Systematic Review and Meta-Analysis

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Perioperative lidocaine infusions for the prevention of chronic postsurgical pain: a systematic review and meta-analysis of efficacy and safety

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Abstract

Chronic postsurgical pain (CPSP) occurs in 12% of surgical populations and is a high priority for perioperative research. Systemic lidocaine may modulate several of the pathophysiological processes linked to CPSP. This systematic review aims to identify and synthesize the evidence linking lidocaine infusions and CPSP. The authors conducted a systematic literature search of the major medical databases from inception until October 2017. Trials that randomized adults without baseline pain to perioperative lidocaine infusion or placebo were included if they reported on CPSP. The primary outcome was the presence of procedure-related pain at 3 months or longer after surgery. The secondary outcomes of pain intensity, adverse safety events, and local anesthetic toxicity were also assessed. Six trials from 4 countries (n = 420) were identified. Chronic postsurgical pain incidence was consistent with existing epidemiological data. Perioperative lidocaine infusions significantly reduced the primary outcome (odds ratio, 0.29; 95% confidence interval, 0.18-0.48), although the difference in intensity of CPSP assessed by the short-form McGill Pain Questionnaire (4 trials) was not statistically significant (weighted mean difference, −1.55; 95% confidence interval, −3.16 to 0.06). Publication and other bias were highly apparent, as were limitations in trial design. Each study included a statement reporting no adverse events attributable to lidocaine, but systematic safety surveillance strategies were absent. Current limited clinical trial data and biological plausibility support lidocaine infusions use to reduce the development of CPSP without full assurances as to its safety. This hypothesis should be addressed in future definitive clinical trials with comprehensive safety assessment and reporting.

Keywords: Chronic pain, Lidocaine, Postoperative pain

1. Introduction

Chronic postsurgical pain (CPSP) occurs in 12% of mixed surgical populations[7] and affects up to half of patients undergoing high-risk procedures.[12,23] Strategies designed to reduce the human, public health, and financial burden of CPSP are therefore a high priority for perioperative research.[5,10] A range of pharmacological interventions have been investigated in small trials for efficacy in attenuating CPSP, including *N*-methyl-D-aspartate (NMDA) receptor antagonists, gabapentinoids, corticosteroids, and nonsteroidal anti-inflammatory drugs. However, a Cochrane systematic review and meta-analysis in 2013 reported that, beside techniques of regional anesthesia,[1] the only systemic drug with encouraging albeit limited evidence to support a reduced incidence of CPSP at 6 months was intravenous ketamine.[8] To address the potential of this drug, a large, international, multicenter trial of perioperative ketamine infusions with CPSP as the primary outcome is scheduled to commence in 2018.[35]

In the Cochrane review in 2013, only a single trial reported on systemic lidocaine administration in relation to CPSP. Since then, investigators have increasingly explored this amide local anesthetic agent in surgical patients, as it stands to modulate many of the pathophysiological processes involved in the development of chronic pain. In a similar fashion to ketamine, lidocaine reversibly antagonizes human NMDA receptors expressed in ex vivo models.[14] This effect is significant and apparent at lidocaine concentrations well within the range of plasma concentrations achieved clinically. The NMDA receptor in the spinal dorsal horn plays a critical role in neuroinflammation[20] and hyperalgesia,[34] phenomena that develop in response to repetitive peripheral nociceptive inputs and underpin chronic pain states. Lidocaine has the added benefit of reducing peripheral nociceptive input, principally through blockade of voltage-gated sodium channels, but also through antagonism of other receptor systems that modulate peripheral signal transduction.[43] Furthermore, lidocaine exhibits potent anti-inflammatory effects across in vitro and in vivo models.[16,30] Inflammation is a key driver of increased nociceptive inputs that occur with peripheral sensitization and also acts to maintain central sensitization through spinal neuroinflammation.[20]

In clinical settings, systemic lidocaine has been successfully used for the treatment of acute and established chronic pain. A recent meta-analysis concluded a modest but statistically significant reduction of surgical pain severity in the first 4 postoperative hours measured by the visual analogue scale (0-10 cm);

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mean difference −0.84 cm, 95% confidence interval (CI) −1.10 to −0.59.[29] Subgroup analyses indicated that this early analgesic effect was only apparent with higher dose (≥2 mg/kg/hours) infusion regimens. An earlier systematic review also identified that 13 of 16 perioperative studies[3] reported a preventive analgesic effect for intravenous lidocaine (defined as analgesia outlasting 5 and a half times the lidocaine plasma half-life[22]), although pain outcomes beyond the inpatient admission were not assessed. Similarly, in patients with chronic pain, therapeutic lidocaine infusions confer effective analgesia at plasma concentrations around 2 to 3 μg/mL, which often outlasts the systemic presence of lidocaine by days and weeks.[4,6,11] Finally, lidocaine infusions at relevant doses (2 mg/kg/hours) reduce experimentally induced hyperalgesia in healthy volunteers.[27,28] In view of this promising multifaceted biological plausibility, we set out to identify and synthesize the evidence linking perioperative lidocaine infusions and CPSP.

2. Materials and methods

This meta-analysis was registered with the International Prospective Register of Systematic Reviews (PROSPERO 2017: CRD42017078602, http://crd.york.ac.uk/PROSPERO).

