MEDwave

**Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)**
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# Is intravenous lidocaine effective for decreasing pain and speeding up recovery after surgery?

**Authors:** María Magdalena González[1,2], Fernando Altermatt[2,3]

**Affiliation:**
[1] Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
[2] Proyecto Epistemonikos, Santiago, Chile
[3] Departamento de Anestesiología, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

**E-mail:** fernando.altermatt@gmail.com

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## Abstract

**INTRODUCTION**
Lidocaine is widely used in anesthesia due to its multiple properties, including its role as analgesic. However, it is not entirely clear which are the real benefits of its use in the perioperative setting.

**METHODS**
To answer this question we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others. We extracted data from the systematic reviews, reanalyzed data of primary studies, conducted a meta-analysis and generated a summary of findings table using the GRADE approach.

**RESULTS AND CONCLUSIONS**
We identified 15 systematic reviews including 53 studies overall, all of them randomized controlled trials. We concluded the use of intravenous perioperative lidocaine probably results in a clinically irrelevant difference in pain and length of hospital stay, but it probably prevents postoperative nausea and vomiting.

### Problem

There are different alternatives used as adjuvants in the various anesthetics techniques, with the objective of diminishing postoperative symptoms and accelerating recovery. It has been proposed that lidocaine, a local anesthetic belonging to the group of the aminoamides which acts by inhibiting sodium channels, would have analgesics effects, among others, that would make it a good alternative in the surgical setting. Nevertheless, it is not yet clear whether its effects bring a real benefit for patients, and also if it is a safe intervention.

### Methods

To answer the question, we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies. We extracted data from the identified reviews and reanalyzed data from primary studies included in those reviews. With this information, we generated a structured summary denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos) using a pre-

established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies when it is possible, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

**Key messages**

- The use of perioperative lidocaine probably leads to a clinically irrelevant reduction in pain at rest at 24 hours, time to first flatus and length of hospital stay.
- The use of perioperative lidocaine probably prevents postoperative nausea and vomiting.
- Considering the marginal clinical relevance of the benefits and the higher costs in comparison to other pharmacological alternatives for postoperative nausea and vomiting, the balance between benefits, risks and costs is not favorable.

