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Review Article

Efficacy and safety of intravenous lidocaine for postoperative analgesia and recovery after surgery: a systematic review with trial sequential analysis†

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Abstract

Background: Improvement of postoperative pain and other perioperative outcomes remain a significant challenge and a matter of debate among perioperative clinicians. This systematic review aims to evaluate the effects of perioperative i.v. lidocaine infusion on postoperative pain and recovery in patients undergoing various surgical procedures.

Methods: CENTRAL, MEDLINE, EMBASE, and CINAHL databases and ClinicalTrials.gov, and congress proceedings were searched for randomized controlled trials until May 2014, that compared patients who did or did not receive continuous perioperative i.v. lidocaine infusion.

Results: Forty-five trials (2802 participants) were included. Meta-analysis suggested that lidocaine reduced postoperative pain (visual analogue scale, 0 to 10 cm) at 1–4 h (MD −0.84, 95% CI −1.10 to −0.59) and at 24 h (MD −0.34, 95% CI −0.57 to −0.11) after surgery, but not at 48 h (MD −0.22, 95% CI −0.47 to 0.03). Subgroup analysis and trial sequential analysis suggested pain reduction for patients undergoing laparoscopic abdominal surgery or open abdominal surgery, but not for patients undergoing other surgeries. There was limited evidence of positive effects of lidocaine on postoperative gastrointestinal recovery, opioid requirements, postoperative nausea and vomiting, and length of hospital stay. There were limited data available on the effect of systemic lidocaine on adverse effects or surgical complications. Quality of evidence was limited as a result of inconsistency (heterogeneity) and indirectness (small studies).

Conclusions: There is limited evidence suggesting that i.v. lidocaine may be a useful adjuvant during general anaesthesia because of its beneficial impact on several outcomes after surgery.

Key words: anaesthesia; lidocaine; outcome; pain; postoperative period

† This review is an abridged version of a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2015, Issue 7, DOI: CD009642 (see www.thecochranelibrary.com for information).[1] Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review.

Editor's key points

- I.V. lidocaine may be a simple and safe adjunctive analgesic technique for some surgeries.
- This complete and complex systematic review collates all relevant, reliable evidence to show that there are likely to be some benefits in perioperative practice.
- The trial sequential analysis reassures us that sufficient evidence is available for some outcomes (but not others).

Common problems immediately after surgery include postoperative pain, nausea and vomiting, ileus, hypercoagulation, and postoperative cognitive dysfunction.[2] Evidence suggests that pain and ileus causing a prolonged hospital stay are major cost drivers in the postoperative period.[3] Fast-track protocols aim to prevent or reduce these complications and speed up early recovery. Opioid medications that are given either i.v. (systemic analgesia) or via epidural catheters (epidural analgesia) to reduce postoperative pain can provoke side-effects including nausea and constipation, slowing postoperative recovery. In addition, recent evidence questions the benefit of epidural analgesia for some patients and types of surgery (e.g. laparoscopic procedures, lower abdominal surgery or patients without pre-existing lung disease), as serious neurologic complications after placement of an epidural catheter, seem to occur more frequently than originally thought.[4–6] Therefore, alternative therapeutic interventions for optimal perioperative care are desirable and may add to the existing analgesic armamentarium.

Postoperative pain can be a mixture of inflammatory and neuropathic pain, often presenting as an increased sensitivity to pain. These are targets of i.v. lidocaine. Numerous other clinical relevant outcomes are thought to be influenced by the administration of lidocaine, including wound-healing, analgesia, coagulation, postoperative cognitive dysfunction, and ileus.[7] By characterizing the beneficial effects of i.v. lidocaine in the perioperative setting, lidocaine may offer a safe and alternative strategy to epidural analgesia for improving perioperative outcome.

The objective of this review was to systematically evaluate the benefits and risks of systemic perioperative lidocaine infusion for an enhanced postoperative recovery, in terms of postoperative pain, gastrointestinal recovery, postoperative opioid consumption, and opioid-related side-effects such as postoperative nausea and vomiting (PONV). This co-publication aims to display an abridged summary of the main research result of the Cochrane Review and intends to disseminate the research findings amongst anaesthetists. In addition, we have explored the reliability of the estimated (positive) treatment effects by information size considerations and adjusted significance thresholds (trial sequential analysis).

Methods

Protocol and registration

The present review is based on a review protocol previously published in the Cochrane Database of Systematic Reviews.[8] Differences between protocol and review are listed in the web-Appendix (supporting information 1).

We have prepared the current manuscript according to the guidelines published by The Cochrane Collaboration,[9] the PRISMA statement for systematic reviews and meta-analysis,[10] and the BJA guidelines.

Eligibility criteria

We included randomized controlled trials which evaluate the effect of i.v. lidocaine infusion on postoperative pain and recovery, in adult patients undergoing surgery on any body part(s) under general anaesthesia. Eligible comparators were either placebo, or no treatment, or epidural analgesia. The lidocaine infusion had to be started intraoperatively before incision and continued at least until the end of the surgical procedure or during the postoperative period. Study-specific outcomes were not considered as criteria for inclusion or exclusion into the current systematic review.

Information source

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 5 2014), MEDLINE (January 1966 to May 2014), EMBASE (1980 to May 2014), CINAHL (1982 to May 2014) and reference lists of articles. We searched the trial registry database clinicaltrials.gov, contacted researchers in the field, and hand-searched journals and congress proceedings. We did not apply any language restrictions.

Search

The search strategy was developed by the Cochrane Anaesthesia, Critical and Emergency Care Group (ACE). The search strategy used for MEDLINE is presented in the web-Appendix (supporting information 2).

Study selection

Three authors scanned the titles of the initial search to exclude irrelevant trials. Two authors independently checked for eligibility of the identified studies according to the PICO (patient, intervention, comparison, and outcome) framework.

Data collection process

Authors independently extracted the data of the included studies as tandems. If there were missing data such as standard deviations, we contacted the authors of the relevant study.