2.1. Systemic literature search

We conducted a systematic literature search of MEDLINE and EMBASE through Ovid, PubMed, CINAHL, and the Cochrane-controlled trial register from the date of the database inception to October 11, 2017. Gray literature was also searched using the Open Gray, the Gray Literature Report, and the National Institute Center on Health Service Research and Health Care technology online search functions. To allow for differences in the search functionality and subject headings, we opted to search each database separately. These strategies were in keeping with the validated methods of the Cochrane collaboration and the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) statement. Search terms included combinations of the Medical Subject Headings and free text: Lidocaine (or Xylocaine or Lignocaine), Pain and chronic or persistent or month in combination, and a reference to surgery (Operative, intra-operative, perioperative, postop*, or surg*). Subject headings were exploded to include all relevant subheadings. Search limits included trials in adults (age greater than 18), and there were no language restrictions (the specific search strategies are included in the supplementary materials; available online at http://links.lww.com/PAIN/A582). Two researchers (M.A.B. and A.J.T.) independently screened the articles by their titles and abstracts to identify studies reporting a CPSP outcome. The full text of these articles was then screened according to fixed eligibility criteria.

2.2. Study selection, data extraction, and quality assessment

Published and unpublished studies that met all the criteria were eligible for inclusion. The eligibility criteria comprised: (1) investigation of a lidocaine infusion that commenced preoperatively or intraoperatively with or without a bolus and continued until the end of the case or into the postoperative inpatient admission; (2) the population underwent noncardiac surgery; (3) the study reported a binary pain outcome at 3 months or longer after surgery; and (4) an English language translation of foreign language studies was available through our institutional library. The predetermined primary outcome was the presence of persistent pain of any severity at the point of direct questioning by investigators at 3 months or longer after surgery, and believed to be attributable to that surgery (in line with the current proposed definition of CPSP in *ICD-11*[42]). Nonrandomized controlled trials and studies of those with preexisting pain syndromes at the surgical site were excluded. Secondary outcomes sought from the identified trials included intensity of the chronic pain measured and any safety outcomes reported by the authors.

Two researchers (M.A.B. and A.J.T.) independently examined trial characteristics and outcomes. A predesigned data abstraction form was used to record surgical procedure, sample size, primary and secondary outcomes, lidocaine infusion dosing and duration, the use of additional local anesthesia techniques, and risk adjustment for variables linked to CPSP. Risk of bias was graded according to the Cochrane approach, and a quality assessment was performed using the Jadad scale.[18]

2.3. Statistical analysis

Statistical Analyses were performed using Review Manager Version 5.3 software (The Cochrane Collaboration, 2014). The presence and extent of heterogeneity between studies was assessed with χ^2 and I^2 statistics. Studies were grouped according to type of surgery and high- (≥ 2 mg/kg/hours) or low-dose (<2 mg/kg/hours) lidocaine infusions.

The primary outcome of pain at 3 months or longer was analyzed with a Mantel–Haenszel test, and a P value <0.05 was taken as statistically significant. A random effects model was chosen. Secondary outcomes assessing the intensity of CPSP were also analyzed where possible with the random effects model and reported as weighted mean differences. If a median and interquartile range were presented, the mean and SD were estimated according to established methods.[44]

3. Results

Figure 1 shows the study selection process. Both screening investigators identified 6 eligible randomized trials.[9,13,19,24,25,40] The 19 studies that did not meet eligibility criteria are summarized in the supplementary materials (supplementary Table 1, available online at http://links.lww.com/PAIN/A582). There were no disagreements between the reviewers in relation to the extracted data.

3.1. Study characteristics

Table 1 summarizes the characteristics of the included studies. All 6 studies included a dichotomous assessment of the presence of chronic pain related to surgery at 3 months (4 trials) or 6 months (2 trials), as either a primary or secondary outcome. These dichotomous pain outcomes were defined as any pain attributable to surgery in 5 studies, and as surgical pain scoring above 3 on the Douleur Neuropathique 4 questionnaire in 1 study.[19] These dichotomous data formed the basis of the primary meta-analysis (**Table 1**). In only 3 studies, a chronic surgical pain criterion was the primary outcome.[13,24,40] Two other studies assessed early quality of recovery as the primary outcome,[9,25] and 1 study assessed early morphine consumption as the primary outcome.[19] Four of the 6 studies featured patients undergoing breast surgery, focusing primarily on mastectomy procedures with only 1 trial including wide local excisions.[13] The other 2 studies examined patients undergoing robotic thyroidectomies[9] and those undergoing open nephrectomies.[19]