**About the body of evidence for this question**

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| What is the evidence.<br>See evidence matrix in Epistemonikos later | We identified 15 systematic reviews [1],[2],[3],[4],[5],[6],[7],[8],[9],[10],[11],[12], [13],[14],[15], including 53 primary studies overall, reported in 55 references [16],[17],[18],[19],[20],[21],[22],[23],[24],[25],[26],[27],[28],[29],[30],[31],[32], [33], [34], [35],[36],[37],[38],[39],[40],[41],[42],[43],[44],[45],[46],[47],[48],[49], [50],[51],[52],[53],[54],[55],[56],[57],[58],[59],[60],[61],[62],[63],[64], [65],[66], [67],[68],[69],[70]. All of the studies corresponded to randomized controlled trials.<br>One of the reviews [10] presented data from one trial that was not included in any other review (Harvey 2006), in a way in which it was not possible to reanalyze it. The reference to this trial is not included in the review, it was not possible to identify it by other means and the author did not reply after to our contact. |
| What types of patients were included* | Twenty five trials included adults from 18 to 75 years old [16],[17],[18],[19],[20],[21], [22],[23],[24],[25],[26],[27],[28],[29],[31],[32],[33],[34],[35],[36],[38],[39],[40], [41],[42] and in 28 trials this information was not available [43],[44],[45],[46],[47], [48],[49],[50],[51],[52],[53],[54],[55],[56],[57],[58],[59],[60],[61],[62],[63],[64], [65],[66],[67],[68],[69],[70].<br>Seven trials only included women [18],[21],[42],[44],[49],[50],[52], three included only men [26],[53],[60], the remaining 43 trials did not restrict by sex.<br>Fourteen trials included ASA I-II patients [16],[18],[19],[28],[34],[36],[41],[42],[44], [50],[52],[53],[65],[68], ten ASA I-III [20],[21],[22],[24],[31],[35],[38],[39], [60],[69], one trial included ASA I patients only [66] and in 28 trials this information was not available.<br>In 24 trials the patients underwent abdominal surgery; of these, 13 only included digestive surgery [17],[22],[24],[27],[28],[39],[41],[48],[58],[63], [65],[67],[68], five gynecological [21],[42],[44],[49],[50], three urological [53],[60],[69], in two trials the type of abdominal surgery was not specified [16],[59], and in one it corresponded to inguinal herniorrhaphy [25]. Seven trials included cardiovascular surgeries; four only vascular [23],[26],[29],[40], two cardiac and vascular surgeries [33],[62], and one only included cardiac surgeries [32]. Of the remaining, three trials addressed breast surgery [18],[38],[52], two spine surgery [20],[55], two thoracic surgery [19],[35], one total hip arthroplasty [61], one diverse ophthalmologic surgeries [36], one outpatient surgery under general anesthesia [31] and two otorhinolaryngology surgery; one functional endoscopic sinus surgery [34] and one elective tonsillectomy [66]. Ten trials did not report the type of surgery [43],[45],[46],[47],[51],[54],[56],[57],[64],[70].<br>Twenty-two trials excluded patients with chronic pain conditions, chronic pain treatments or pain treatment in the last week with any analgesic drug [19],[21],[22],[24], [25], [28], [34],[35],[39],[41],[42],[44],[48],[49],[52],[53],[59],[60],[61],[65],[68],[69]. |
| What types of interventions were included* | All of the trials used intravenous systemic lidocaine.<br>Forty seven trials started lidocaine intraoperatively; of these, forty six initiated it before skin incision [16],[17],[18],[19],[20],[21],[22],[23],[24],[25],[26],[27],[28],[29], 31], [32],[33],[34],[35],[36],[38],[39],[41],[42],[44],[47],[48],[49],[50],[51],[52],[53], [55],[56],[57],[59],[60],[61],[62],[63],[64],[65],[66],[67],[68],[69], and one before the opening of the pericardium [40].<br>Forty two trials used a lidocaine bolus (1 mg/kg to 3 mg/kg) followed by an infusion (20 µg/kg/min to 4 mg/min); from these, 17 maintained the infusion only during the intraoperative period [18], [25],[27],[28],[29],[34],[35],[40],[41],[42],[44],[48],[49], [51],[55],[56],[65], 12 until completing 24 hours [16],[22],[31],[33],[38],[50],[52], [53],[59],[61],[64],[66], nine for 24 hours postoperatively [17],[21],[24],[39],[57], [60],[63],[67],[69], two for 48 hours postoperatively [32],[62], one for 48 hours postoperatively or discharge from the intensive care unit [23] and one did not report |

| | |
|---|---|
| | when the infusion ended [26]. Four trials did not use a bolus, but only an infusion (33 µg/kg/min to 3 mg/kg/h), from which three kept it only during the intraoperative period [19],[36],[68] and one until discharge from post-anesthesia care unit or for eight hours [20]. One trial used three lidocaine boluses (2 mg/kg) during the intraoperative period and after that a PCA (patient-controlled analgesia) pump of lidocaine was used (23 mg) according to patient's requirement, without reporting an end time [47].<br>Four trials started lidocaine postoperatively; one as a bolus (1.5 mg/kg) and then continued with an infusion (2 mg/kg/h) for two hours [43]; of the remaining three, one used lidocaine infusion (60 mg/h) for 24 hours [54] and two a PCA without referring an end time [45],[46].<br>One trial started lidocaine preoperatively [58] with a bolus (1.5 mg/kg) followed by an infusion (2 mg/kg/h) only during the intraoperative period.<br>It was not possible to extract data related to the characteristics from one trial [70] because it was included in only one systematic review [15], and the author did not reply after attempting to contact him.<br>One trial was included in a systematic review with preliminary data before being published [35].<br>All of the trials compared lidocaine against placebo or no treatment. |
| What types of outcomes were measured | The outcome were grouped by the systematics reviews as follows: Postoperative pain, intraoperative and postoperative analgesic consumption, chronic pain, opioid related adverse effects, postoperative nausea and vomiting, postoperative ileus and functional gastrointestinal recovery (evaluated by time to first flatus, feces, or bowel movement), length of hospital stay and length of post-anesthesia care unit stay, surgical complications, adverse events, mortality, cognitive outcomes, patient satisfaction, cessation of the intervention, systemic lidocaine toxicity, plasma levels of cytokines. |

* The information about primary studies is extracted from the systematic reviews identified, unless otherwise specified.