Data items

Data were extracted using a standardized data extraction form based on PICO containing inclusion and exclusion criteria, patient's characteristics, type of surgery, details on lidocaine administration and the investigated comparator, anaesthesia regimen, follow-up, concomitant medication, funding. Data on the following relevant clinical outcomes were extracted:

Primary outcomes

1. Pain score (0–10 cm, 0–100 mm VAS, numeric rating scale (NRS), verbal rating scale (VRS))
2. Postoperative ileus (dichotomous).
3. Functional gastrointestinal recovery (either time to defecation, time to first flatus, or time to first bowel movement/sounds).

Secondary outcomes

1. Length of hospital stay
2. Surgical complication (postoperative infections, thromboembolism, wound breakdown, etc.)
3. Adverse events (e.g. death, arrhythmias, other heart rate disorders, signs of lidocaine toxicity)
4. Postoperative nausea and vomiting (PONV)

5. Intra- and postoperative opioid requirements
6. Functional postoperative neuropsychological status scale
7. Patient satisfaction
8. Cessation of the intervention

In the current version of this systematic review only the results of those outcomes that could be analysed in a quantitative meta-analysis were included. Criteria for performing a meta-analysis were clinical combinability of data and at least two reporting studies. Further, in the current manuscript emphasis was put on meaningful results to guide clinical decision-making. The full range of analysed outcomes was described in the full report of the Cochrane review.[1]

Risk of bias in individual studies

Two authors independently assessed the methodological quality of the individual studies according to the criteria of the Cochrane Collaboration.[9] The standard risk of bias domains included random sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, and selective reporting. We classified each domain on the study level as being either: low risk of bias, high risk of bias or unclear risk of bias.

Summary measures and synthesis of results

Data were analysed using Review Manager, version 5.3.5 (RevMan, The Cochrane Collaboration, Oxford, United Kingdom). We pooled studies for meta-analysis which compared i.v. perioperative lidocaine either with no treatment, or placebo, or with an active comparator, namely epidural analgesia.

For the outcome pain we combined all data presented on either VAS 0–10 cm, VAS 0–100 mm, NRS 0–10, and VRS 0–10 and transformed all into VAS 0–10 cm and presented the effect estimates as mean differences (MD).

For the outcomes intra- and postoperative opioid requirements all different opioid quantities were transformed into i.v. Morphine Equivalents (MEQ in mg) as described in detail elsewhere (http://www.whocc.no/atc_ddd_index).

Dichotomous data were extracted as reported in the original trials and the relative risk (RR) with 95% confidence intervals (CI) were calculated at the study level, from the intervention and control event rates and combined using the inverse variance approach as statistical method. Continuous data were extracted as means with standard deviations (SD) or standard errors (SE) and median with interquartile range (IQR). The median with interquartile range (IQR) was transformed into mean with SD and SE was transformed into SD according to the recommendations published by Higgins.[9] MDs were calculated at the study level and pooled into weighted (according to the inverse of the reported variance) MDs with 95% CI. RRs with the range of the lower and upper bounds of the 95% CI not crossing one and MDs with the range of the lower and upper bounds of the 95% CI not crossing zero were considered as statistically significant effect sizes.

We used the random effects model to analyse the data according to the assumption that clinical heterogeneity existed between the analysed patient populations, interventions and clinical settings.[11]

We assessed clinical and methodological heterogeneity of included studies to decide whether the studies were sufficiently homogenous to be combined. Furthermore, we reported statistical heterogeneity using the I^2 statistics. Heterogeneity was classified according to the interpretation described within the *Cochrane Handbook of Systematic Reviews of Interventions*.[9]

Additional analyses – assessment of the evidence

We performed subgroup analysis to consider the magnitude of clinical heterogeneity. Data were analysed using the random-effects model heterogeneity I^2 statistic to compare different subgroups of surgical procedures (open abdominal, laparoscopic-abdominal, and other surgery).

To assess the robustness of the results we performed a sensitivity analysis investigating the impact of high risk of bias studies.

We assessed the risk of bias across studies (publication bias) for the outcomes pain 'early', postoperative opioid consumption, and PONV 'late'. We created funnel plots which served as a visual tool for detecting risk of bias across studies, which may indicate reporting bias and small study effects. In addition, the relation of treatment effect and study size was further analysed by linear regression analysis, by methods of moments using an arcsine transformation for RR and weighted regression for MD.

In a *post hoc* analysis, we applied trial sequential analysis[12] as cumulative meta-analyses are at risk of producing type *I* errors, as a result of sparse data and repetitive testing of accumulating data.[13–16] The required information size (IS; the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) and the sequential monitoring boundaries (testing for statistical significance before the IS has been reached) provided us with relevant information to estimate the level of evidence for the experimental intervention. The required IS was derived using the formula $IS=2\times(Z_{1-\alpha/2}+Z_{1-\beta})^2\times2\times\sigma^2/\delta^2$ where $Z_{1-\alpha/2}$ and $Z_{1-\beta}$ are the $(1-\alpha/2)$ and $(1-\beta)$ standard normal distribution quantiles. For binary data, $\delta=P_C-P_E$ denoted an estimate for a realistic important intervention effect (P_C and P_E being the proportion with an outcome in the control group and in the intervention group, respectively) and σ^2 is the associated variance. For continuous data, δ denoted an estimate of the realistic difference between means in the two intervention groups and σ^2 denoted the associated variance. The trial sequential monitoring boundaries also known as O'Brien-Fleming monitoring boundaries were based on the Lan-DeMets α-spending function.