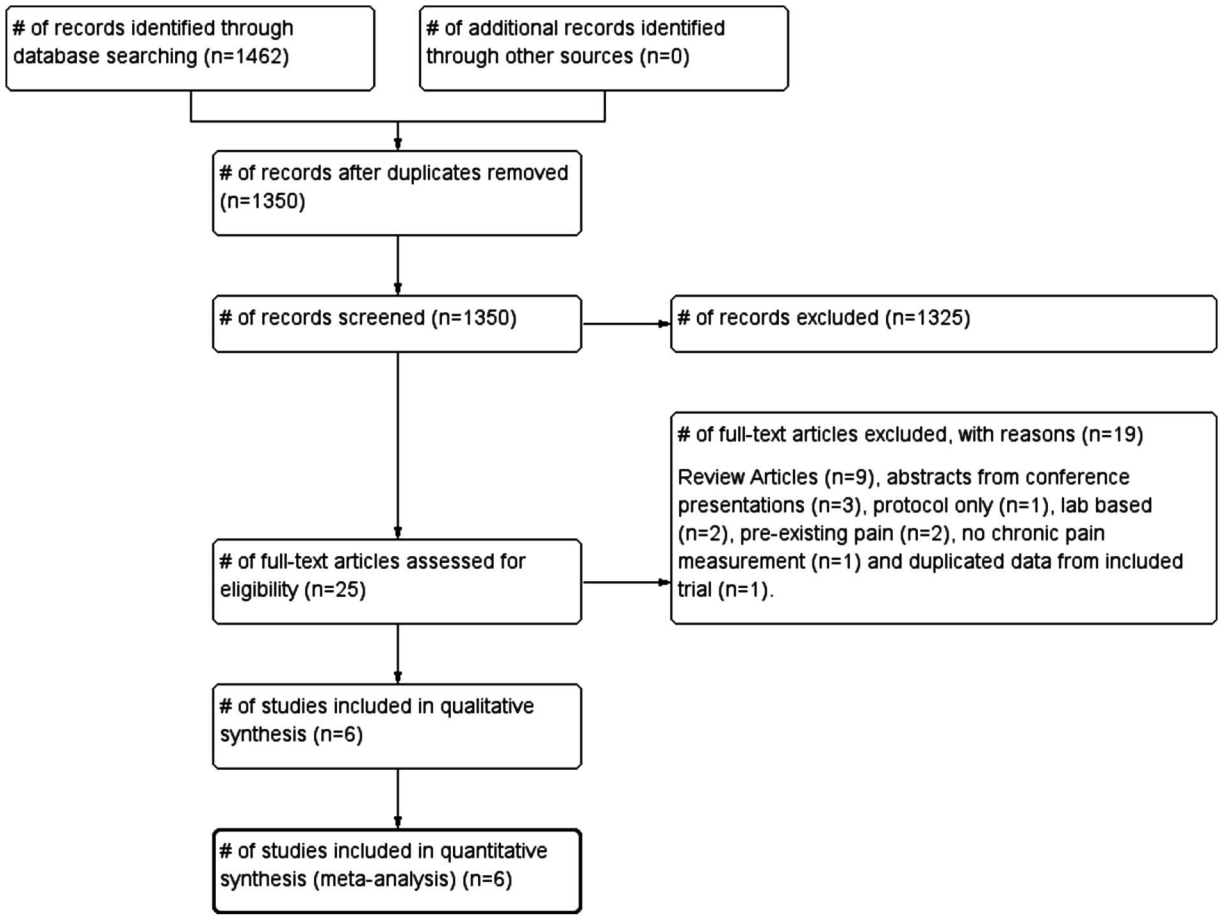

Figure 1. Flow chart of study selection.

In total, the lidocaine trials reporting on a CPSP outcome enrolled 420 patients from 4 different countries, including 296 patients having breast surgery. The range of sample sizes was 36 to 121. Two of the studies were 3-arm trials that in addition to lidocaine and placebo also investigated ketamine and magnesium infusions, respectively.[19,25] The lidocaine regimens all delivered an intravenous bolus around induction of anesthesia (before surgical incision) and an ongoing intravenous infusion that ceased at wound closure (4 studies), 2 hours after arrival in the recovery area (1 study), or 24 hours after surgery (1 study). There were no studies identified where the lidocaine infusion started preoperatively before induction of anesthesia. Bolus doses ranged from 1.5 to 2 mg/kg and infusions ranged from 1 to 3 mg/kg/hours. Only 2 studies were categorized as low dose based on infusion rates <2 mg/kg/hours.

3.2. Outcomes

The incidence of CPSP in patients allocated to a placebo arm ranged from 29% to 47%, with a mean across the 6 trials of 37%. The incidence in patients allocated to the lidocaine arm ranged from 5% to 18%, with a mean of 13%. Perioperative lidocaine infusion resulted in a reduction in the incidence of CPSP (odds ratio [OR], 0.29; 95% CI, 0.18-0.48; $P < 0.00001$), with low heterogeneity according to the I^2 statistic (**Fig. 2**). A similar and statistically significant effect size was apparent for patients undergoing breast surgery (OR, 0.32; 95% CI, 0.18-0.58; $P = 0.0002$) (supplementary materials, Fig. 1, available online at http://links.lww.com/PAIN/A582) and nonbreast surgery (OR, 0.19; 95% CI, 0.05-0.72; $P = 0.01$), although the latter encompassed only 2 trials. The effect size was also significant and consistent across trials categorized as high-dose (4 trials: OR, 0.32; 95% CI, 0.18-0.55; $P < 0.0001$) and low-dose (2 trials: OR, 0.18; 95% CI, 0.04-0.82; $P = 0.03$) lidocaine infusions.

The only secondary pain outcome suitable for meta-analysis was the short-form McGill Pain Questionnaire score, reported in 4 of the 6 trials (**Fig. 3**). This was used as an indicator of the intensity of CPSP when it was present and did not show a statistically significant difference between lidocaine and placebo exposure: weighted mean difference, −1.55 (95% CI, −3.16 to 0.06, $P = 0.06$). In 3 of these 4 studies, the mean McGill Pain Questionnaire score was less than 2 of a possible 45 (15 pain modalities scored between zero and 3).

