropathy in breast cancer patients at a dose of 2 mg/kg. In our study, it is observed that patients with neuropathic pain received a higher average dose of lidocaine (1.9 mg/kg/h) compared to other types of pain, suggesting a potentially more effective response in terms of neuropathic pain relief. [22]

Regarding the DN4 questionnaire, our study proposed a decrease of 3 points from the baseline value; however, this goal was achieved by 10.2% of patients with neuropathic pain, contrasting with the aforementioned study where lidocaine patients showed an incidence of 5% of DN4 greater than 4 points.

Concerning visceral pain, in a meta-analysis of eight RCTs conducted by E. Marret et al.'s study on intravenous lidocaine and postoperative recovery after abdominal surgery, a significant reduction in pain and postoperative ileus was demonstrated.[23] In our study, patients with visceral pain showed a 60.6% decrease in NRS.

Regarding opioid sparing, which was part of the objectives, no reduction was observed in opioid consumption measured by MEDD in any of the three pain syndromes. Therefore, it cannot be asserted that lidocaine promotes opioid sparing.

## CONCLUSION:

This retrospective study conducted at an oncology institution demonstrated that the adjuvant analgesic use of intravenous lidocaine infusion is an effective and well-tolerated analgesic intervention for patients, with few non-serious adverse effects. However, additional prospective studies are needed to confirm these observations. These studies should incorporate clinical variables such as albumin levels, chronic diseases, and liver and kidney function to assess whether they influence analgesic responses. Additionally, the inclusion of other adjuvants required for pain management and the standardization of lidocaine loading and maintenance doses will contribute to a more homogeneous evaluation of results.

Conflict of interests: The authors declare no conflicts of interest.

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