On the basis of a risk for a type *I* error of 5% and a type II error of 10% (90% power) and the following assumptions for the outcomes pain (assumed MD on the basis of a clinical relevant estimate: MD=−1.0 (VAS 0–10 cm), SD=2), opioid consumption (assumed MD on the basis of the low-risk of bias studies by Bryson and colleagues,[17] De Oliveira and colleagues,[18 19]: MD=−8.97 mg (MEQ), SD=25.12), and PONV (clinically relevant estimate of RRR 20% and an incidence of 30% in the control arm), we estimated the required IS and constructed the trial sequential monitoring boundaries, using the TSA software v0.9 Beta (Copenhagen Trial Unit). High risk of bias trials (defined as: high risk at least in one risk of bias domain or unclear risk of bias in all domains) were excluded from the analysis. All information sizes were heterogeneity adjusted by using the estimate of diversity D^2 (assumed D^2=25%) and multiplying the required IS by 1 $(1-D^2)^{-1}$.[12] This may correspond to the heterogeneity adjustment in a multi-centre trial. We performed TSA for both the pooled meta-analysis and the individual subgroups (open abdominal, laparoscopic-abdominal, and other surgeries). TSA results were graphically presented. The cumulative *Z*-curves (green) were constructed, with each cumulative *Z*-value calculated after the addition of a new trial according to publication date. *Z*-values on the upper half of the y-axis indicate benefit of the intervention, whereas *Z*-values on the lower half indicate harm. Crossing of the two-sided *Z*=+1.96 and *Z*=−1.96 (pink

lines) provides a traditionally significant result (p=0.05). For the positive half of the y-axis the red inward-sloping lines represented the trial sequential monitoring boundaries and the red upward-sloping lines displayed the futility boundaries. The monitoring boundaries quantify the risk of random error at any meta-analytical stage and are conservative boundaries at early stages when large fluctuations in meta-analyses occur, as a result of random error and heterogeneity. Crossing of monitoring boundaries is needed to obtain reliable evidence.

To assess the validity of TSA results based on clinically relevant estimates we performed a sensitivity analysis and conducted TSA with the empirical pooled estimates and the model-variance-based heterogeneity correction.

Results

Study selection

We identified 4 162 records through database searching (15th of May 2014) and 798 records by searching clinicaltrials.gov and reference lists of the included studies and related review articles (Fig. 1). After removal of duplicates we retrieved 2883 records and selected 65 full-text articles for assessment of eligibility. Eighteen articles were excluded and the remaining 45 studies (and two co-publications) were included in the qualitative synthesis of this review, whereby 42 studies contribute to the quantitative analysis of the current review.

Of the 45 included studies, one trial was published in Persian,[20] all others were published in English. For one study we only obtained the abstract.[21]

Study characteristics

A total of 45 RCTs published between 1985 and 2014 containing data on 2802 participants were included. Of all patients, 1395 received i.v. lidocaine and 1407 participants served as a control. In 41 trials patients in the comparator arm received placebo treatment with saline, in two trials patients remained untreated.[22 23] The remaining two trials used thoracic epidural analgesia with bupivacaine and hydromorphone[24] or morphine[25] as a comparator. The characteristics of the trials were described in the web-Appendix (supporting information 3) and more detailed in the extended version of this systematic review in the Cochrane Database of Systematic Reviews.[1]

Studies were conducted in patients undergoing either open abdominal surgery,[17 24 26–35] or laparoscopic abdominal surgery,[18 19 23 25 36–44] or various other surgical procedures including amongst others cardiac, thoracic, extremity and minor surgical procedures.[20–22 45–61]

The perioperative administration of i.v. lidocaine strongly varied between the studies concerning the dose of the lidocaine bolus (100 mg or 1–3 mg kg^{-1}) and the infusion (1–5 mg kg^{-1} h^{-1} or 2 to 4 mg min^{-1}) and the duration of the infusion (web-Appendix, supporting information 3).

Quantitative meta-analysis was performed for most of the outcomes of interest in the present review. As a result of the lack of either clinical combinability or an insufficient number of studies the pre-specified secondary outcomes 'functional postoperative neuropsychological status scale', 'patient satisfaction', and 'cessation of the intervention' could not be pooled and meta-analysed.

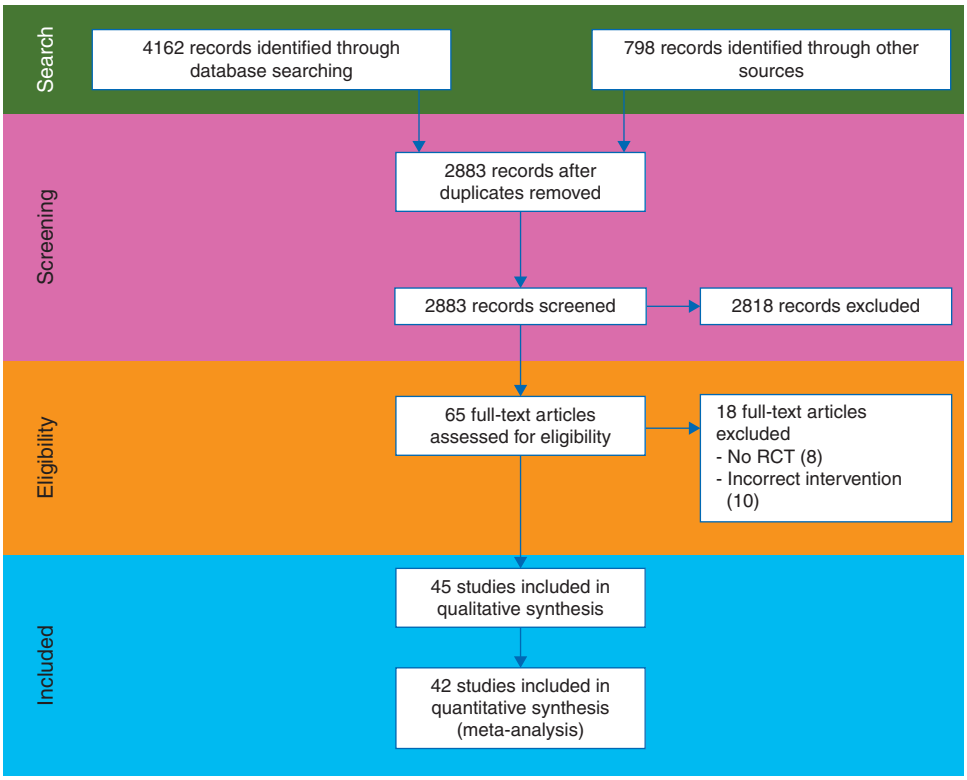

Fig 1 Flow chart of search strategy. (RCT) randomized controlled trials.