In each of the 6 studies included, authors explicitly stated that there were no complications nor adverse events attributable to the lidocaine infusions (**Table 2**). No other quantitative nor qualitative data on safety outcomes were reported, and consequently, no meta-analyses were performed. No studies referred to early symptoms nor signs of toxicity, and physiological differences between the groups were not described.

3.3. Bias and quality

The funnel plot indicates that the less precise studies reported a greater reduction of CPSP with lidocaine infusions (**Fig. 4**). Five of 6 trials exhibited a high risk of bias in at least 1 category using the Cochrane approach (**Fig. 5**). Overall, trials were of high quality according to the Jadad scale (**Table 1**).

Table 1

Characteristics of the included studies.

Author, country, journal, year	Surgery type (n)	Lidocaine regime	Other local anesthetic	Risk factors reported/ adjusted	Primary outcome of included study	Secondary chronic pain outcomes of included study	Jadad scale
Grigoras et al., Ireland, The Clinical Journal of Pain, 2012	Mastectomy and WLE (n = 36)	1.5 mg/kg bolus (10 min) then 1.5 mg/kg/hours stopped 60 min after skin closure (mean plasma level 1.11 μg/mL, n = 17)	No	Age Baseline HADS/ PCS Operative factors Adjuvant therapy No statistical adjustment	*Any chronic surgical pain at 3 months*	McGill Pain Questionnaire, PCS, HADS, and peri-incisional hyperalgesia area	5
Terkawi et al., USA, Pain Physician, 2015	Mastectomy only (n = 61)	1.5 mg/kg bolus then 2 mg/kg/hours until 2 hours into PACU (no plasma levels)	No	Age Operative factors Adjuvant therapy Logistic regression model	*Any chronic surgical pain at 6 months*	Use of analgesia and numerical pain score.	5
Kim et al., Korea, PLoS One, 2017	Mastectomy only (n = 78 and 38 more receiving magnesium)	2 mg/kg bolus (15 minutes) then 2 mg/kg/ hours until leaving theatre (no plasma levels)	No	Age Operative factors No statistical adjustment	QoR-40 on day 1	*Presence of any surgical pain at 3 months*, McGill Pain Questionnaire.	5
Kendall et al., USA, Pain Practice, 2017	Mastectomy only (n = 121)	1.5 mg/kg bolus then 2 mg/kg/hours of lidocaine up to 1200 mg or stopped when closure was complete. (no plasma levels)	No	Age Operative factors Adjuvant therapy No statistical adjustment	Chronic pain in keeping with IMMPACT criteria at 3 and 6 months	*Any pain attributable to surgery at 6 months*. BPI, McGill Pain Questionnaire, LANSS at 3 and 6 months.	5
Choi et al., Korea, World Journal of Surgery, 2016	Robotic thyroidectomy (n = 84)	2 mg/kg bolus (15 min) then 3 mg/kg/hours until extubation (no plasma levels)	No	Age/sex Operative factors No statistical adjustment	QoR-40 at 24 hours postsurgery	*Presence of any surgical pain at 3 months*, McGill Pain Questionnaire.	5
Jendoubi et al., Saudi Arabia, Saudi Journal of Anesthesia, 2017	Open nephrectomy (n = 40 plus 20 receiving ketamine)	1.5 mg/kg bolus then 1 mg/kg/hours for 24 hours (no plasma levels)	No	Age/sex Operative factors No statistical adjustment	In-hospital opioid use	*Presence of surgical pain scoring >3 on Douleur Neuropathique 4 (DN4) at 3 months*	4

Outcomes used for primary meta-analysis are italicised.

BPI, Brief Pain Inventory; HADS, Harvard Anxiety Depression Score; IMMPACT, Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials; LANSS, Leeds Assessment of Neuropathic Signs and Symptoms; PACU, post anesthesia care unit; PCS, Patient Catastrophizing score; QoR, Quality of Recovery; WLE, wide local excision.

4. Discussion

The main finding of this meta-analysis is that perioperative lidocaine infusions seem to reduce the incidence of CPSP when assessed between 3 and 6 months after surgery. The effect size is considerable for both breast and nonbreast surgical procedures, indicating that for every 5 patients exposed to lidocaine, at least 1 will be spared the development of CPSP, an absolute risk reduction approximating 22% (OR 0.29, 95% CI 0.18-0.48). This compares favorably with the meta-analysis by Chaparro et al.,[8] which reported limited support for intravenous ketamine to