**Summary of Findings**

The information about the effects of the intravenous systemic lidocaine is based on 37 randomized trials including 2253 patients [16],[17],[18],[20],[21],[22],[23],[24],[25],[27],[28],[31],[32],[33], [35], [39],[40],[41],[42],[44],[48],[49],[51],[52],[53],[54],[57],[58],[59],[60],[61],[62],[63],[65], [66],[68],[69]. Twenty five trials reported the outcome pain at rest at 24 hours [16],[17],[18],[20], [22],[24],[25],[27],[28],[31],[35],[39],[41],[42],[44],[52],[53],[57],[58],[59],[60],[61],[65],[68], [69], 16 reported time to first flatus [18],[22],[24],[25],[28],[41],[51],[53],[54],[57],[59],[60],[63], [65],[68],[69], 24 measured length of hospital stay [18],[20],[22],[23],[24],[25],[27],[28],[32], [33],[39],[40],[41],48],[51],[53],[54],[57],[58],[59],[60],[61],[62],[69] and 24 reported postoperative nausea and vomiting [16],[17],[18],[20], [21],[24],[25],[27],[28], [31],[35],[39],[41],[44],[49],[57],[58],[59],[60],[63],[65],[66],[68],[69].

The summary of findings is the following:

- The use of perioperative lidocaine probably leads to a clinically irrelevant reduction of pain at rest at 24 hours. The certainty of the evidence is moderate.
- The use of perioperative lidocaine probably leads to a clinically irrelevant reduction of time to first flatus. The certainty of the evidence is moderate.
- The use of perioperative lidocaine probably leads to a clinically irrelevant reduction of length of hospital stay. The certainty of the evidence is moderate.
- The use of perioperative lidocaine probably prevents postoperative nausea and vomiting. The certainty of the evidence is moderate.

**Perioperative intravenous systemic lidocaine**

Patients: Surgery with general anesthesia
Intervention: Intravenous systemic lidocaine
Comparison: Placebo or no treatment

| Outcome | Absolute effect* | | Relative effect (95% CI) | Certainty of evidence (GRADE) |
|---|---|---|---|---|
| | WITHOUT Lidocaine | WITH Lidocaine | | |
| Pain at rest at 24 hours<br>Evaluated with VAS 0-10 points | 2.7 points** | 2.31 points | -- | ⊕⊕⊕◯[1] moderate |
| | MD: 0.39 points better<br>(Margin of error: 0.21 to 0.56 better) | | | |
| Time to first flatus | 1.4 days** | 1.28 days | -- | ⊕⊕⊕◯[1] moderate |
| | MD 0.22 days less<br>(Margin of error: 0.12 to 0.31 less) | | | |
| Length of hospital stay | 6 days ** | 5.75 days | -- | ⊕⊕⊕◯[1] moderate |
| | MD 0.25 days less<br>(Margin of error: 0.10 to 0.40 less) | | | |
| Postoperative nausea and vomiting | 372 per 1000 | 275 per 1000 | RR 0.74<br>(0.63 a 0.88) | ⊕⊕⊕◯[2] moderate |
| | Difference: 97 patients less<br>(Margin of error: 45 to 138 less) | | | |

Margin of error: 95% confidence interval (CI).
RR: Risk ratio.
MD: Mean difference.
GRADE: Evidence grades of the GRADE Working Group (see later).