Risk of bias within studies

The overall risk of bias concerning selection bias (random sequence generation), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), and attrition bias (incomplete outcome data) revealed low risk of bias in more than 50% of the included studies (Fig. 2). For allocation concealment and selective reporting the quality assessment yielded low risk of bias for only ~20% of the included studies.

The results of the quality assessments on the study level according to the Cochrane Risk-of-Bias assessment tool are graphically presented on the study level in the web-Appendix (supporting information 4).

Synthesis of results

Lidocaine i.v. vs placebo

Primary outcomes. **Postoperative pain (at rest).** Meta-analysis of pain data revealed a significantly lowered pain score (VAS 0 to 10 cm) in the lidocaine group compared with the control group at 1–4 h (MD −0.84, 95% CI −1.10 to −0.59; I^2=86%; 23 RCTs; n=1 286)[17 23 27 29 30 32 35–37 39–46 48 50 51 55 58 61] and at 24 h (MD −0.34, 95% CI −0.57 to −0.11; I^2=91%; 25 RCTs; n=1393)[17 22 23 27 29–32 35–37 39–45 48 50 51 53 55 58 61] after surgery (Table 1). However, at 48 h subjects in the intervention group did no longer benefit from lidocaine administration when compared with subjects in the control group (MD −0.22, 95% CI −0.47 to 0.03; I^2=92%; 19 RCTs; n=1 077)[17 22 29–32 35–37 40–42 44 45 48 50 51 53 61] (Table 1).

Gastrointestinal recovery. Postoperative ileus occurred in 4.8% (5 : 104) of participants in the lidocaine group and in 13.9% (14 : 101) of participants in the control group (RR 0.38, 95% CI 0.15 to 0.99; I^2=0%; 3 RCTs; n=205)[30 43 45] (Table 1).

The administration of lidocaine i.v. did not significantly reduce the time (h) to first defecation in comparison with the control group (MD −9.52, 95% CI −23.24 to 4.19; I^2=85%; 4 RCTs; n=214)[22 30 33 41] (Table 1).

Systemic lidocaine significantly shortened the time (h) to first flatus (MD −5.49, 95% CI −7.97 to −3.00; I^2=88%, 11 RCTs; n=566)[22 30 32 33 36 38–41 49 51] and the time (h) to first bowel movement[31 38 43 49] or sounds[30 44] (MD −6.12, 95% CI −7.36 to −4.89; I^2=0%; 6 RCTs; n=288) in subjects when compared with control subjects (Table 1).

Secondary outcomes. **Length of hospital stay.** I.V. lidocaine administration led to a significant reduction of the length of hospital stay of about 8 h (MD −0.31, 95% CI −0.56 to −0.07; I^2=75%; 21 RCTs; n=1424)[19 22 30–32 36–38 41–45 49–51 53 54 56 57 59] (web-Appendix, supporting information 5).

Surgical complications – postoperative infections. Postoperative infections occurred in 2.16% (3 : 139) of participants in the lidocaine group and in 1.44% (2 : 139) of participants in the placebo-treated group (RR 1.19, 95% CI 0.25 to 5.67; I^2=0%; 4 RCTs; n=278)[38 41 43 45] (web-Appendix, supporting information 5).

Other surgical complications reported by the included studies were urinary retention,[43 45] bleeding,[38 45] anastomotic leak,[30 43]

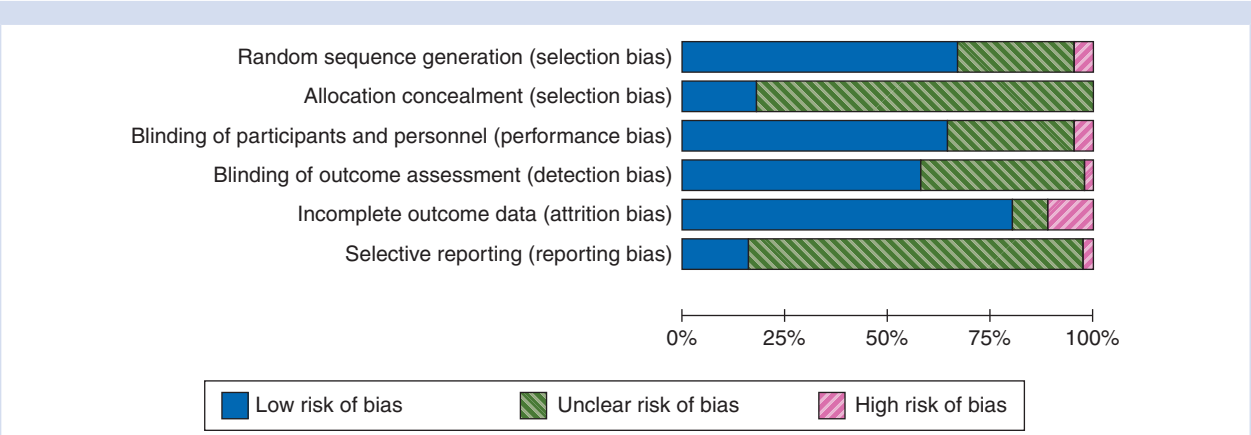

Fig 2 Risk of bias graph. Review authors' judgments about each risk of bias item presented as percentage across all included studies.