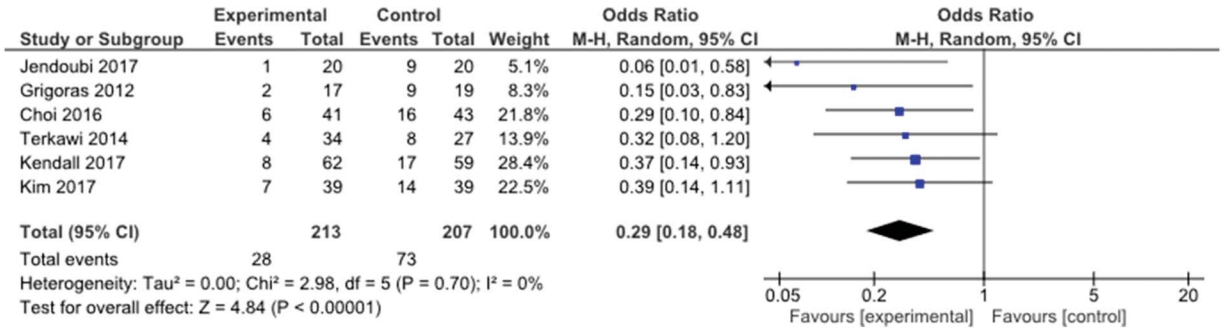

Figure 2. Effect of perioperative lidocaine infusions on CPSP in all surgery types. CPSP, chronic postsurgical pain.

reduce CPSP at 3 months (5 studies, OR 0.74, 95% CI 0.45-1.23) and 6 months (8 studies, OR 0.50, 95% CI 0.33-0.76). The high observed incidence of CPSP in patients allocated to a placebo arm within a lidocaine trial is consistent with the current epidemiological literature.[12,23] The scale of this CPSP problem is often underappreciated outside of clinical trials in the absence of targeted questioning[17] and reinforces the importance of identifying preventive strategies.

The concept that lidocaine can reduce the development of CPSP has multifactorial biological plausibility. Although the pathophysiology of chronic pain is complex and rapidly evolving, current understanding implicates the establishment and maintenance of central sensitization in dorsal horn nociceptive neurons as the key pathological process.[31] Central sensitization is triggered by intense repetitive activation of peripheral pain neurons, is maintained by glial cell–mediated neuroinflammation, and culminates in the experience of increased pain because of painful stimuli (hyperalgesia) and pain even with nonpainful stimuli (allodynia).[20] Persistent low-grade peripheral inputs that can arise after nerve injury from spontaneous neural activity are also sufficient to maintain central sensitization but not to establish it.[26]

Systemic lidocaine stands to modify central sensitization by reducing the initial barrage of nociceptive inputs because of sodium channel blockade and, in a similar fashion to the theory regarding ketamine, by antagonizing the NMDA receptor, a critical mediator and effector of central sensitization.[34] Ex vivo models that express recombinant human spinal NMDA receptors in Xenopus oocytes have demonstrated a dose-responsive reduction of glutamate-/glycine-induced peak currents with exposure to a range of amide local anesthetics.[14] This phenomenon was most marked for lidocaine where at concentrations as low as 1×10^{-7} Molar (0.023 μg/mL), peak currents were 62% of baseline. Indeed, in healthy volunteers, lidocaine infusions reduce experimentally induced hyperalgesia[27,28] at doses (2 mg/kg/hours) that generate total and unbound plasma levels around 2[21] and 0.6 μg/mL, respectively. However, other agents with antagonistic properties at the NMDA receptor have failed to translate biological plausibility into a clinical reduction in CPSP, most notably nitrous oxide.[7] Non-NMDA lidocaine actions may also therefore be important, including antagonism of other receptor types that contribute to peripheral and central sensitization, such as G-protein-coupled receptors.[43] Furthermore, lidocaine exhibits potent anti-inflammatory effects in vitro and in vivo.[16] Consequently, it may act to reduce both peripheral and central sensitization by suppressing inflammation at the site of injury and in the dorsal horn.

Although the potential for lidocaine to modify the pathophysiology underlying the development of CPSP is interesting, the findings of this meta-analysis must be interpreted in the light of the significant limitations of the 6 clinical trials that have been performed to date. They are all relatively small, single-center studies, with 5 of these showing a high risk of bias in at least 1 area according to the Cochrane approach to bias assessment. This observation is corroborated by the marked asymmetry of the funnel plot. Furthermore, only 3 trials examined CPSP as a primary outcome. Although assessment using the Jadad scale suggests that these trials are of high quality, these scores do not reflect a range of methodological weaknesses that are discussed in more detail below.

The most striking limitation pertains to the small study sample sizes, which in turn limits the risk adjustment that can be performed for genetic, demographic, psychosocial, pain, clinical, and surgical factors that are implicated in the development of CPSP.[36] For breast cancer surgery, comprising 4 of the 6 trials in this meta-analysis, factors including age, axillary dissection, and adjuvant radiotherapy are strongly linked to CPSP.[12] Similarly, in the mixed surgical population of the ENIGMA-II study, a secondary analysis examining CPSP at 12 months identified age, sex, ethnicity, duration of surgery, and wound infection as multivariate predictors.[7] Other baseline factors such as anxiety and the propensity to catastrophize painful sensations have also emerged as potential predictors of CPSP.[41] Only 2 trials in this meta-

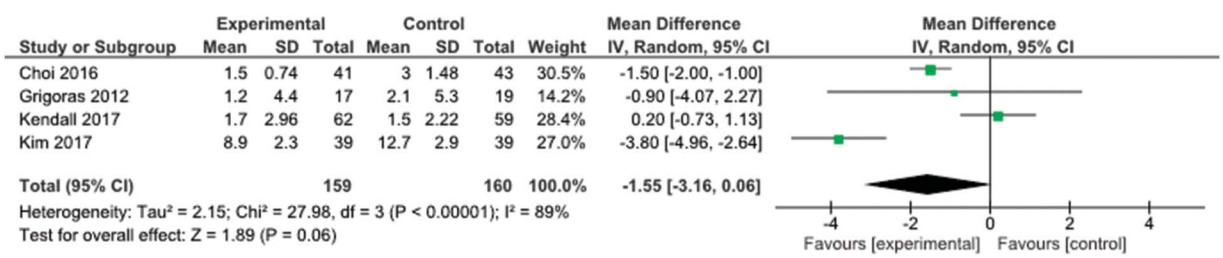

Figure 3. Effect of perioperative lidocaine infusions on pain intensity using the total score derived from the short-form McGill Pain Questionnaire.