*The risk **WITHOUT lidocaine** is based on the risk in the control group of the trials. The risk **WITH lidocaine** (and its margin of error) is calculated from relative effect (and its margin of error).
** Approximate median of the control group in the trials included in the meta-analysis

[1] The certainty of the evidence was downgraded in one level due to inconsistency.
[2] The certainty of the evidence was downgraded in one level due to risk of publication bias.

**About the certainty of the evidence (GRADE)***

⊕⊕⊕⊕

**High:** This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯

**Moderate:** This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate

⊕⊕◯◯

**Low:** This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯

**Very low:** This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.

† Substantially different = a large enough difference that it might affect a decision.

## Other considerations for decision-making

### To whom this evidence does and does not apply

- The results of this summary apply to adult patients without chronic pain, who undergo surgery under general anesthesia including digestive, urological, ginaecological, breast, thoracic, vascular, cardiac, spine, otorhinolaringologic, traumatologic and ophtalmologic surgery.
- We believe this evidence is better applied to patients who undergo abdominal surgeries due to the number of trials evaluating this specific group.

### About the outcomes included in this summary

- The outcomes selected are those considered critical for decision-making by the authors of this summary. Considering the wide variety of outcomes reported by the systematic reviews, the ones who were chosen were considered to be clinically relevant outcomes (considering, for instance, that opioid consumption would be substitute to pain level). In general, they coincide with the outcomes most frequently reported by the identified reviews.
- No substitute outcomes were selected, for instance intraoperative consumption of analgesics.

### Balance between benefits and risks, and certainty of the evidence

- Even though it probably prevents postoperative nausea and vomiting, the application of this intervention is more complex than applying other pharmacological interventions for the prevention of postoperative nausea and vomiting.
- Most trials explicitly excluded patients with a history or suspicion of adverse reactions or hypersensitivity to local anesthetics. Furthermore, as screening for this condition is part of the preanesthetic evaluation, the trials included low-risk patients. Despite this, two systematics reviews [6],[8] reported secondary effects related to lidocaine, which were considered mild and did not require therapeutic intervention.

### Resource considerations

- This intervention probably prevents postoperative nausea and vomiting, but it has a higher cost than other pharmacological alternatives, such as dexamethasone and ondansetron.
- On the other hand, it is an intervention with little or no benefit, so it does not seem reasonable to make an estimation of the balance between costs and benefits.

### What would patients and their doctors think about this intervention

- Faced with the evidence presented in this summary most clinicians should be inclined against the routine use intravenous systemic lidocaine perioperatively.
- Even though there is no clear data in the analyzed evidence, the clinicians may be inclined to use intravenous systemic lidocaine perioperatively as an initial approach when other alternatives for the management of postoperative nausea and vomiting are not possible, or in case the patient requires multiple interventions for the prevention of these symptoms, due to high preoperative risk of this condition or in surgeries where it is desirable to avoid the increase of abdominal pressure postoperatively.

### Differences between this summary and other sources

- Most systematics reviews included in this summary reached similar conclusions regarding time to first flatus, postoperative nausea and vomiting, and pain at rest at 24 hours. On postoperative nausea and vomiting, the reviews that did not find an effect posed the explanation would be the low incidence of the event or the insufficient statistical power to detect this difference. On the outcome pain at rest at 24 hours, only one review [13], exclusively including patients with breast surgery, did not find any difference in the reduction of pain. Lastly, length of stay was the outcome with the least agreement between reviews; about half reported there was a significant effect while the other half did not find this effect.
- The guideline 'Perioperative Use of Intravenous Lidocaine' [71] by the American Society of Anesthesiologists mentions lidocaine is effective but its clinical effect varies between surgeries. It would reduce pain in abdominal, spine and thoracic surgeries, and in open prostatectomy, while it would not be effective in abdominal hysterectomy, total hip arthroplasty, and renal surgery. It also mentions that for other the surgeries the evidence is still limited, and suggests lidocaine may be useful as an adjuvant in enhanced recovery protocols. This conclusion disagrees with our summary, where we found no clinically relevant

effect for pain management in surgeries in general, which is especially applicable to abdominal surgeries.