Table 1 Primary outcomes – comparison: lidocaine vs control (placebo/untreated). Effect sizes were reported as MD or RR with 95% CI. Effect sizes <0 for continuous data (MD) and <1 for dichotomous data (RR) indicate 'favour of' lidocaine treatment. Pain data were presented at 'early' (1–4 h), 'intermediate' (24 h), and 'late' (48 h) time points postoperatively. Statistical heterogeneity between trials was reported using I^2. IV (inverse variance)

Outcome	No. of studies (participants)	Lidocaine (n)	Placebo (n)	Statistical method	Effect size	Hetero-geneity (I^2)
Pain 'early', (VAS 0–10)	23 (1286)	645	641	MD (IV, Random, 95% CI)	−0.84 [−1.10, −0.59]	86%
Pain 'intermediate', (VAS 0–10)	25 (1393)	696	697	MD (IV, Random, 95% CI)	−0.34 [−0.57, −0.11]	91%
Pain 'late', (VAS 0–10)	19 (1077)	538	539	MD (IV, Random, 95% CI)	−0.22 [−0.47, 0.03]	92%
Postoperative ileus (dichotomous)	3 (205)	104	101	RR (IV, Random, 95% CI)	0.38 [0.15, 0.99]	0%
Time to first defecation (h)	4 (214)	108	106	MD (IV, Random, 95% CI)	−9.52 [−23.24, 4.19]	85%
Time to first flatus (h)	11 (566)	283	283	MD (IV, Random, 95% CI)	−5.49 [−7.97, −3.00]	88%
Time to bowel movement/sound (h)	6 (288)	145	143	MD (IV, Random, 95% CI)	−6.12 [−7.36, −4.89]	0%

thromboembolic disease,[45 49] wound healing disturbances,[30] and need for pyelonephrostomy after renal surgery.[41] None of the studies analysing those complications reported significant differences between the lidocaine and control groups.

Adverse events. Seventeen trials reported that no significant difference in the occurrence of adverse events was observed between the investigated groups during the study.[18 19 27 28 31 37 41–49 53 58] Four trials including patients undergoing cardiac surgeries reported that patients died during the study period.[50 56 57 59] However, none of these events could be plausibly linked to lidocaine administration. One study reported bradycardia in three patients of the lidocaine group[32] and another mentioned arrhythmia in one patient from each group.[40] Lee and colleagues[60] reported on atrial fibrillation and other arrhythmia in both groups after cardiac surgery, however, without significant differences. Three trials reported neuropsychological disturbances in patients of the lidocaine group (e.g. light-headedness) (three patients),[26] dizziness and visual disturbances (one),[55] and drowsiness (two).[34] The remaining trials did not comment on adverse events or lidocaine-related side-effects.

Postoperative nausea and vomiting. At PACU PON/PONV occurred in 20.1% (45 : 218) of participants in the lidocaine group and in 28.4% (63 : 222) of participants in the control group (RR 0.72, 95% CI 0.53 to 0.99; I^2=0%; 7 RCTs; n=440)[19 20 23 29 45 46 48] (supporting information 5). PON/PONV within 72 h postoperatively occurred in 26.6% (154 : 545) of lidocaine subjects and in 35.6% (192 : 539) of control subjects (RR 0.82, 95% CI 0.70 to 0.97; I^2=0%; 21 RCTs; n=1084)[22 23 26 27 29 31–33 36–45 51 55 61] (web-Appendix, supporting information 5).

Postoperative vomiting at PACU appeared in 2.6% (4 : 150) of participants in the intervention group and in 5.8% (9 : 155) of participants in the placebo-treated group (RR 0.49, 95% CI 0.16 to 1.48; I^2=0%; 4 RCTs; n=305)[19 20 29 45] (web-Appendix supporting information 5). At 'late' time points after surgery vomiting occurred in 17.4% (64 : 367) of participants in the lidocaine group and in 20.1% (73 : 364) of participants in the control group (RR 0.92, 95% CI 0.68 to 1.24; I^2=0%; 13 RCTs; n=731)[22 27 29 31 33 39 41–45 51 55] (web-Appendix, supporting information 5).

Opioid requirements. Pooled meta-analysis revealed significantly reduced opioid requirements (MEQ, mg) during anaesthesia in the lidocaine group in comparison to the control group (MD −3.30, 95% CI −6.59 to −0.02; I^2=86%; 12 RCTs; n=667)[17 23 33–36 39 41 48 55 59 61] (web-Appendix, supporting information 5).

Altogether, 32 trials reported postoperative opioid consumption.[17–20 22 23 27 29–42 44 45 47–51 53 55 58 61] Combined analysis on opioid consumption showed significantly reduced opioid consumption in the lidocaine group compared with control, during stay in PACU (MD −4.17 mg, 95% CI −6.40 to −1.94; I^2=94%; 18 RCTs; n=1 001) and during the whole postoperative period (MD −5.36 mg, 95% CI −7.12 to −3.59; I^2=77%; 29 RCTs; n=1553) (web-Appendix, supporting information 5).

Lidocaine i.v. vs thoracic epidural analgesia (TEA)

The second comparison analysed lidocaine i.v. vs TEA. For this comparison, we were able to identify two studies.[24 25] Because of the low number of identified studies analysing the effect of i.v. lidocaine compared with TEA the summarized effects for each outcome in this comparison were only of very low evidence (web-Appendix, supporting information 6). In summary, we were not able to identify any evidence of effect in terms of all analysed outcomes (postoperative pain, functional gastrointestinal recovery, length of hospital stay, and intraoperative opioid requirements).

Additional analyses – assessment of the evidence

Further analyses were conducted to investigate (1) which patient's population may benefit from perioperative lidocaine i.v. administration (subgroup analysis), (2) the robustness of the results in terms of risk of bias from individual studies (sensitivity analysis), (3) the occurrence of risk of bias across studies (publication bias), and (4) the required information size and level of evidence reached (TSA). By this means we investigated the outcomes pain 'early', postoperative opioid requirements, and PONV 'late' to examine validity for those outcomes.