Table 2

Acute pain and safety outcomes of the included studies.

Author, country, journal, year, surgery type (n)	Lidocaine regime	Adverse events reported	Monitoring	Acute pain outcomes
Grigoras et al., Ireland, The Clinical Journal of Pain, 2012, mastectomy and WLE (n = 36)	1.5 mg/kg bolus (10 min) then 1.5 mg/kg/hours stopped 60 minutes after skin closure (mean plasma level 1.11 μg/mL, n = 17)	No side effects related to lidocaine were observed	Standard monitoring	VAS pain scores (100 mm) at rest 4 hours postoperatively were less in the lidocaine group compared with the control group (11.8 ± 14.1 vs 29.5 ± 24.7; $P = 0.012$). There were no statistically significant differences in opioid consumption within the first 7 days of surgery.
Terkawi et al., USA, Pain Physician, 2015, mastectomy only (n = 61)	1.5 mg/kg bolus then 2 mg/kg/hours until 2 hours into PACU (no plasma levels)	No toxicity cases were reported in our cohort	Standard monitoring until leaving PACU at which point infusion had been ceased.	Overall, pain scores in both groups were similar with no statistical difference at both rest and on movement. There were no statistically significant differences in postoperative opioid consumption.
Kim et al., Korea, PLoS One, 2017, mastectomy only (n = 78 and 38 more receiving magnesium)	2 mg/kg bolus (15 min) then 2 mg/kg/hours until leaving theatre (no plasma levels)	No adverse or unintended effects were seen in the 3 groups	Standard monitoring	In PACU: Mean (SD) pain NRS (0-10) was 2.8 (0.4) in control vs 2.2 (0.7) in lidocaine ($P < 0.001$). Postoperative day 1: At 6 hours, mean (SD) pain NRS (0-10) was 3.3 (0.9) in control vs 2.8 (0.8) in lidocaine ($P = 0.017$). At 24 hours, mean (SD) pain NRS (0-10) was 2.9 (0.7) in control vs 2.4 (0.7) in lidocaine ($P = 0.001$). There were no statistically significant reductions in opioid consumption.
Kendall et al., USA, Pain Practice, 2017, mastectomy only (n = 121)	1.5 mg/kg bolus then 2 mg/kg/hours of lidocaine up to 1200 mg or stopped when closure was complete (no plasma levels)	No subject experienced an unanticipated adverse event during the study period.	Standard monitoring	There were no statistically significant differences in pain burden, opioid consumption, and quality of recovery between the 2 groups.
Choi et al., Korea, World Journal of Surgery, 2016, robotic thyroidectomy (n = 84)	2 mg/kg bolus (15 min) then 3 mg/kg/hours until extubation (no plasma levels)	No cases of systemic toxicity occurred during this study	Standard monitoring	Difference in VAS (0-10) at 10 minutes into PACU admission (median was 5 in both groups—$P = 0.044$), but at 20 minutes in and at PACU discharge, there were no significant differences. There was no significant difference in opioid consumption.
Jendoubi et al., Saudi Arabia, Saudi Journal of Anesthesia, 2017, open nephrectomy (n = 40 plus 20 receiving ketamine)	1.5 mg/kg bolus then 1 mg/kg/hours for 24 hours (no plasma levels)	There were no notable lidocaine-related adverse effects. No patients complained of hallucinations or dysphoria	Patients were managed in the surgical ward without ongoing cardiac monitoring.	The VAS (0-10) scores at rest, during movement, and during coughing were statistically different until 48 hours post-op. The difference was greatest in PACU (7 vs 3—estimated from figures) and declined thereafter. There was a statistically significant difference in morphine PCA usage with the lidocaine group requiring a mean (SD) of 27.8 mg (5.51) during the admission compared with 47.6 mg (4.98) in the control group.

NRS, numerical rating scale; PACU, post anesthesia care unit; PCA, patient-controlled analgesia; VAS, visual analogue scale; WLE, wide local excision.

