# INPLASY PROTOCOL

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**Conflicts of interest:**
**None declared.**

# Perioperative systemic exposure of lidocaine for postoperative pain control: A meta-analysis of randomized clinical trials

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**Review question / Objective:** **This study aims to synthesize evidence on the effects of systemic exposure of lidocaine on postoperative pain control in terms of opioid consumption, and pain scores in adult surgical patients. This study aims to synthesize evidence on the effects of systemic exposure of perioperative lidocaine on the postoperative pain control n in adult surgical patients.**
**Condition being studied:** **Postoperative pain control in adult surgical patients receiving perioperative lidocaine or placebo administration.**
**Main outcome(s):** **Primary outcome: Pain control and Cumulative postoperative opioid (morphine equivalent) consumption at 24 h after surgery.**

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 August 2021 and was last updated on 12 August 2021 (registration number INPLASY202180046).

## INTRODUCTION

**Review question / Objective:** **This study aims to synthesize evidence on the effects of systemic exposure of lidocaine on postoperative pain control in terms of opioid consumption, and pain scores in adult surgical patients. This study aims to synthesize evidence on the effects of systemic exposure of perioperative lidocaine on the postoperative pain control n in adult surgical patients.**

**Rationale:** **Systemic opioids are considered the gold standard for the management of severe postoperative pain. The administration of opioids, however, carries the risk of side effects such as nausea and vomiting, urinary retention, as well as apnoea especially, in obese patients. The**

chronic use of systemic opioids may also lead to abuse and addiction. The perioperative administration of lidocaine has been shown to produce an opioid-sparing effect, but the findings from clinical trials are not conclusive. The relationship between the steady-state plasma concentrations of lidocaine and its opioid-sparing effect is not usually assessed.

**Condition being studied:** Postoperative pain control in adult surgical patients receiving perioperative lidocaine or placebo administration.

## METHODS

**Search strategy:** Relevant studies will be search in the health-related electronic databases of Pubmed, Ovid, Google Scholar, Scopus, Embase and Cochrane Library. We will use keywords ("lidocaine", "lignocaine", "xylocaine", "surg*", "operat*"," pain", "analges*", intravenous", "concentration", "level", "opioid") with appropriate Boolean operators (AND, OR); for example, (Lidocaine OR lignocaine OR lidocaine OR xylocaine) AND (administration, intravenous OR infusion OR bolus OR intravenous* OR systemic) AND (specialties, surgical OR surgery OR postoperative OR perioperative). Search will be limited to published studies in the English language from inception until June 2021.

**Participant or population:** Adult patients underwent non-cardiac major surgeries.

**Intervention:** Perioperative intravenous administration of lidocaine.

**Comparator:** Normal saline or placebo.

**Study designs to be included:** Randomized controlled trials.

**Eligibility criteria:** Inclusion criteria: (a) full-text original studies published in English; (b) studied patients underwent non-cardiac major surgeries and postoperative opioid administration is anticipated. Exclusion criteria (a) No documented lidocaine plasma concentrations. (b) Studies with magnesium or ketamine or regional blocks, (c) Non-randomized controlled trials, editorials, letters, case reports, conference reports, non-human research, and abstracts without full articles.

**Information sources:** Pubmed, Scopus, Embase, and the Cochrane Library.

**Main outcome(s):** Primary outcome: Pain control and Cumulative postoperative opioid (morphine equivalent) consumption at 24 h after surgery.

**Additional outcome(s):** Secondary outcomes: Pain control and cumulative postoperative opioid (morphine equivalent) consumption at 12, 48 h, and up to 72 hours after surgery, the duration of hospital stay, adverse events, and their respective means, standard deviations, or 95% confidence intervals.

**Data management:** The PRISMA 2020 checklist will be used as methodological support for the systematic review. Data extraction: Foong, Keng Wah (FKW), Chaw, Sook Hui (CSH), and Lo, Yoke Lin (LYL) will independently screen the titles and abstracts of the citations from the literature search for relevant articles using Endnote 20 literature management software and retrieve full-text of all relevant articles. If studies have duplicated publications, the maximum amount of data will be extracted from available publications. The FKW, SCH, and LYL will then check the full-text articles and appraised them for eligibility based on the eligibility criteria. The investigators will use a standard excel template that contains: Authors, countries, publication year & participant's characteristics, study design, type of surgery, control, details of lidocaine dosing regimen, sampling times, plasma concentrations, postoperative analgesic consumption, postoperative recovery outcomes, and outcome measurements, their means, standard deviations, and 95% confidence intervals from the included trials. Any discrepancies between data extracted by the three investigators will be discussed and the decision is made by consensus. If there is a dispute, a fourth rater, Loh, Pui San (LPS)

will be consulted until consensus is achieved. If important data are missing or are ambiguous, corresponding authors will be contacted to get additional information.

**Quality assessment / Risk of bias analysis:** Three independent reviewers FKW, CSH, and LYL will assess the quality of eligible records using the Cochrane Risk of Bias Tool. Any discrepancy will be resolved by consensus with a fourth investigator, LPS. A summary of the quality of evidence for each outcome will be presented using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) framework.

**Strategy of data synthesis:** In each included study, pain relief will be analyzed at 12, 24, 48, and 72 hours following surgery. The cumulative consumption of postoperative opioids will be estimated using morphine equivalence. The heterogeneity of the included studies will be evaluated with I2 coefficient and predetermined limits for low (25-49%), moderately (50-74%), and high (> 75%) levels. A random-effect model will be applied when the heterogeneity was moderate or high, otherwise, a fixed effect module will be employed. Data synthesis will be performed by conducting a meta-analysis using the Metafor package with the R statistical software environment.

**Subgroup analysis:** If data permit, subgroup analyses by different body mass indices (BMIs) or different types of surgery will be carried out.

**Sensitivity analysis:** We will analyze again articles excluding poor-quality studies. If more than 10 studies are included, we will investigate publication bias by visual inspection of the funnel plot symmetry. If the heterogeneity is apparent, sensitivity analysis is used to explore the source of heterogeneity.

**Language:** English.

**Country(ies) involved:** Malaysia.

**Other relevant information:** The strength of the body of evidence will be evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guideline.

**Keywords:** Lidocaine, systematic review, meta-analysis, opioid consumption, pain score, postoperative outcome.

**Contributions of each author:**

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