- (1) Subgroup analysis. Subgroup analysis was conducted to explore the effects of lidocaine i.v. in different surgical populations (open abdominal, laparoscopic abdominal, other surgical procedures) and to analyse the influence of different surgical procedures on statistical heterogeneity between studies. For the outcomes postoperative pain 'early' (1–4 h) (Table 2, Fig. 3A), postoperative opioid requirements (Table 2, Fig. 4A), and PONV 'late' (Table 2, Fig. 5A) lidocaine administration was most beneficial for patients undergoing laparoscopic abdominal procedures. For patients undergoing open abdominal surgery lidocaine administration was advantageous in terms of pain 'early' and postoperative opioid requirements. The mixed population other surgery did not benefit from perioperative lidocaine i.v. infusion in terms of postoperative pain, opioid consumption, and PONV.

  The high statistical heterogeneity (I^2) observed for the outcomes pain 'early' (I^2=87%) and postoperative opioid requirements (I^2=77%) was only decreased for the subgroup open abdominal surgery to 0% and 13%, respectively. Heterogeneity for all other subgroups remained substantial to considerable.

- (2) Sensitivity analysis. We excluded all trials which were identified as high risk of bias (= judged as high risk at least in one risk of bias domain or as unclear risk of bias in all domains) and performed a sensitivity meta-analysis to test robustness of the results. The pooled estimates of the sensitivity analysis were similar to the original meta-analysis with respect to effect sizes and CIs for the outcomes pain

Table 2 Subgroup analyses – comparison: lidocaine vs control (placebo/untreated). Subgroups were built for patients undergoing either open abdominal, laparoscopic abdominal, and other surgeries. Effect sizes were reported as MD or RR with 95% CI. Effect sizes <0 for continuous data (MD) and <1 for dichotomous data (RR) indicate 'favour of' lidocaine treatment

Subgroup	Pain 'early', (VAS 0–10 cm)	Opioid requirements, 'post-OP' (MEQ, mg)	PON(V) 'late', 0–24 h, −48 h, −72 h
Open abdominal surgery	−0.72 [−0.96, −0.47]	−3.26 [−4.80, −1.71]	0.87 [0.67, 1.13]
Laparoscopic abdominal surgery	−1.14 [−1.51, −0.78]	−7.40 [−11.41, −3.38]	0.73 [0.54, 0.98]
Other surgery	−0.30 [−0.89, 0.28]	−7.28 [−12.91, −1.65]	0.83 [0.57, 1.22]
Overall	−0.84 [−1.10, −0.59]	−5.36 [−7.12, −3.59]	0.82 [0.70, 0.97]