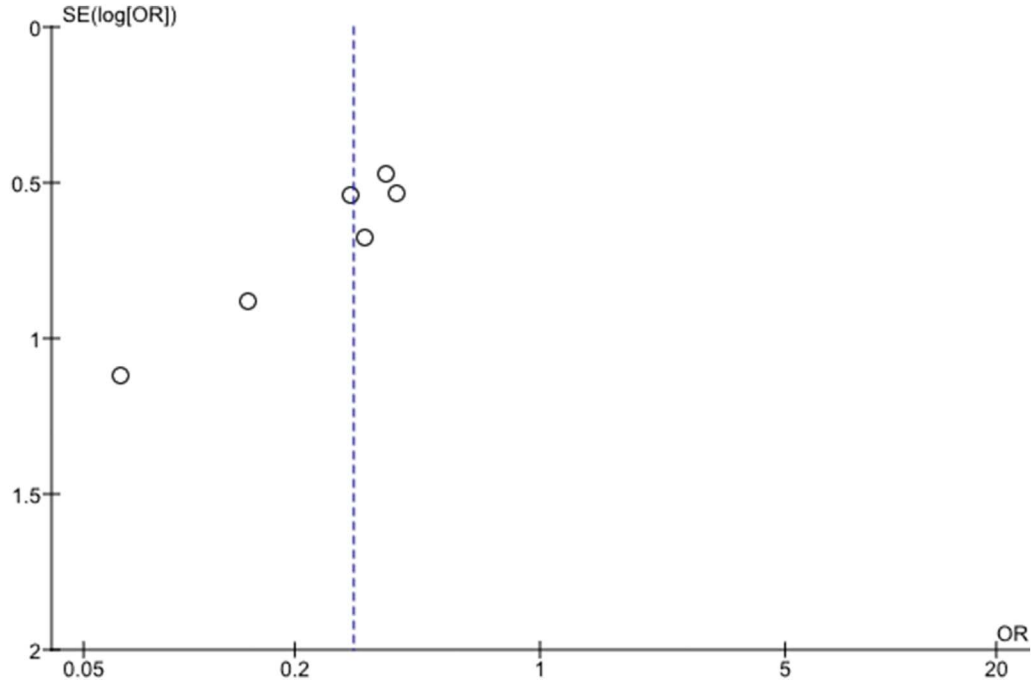

Figure 4. Funnel plot of studies investigating CPSP (yes/no) as a primary or secondary outcome. CPSP, chronic postsurgical pain; OR, odds ratio.

analysis report patient and procedure-specific risk factors comprehensively, and neither of these go on to perform a risk-adjusted statistical analysis (**Table 1**). Furthermore, hereditary predispositions towards chronic pain states[47] may influence the impact of lidocaine on the development of CPSP, and this is yet to be explored.

The component trials in this meta-analysis also demonstrate that simplistic assessments of CPSP do not illuminate the true public health burden of the condition. Four of 6 trials used pain outcomes at 3 months, with only 2 trials assessing pain outcomes at 6 months. Although such early CPSP remains important to the patient, pain assessment at 6 months and beyond is more relevant to an assessment of chronic disablement and allows for better adjustment for adjuvant cancer therapies. Moreover, the intensity of the CPSP detected in this meta-analysis is low (**Fig. 3**). This may reflect that these early CPSP trials have focused on operative procedures that are associated with a high incidence rather than a high severity of CPSP, to have sufficient power within a limited sample size. Kendall et al. focused on important CPSP after breast surgery by applying the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) criteria to detect pain that limits physical and emotional functioning. Although they reported a significant reduction in "yes or no" CPSP at 6 months with perioperative lidocaine, the incidence of CPSP meeting IMMPACT criteria was low, and no difference in the lidocaine and placebo arms (3% vs 3%, $P = 1.0$). For breast surgery linked to low severity chronic pain, it is clear that even a modest therapeutic effect with lidocaine may translate into more patients being completely free of CPSP. The efficacy of perioperative lidocaine for surgical procedures linked to severe CPSP (spinal surgery, orthopedics, and major plastics reconstruction[7]) remains unknown.

Another important limitation of the lidocaine literature reporting on CPSP is an absence of trials explicitly stating the use of parallel local anesthetic techniques that would normally comprise routine practice, namely wound infiltration or regional analgesia with longer-acting amide local anesthetic agents. This theme is also strongly apparent in the far greater number of trials (n = 45) examining perioperative lidocaine for the reduction of acute pain,[29] and likely reflects uncertainty about the risk of additive local anesthetic toxicity.[33] However, it is possible that routine local anesthetic techniques may themselves modify the CPSP development, by attenuating early peripheral nociceptive signal generation at the site of injury.[1] Furthermore, a class effect for amide local anesthetics absorbed into the systemic circulation cannot be ruled out.[39]

The optimal dosage and duration of systemic lidocaine administration for the reduction of CPSP is also unclear, and this is reflected by the considerable variation within the 6 trials examined. In a meta-analysis of perioperative lidocaine for the reduction of acute pain, infusions at 2 mg/kg/hours or above seemed effective, whereas lower doses did not.[29] We examined this threshold in our subgroup analyses, but the data proved difficult to interpret given the low number of trials. As there is a clear associative link between acute and chronic pain,[37] and patients with established chronic pain derive analgesia during lidocaine infusions when plasma concentrations reach 2 to 3 μg/mL,[11] higher dosing regimens in CPSP trials warrant investigation. The proposed mechanisms by which lidocaine modifies the pathophysiology that underpins CPSP also point towards greater efficacy with prolonged lidocaine exposure. In this respect, perioperative lidocaine infusions extending up to 24 hours after surgery for the reduction of acute pain are well described in a recent systematic review.[45] Yet, only one trial in this CPSP meta-analysis extended lidocaine exposure beyond the recovery room.[19] This may reflect that many operative procedures associated with a high incidence of CPSP occur in day surgery (eg, inguinal hernia repair) or short-stay (breast wide local excision) units, and this imposes practical limitations on infusion durations.