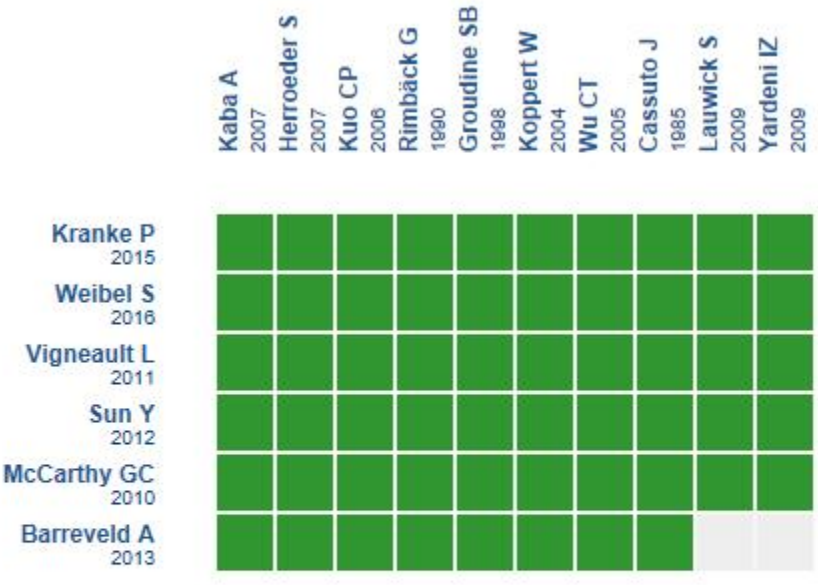
- We found recomendations about the use of this intervention in the guideline 'Acute pain management: scientific evidence' [72] from the Australian and New Zealand College of Anaesthetists (ANZCA). In this guideline it is mentioned that intravenous systemic lidocaine improves pain outcomes, length of hospital stay, postoperative nausea and vomiting, and postoperative ileus in abdominal surgeries, it would also improve pain outcomes in spine surgery. This conclusion disagrees with the conclusions reached in this summary, although the guideline recognizes that probably more evidence is needed for the evaluation of the outcomes in spine surgery.

**Could this evidence change in the future?**

- It is unlikely that future trials change the conclusions presented in this summary on the outcomes pain at rest at 24 hours, time to first flatus, length of hospital stay and postoperative nausea and vomiting, due to the certainty of the evidence.
- We conducted a search in the International Clinical Trial Registry Platform of the World Health Organization, and did not find any ongoing trial addressing this question. In a search in PubMed we identified at least 22 [73],[74],[75], [76],[77],[78],[79],[80],[81],[82],[83],[84],[85],[86],[87],[88],[89],[90],[91], [92],[93],[94] randomized trials that address this issue and are not included in the identified systematic reviews.
- At least four [95],[96],[97],[98] systematics reviews were identified in the International Prospective Register of Systematic Reviews (PROSPERO) that address this question.

### How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.




An evidence matrix is a table that compares systematic reviews that answer the same question.
Rows represent systematic reviews, and columns show primary studies.
The boxes in green correspond to studies included in the respective revisions.
The system automatically detects new systematic reviews including any of the primary studies in the matrix, which will be added if they actually answer the same question.

Follow the link to access the **interactive version:** Intravenous lidocaine versus placebo or no treatment on perioperative analgesia

## Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier.

After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

This article is part of the Epistemonikos Evidence Synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and internal peer review process. Each of these articles corresponds to a summary, denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question, with a friendly format to clinical professionals. Its main resources are based on the evidence matrix of Epistemonikos and analysis of results using GRADE methodology. Further details of the methods for developing this FRISBEE are described here (http://dx.doi.org/10.5867/medwave.2014.06.5997)

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org).

**Potential conflicts of interest**
The authors do not have relevant interests to declare.

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**Author address:**
[1] Centro Evidencia UC
Pontificia Universidad Católica de Chile
Centro de Innovación UC Anacleto Angelini
Avda.Vicuña Mackenna 4860
Macul
Santiago
Chile