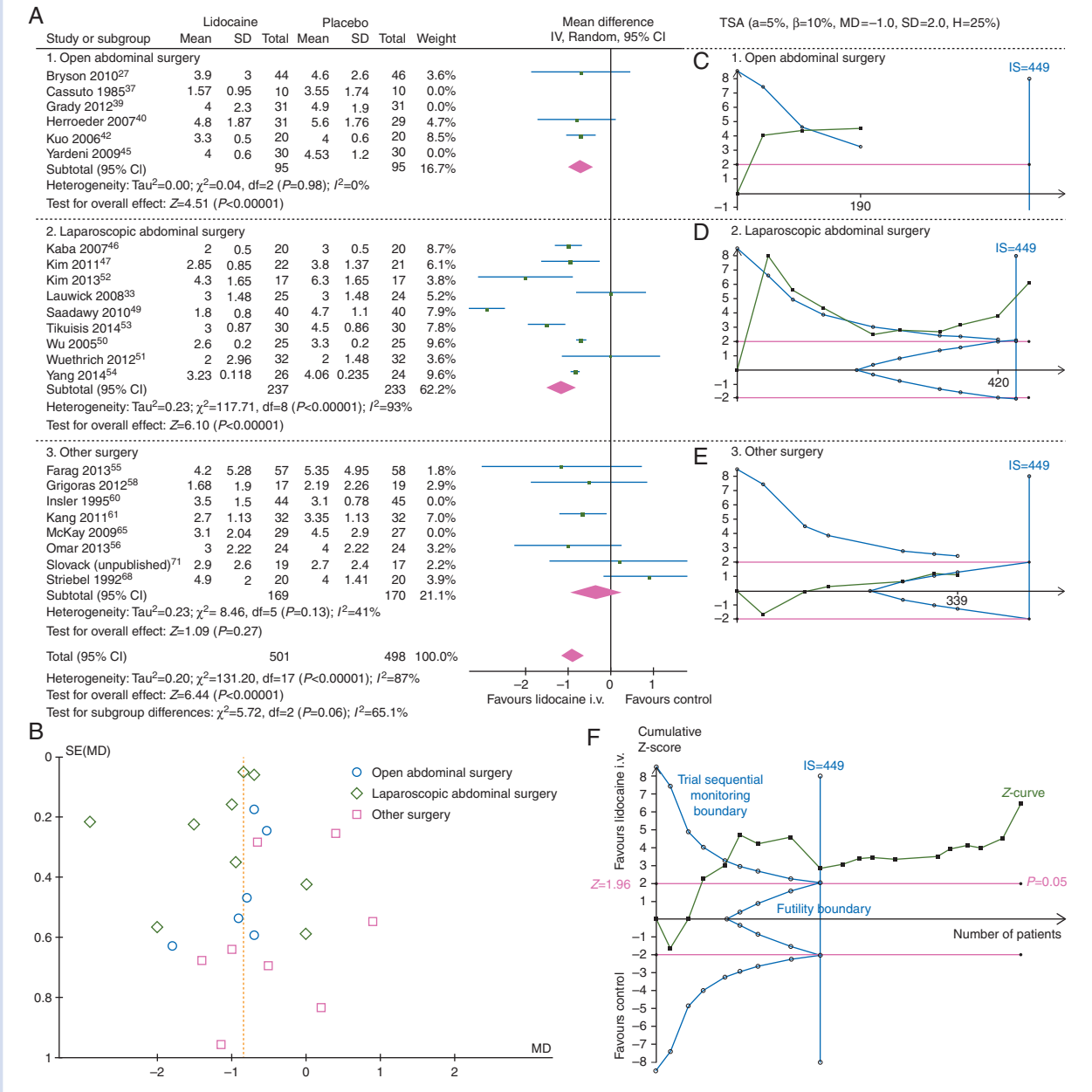

Fig 3 Comparison: lidocaine vs control (placebo/untreated), outcome: pain 'early' (0–4 h, PACU), VAS 0–10 cm, at rest. (A) Forest plot with subgroup analysis 'open abdominal surgery', 'laparoscopic abdominal surgery', and 'other surgery'. Trials appraised as high risk of bias for at least one domain or as unclear risk of bias for all domains were excluded from the analysis. (B) Funnel plot of all trials. (C–F) Trial sequential analysis (TSA) was used to demonstrate or reject an anticipated mean difference (MD) of −1.0 (VAS 0–10) and a standard deviation (SD) of 2.0 (clinical relevant estimate), an alpha of 5%, and a beta of 10%. The heterogeneity-adjusted (H: D^2=25%) required information size (IS) is 449 patients (vertical blue line). Details to the graphical presentation of TSA are explained within the Methods. TSA revealed firm evidence for the anticipated intervention effect for the subgroups 'open abdominal surgery' (C: Number of participants does not reach the IS, but the Z-curve (green) does cross the monitoring boundary (blue)) and 'laparoscopic abdominal surgery' (D: Number of participants does reach the IS and the Z-curve does cross the monitoring boundary). TSA revealed firm evidence that the lack of significance for the subgroup 'other surgery' is because of the underlying equivalency between intervention and control (E: Number of participants does not reach the IS, but the Z-curve does cross the futility boundary (blue)). TSA of the pooled meta-analysis (F) revealed firm evidence for the anticipated intervention effect.

'early' (18 studies: −0.91 [−1.18, −0.63]), postoperative opioid requirements (23 studies: −4.85 mg [−6.72, −2.98]), and PONV 'late' (17 studies: 0.76 [0.62, 0.93]).

- (3) Risk of bias across studies: Risk of bias across studies was determined using funnel plots and corresponding linear regression tests of funnel plot asymmetry. For pain 'early', the funnel plot showed symmetry around the Y axis with balanced distribution along the Y axis, indicating no evidence of reporting bias (Fig. 3B). No obvious funnel asymmetry was detectable for opioid consumption (Fig. 4B). For the outcome