Finally, clinicians considering interventions for the reduction of CPSP must weigh up the balance between risks and benefits. In particular, systemic lidocaine has the potential to cause local anesthetic toxicity. As plasma concentrations increase, toxicity

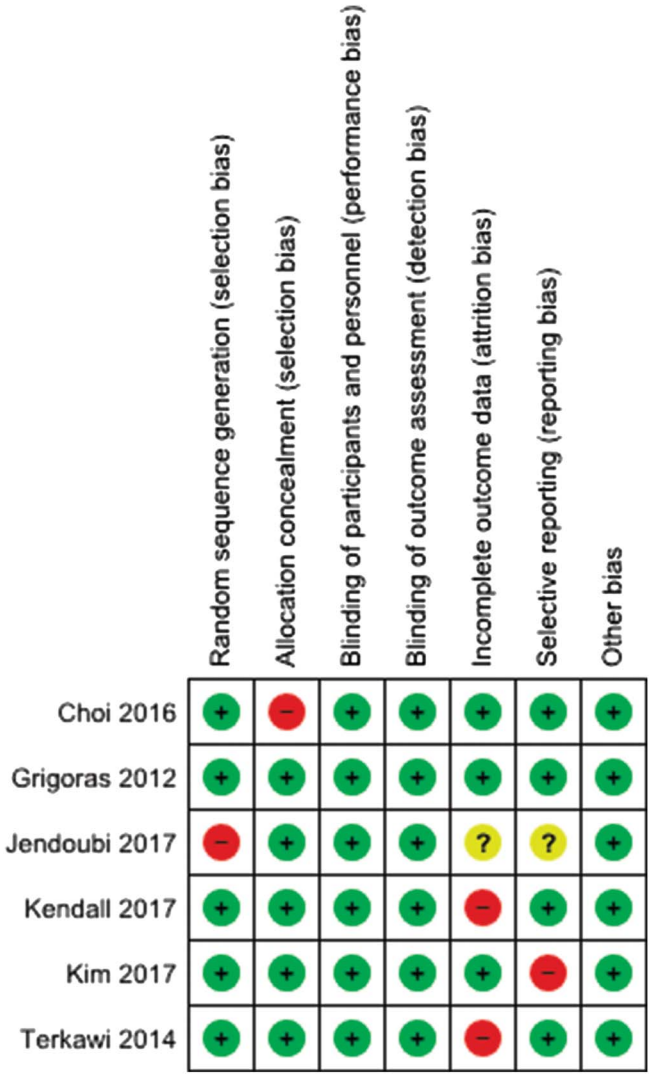

Figure 5. Cochrane collaboration risk of bias.

manifests first as sensory disturbances (more likely above 5 μg/mL), then seizures (more likely above 10 μg/mL), and at extremely high levels, cardiovascular collapse.[2] Some institutions mandate high dependency care or continuous cardiac monitoring when infusions outlast the recovery area and others do not. Although no safety outcomes could be meta-analyzed in this work, the 6 studies reviewed all used standard care monitoring strategies and explicitly reported an absence of adverse events related to lidocaine exposure (**Table 2**). Similarly, in the Cochrane Review of 45 lidocaine trials (n = 2802) reporting primarily on acute postoperative pain and recovery, adverse events were collated as a secondary outcome.[29] Again, these were not amenable to meta-analysis but were described qualitatively. The authors report that only 17 trials systematically analyzed the occurrence of safety outcomes, and there was no evidence that intravenous lidocaine was associated with an increased risk of adverse events such as death, arrhythmias, other heart rate disorders, or lidocaine toxicity. Indeed, even in massive inadvertent overdose (a 10-fold dosing error leading to 1 g administration on induction) in a recent trial, only transient hypotension was described.[46] Despite these reassuring findings, the limitations of lidocaine trials to date with respect to safety surveillance and reporting should be addressed in future work with a structured, quantifiable toxicity questionnaire and clear documentation of differences in physiological observations. Furthermore, off-target effects of lidocaine through, eg, immune alterations have not been fully evaluated using global measures of patient outcomes. Until this knowledge gap with respect to safety is bridged by future trials, the risk of perioperative lidocaine infusions at a population level remains uncertain. This needs to be addressed before this strategy is likely to receive strong recommendations from guideline developers.

In conclusion, the findings of this meta-analysis are consistent with the concept that systemic lidocaine administration reduces the development of CPSP. However, several important limitations are apparent in the trials performed to date and higher quality evidence is required before a widespread change in practice is justified. Indeed, meta-analyses reporting a positive effect for an intervention are rarely corroborated in subsequent definitive large-scale trials,[32,38] and it has been argued that the primary purpose of a meta-analysis is in hypothesis generation rather than hypothesis testing.[15] Although there are a number of registered trials currently investigating perioperative lidocaine with CPSP as the primary outcome (NCT01619852 and NCT02862769), it is our view that none are sufficiently powered to detect the most plausible outcome of a small to moderate benefit or harm. The hypothesis that perioperative lidocaine reduces CPSP should therefore be tested in a large, definitive, multicenter clinical trial that overcomes the limitations identified to date by measuring safety outcomes in detail.

Conflict of interest statement

The authors have no conflict of interest to declare.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/A582.

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