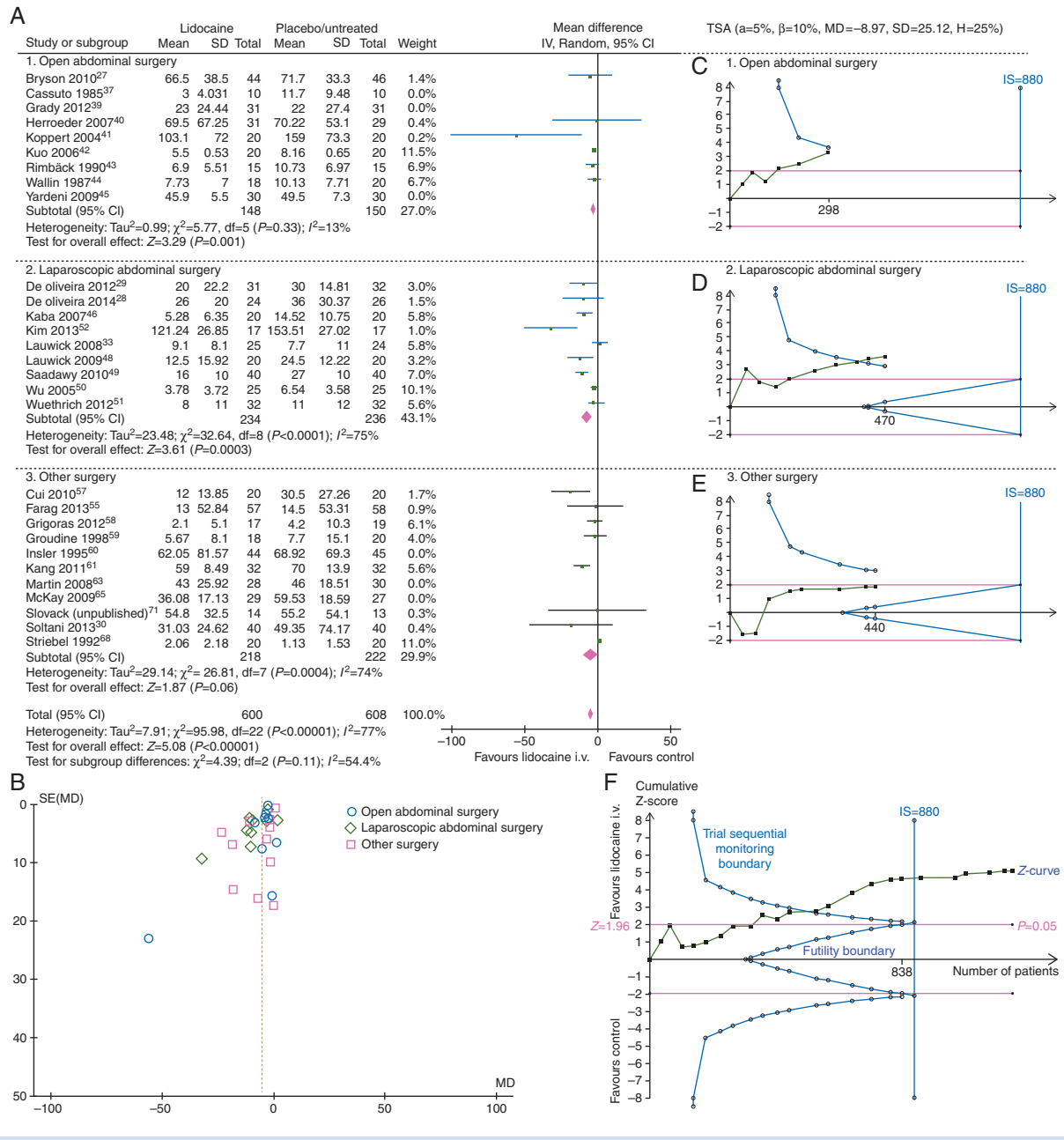

Fig 4 Comparison: lidocaine vs control (placebo/untreated), outcome: postoperative opioid consumption (MEQ, mg). (A) Forest plot with subgroup analysis 'open abdominal surgery', 'laparoscopic abdominal surgery', and 'other surgery'. Trials appraised as high risk of bias for at least one domain or as unclear risk of bias for all domains were excluded from the analysis. (B) Funnel plot of all trials. (C–F) Trial sequential analysis (TSA) was used to demonstrate or reject an anticipated mean difference (MD) of −8.97 mg and a standard deviation (SD) of 25.12 ('low-bias based', Bryson 2010, De Oliveira 2012+2014), an alpha of 5%, and a beta of 10%. The heterogeneity-adjusted (H: D^2=25%) required information size (IS) is 880 patients (vertical blue line). Details to the graphical presentation of TSA are explained within the Methods. TSA revealed firm evidence for the anticipated intervention effect for the subgroup 'laparoscopic abdominal surgery' (D: Number of participants does not reach the IS, but the Z-curve (green) does cross the monitoring boundary (blue)). TSA revealed absence of evidence for the subgroups 'open abdominal surgery' and 'other surgery' (C, E: Number of participants does not reach the IS and the Z-curve does not cross neither the monitoring boundary nor the futility boundary (blue)). TSA of the pooled meta-analysis (F) revealed firm evidence for the anticipated intervention effect.

PONV 'late' the funnel plot revealed asymmetry to the left of the Y axis ('significant' studies) with no studies appearing on the right ('non-significant' studies) (Fig. 5B). Further, we analysed the three outcomes for funnel plot asymmetry using a linear regression test (supporting information 7). For PONV 'late' (t=−2.1977, degrees of freedom (df)=19, P=0.041) we found evidence of funnel plot asymmetry.

- (4) Trial sequential analysis (TSA): To minimize random errors and decide on conclusiveness of the positive results of our meta-analysis, we calculated the required IS and

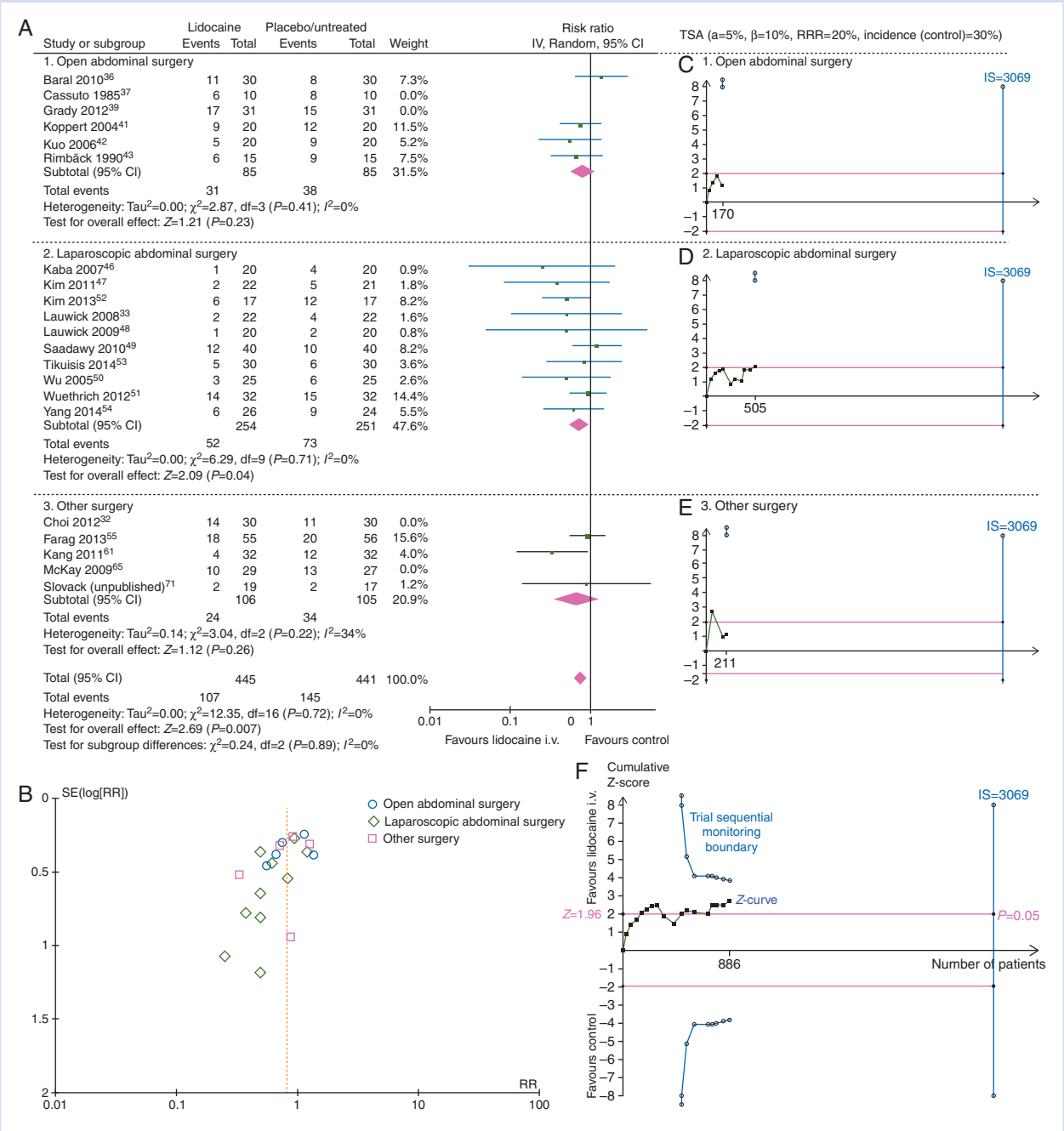

Fig 5 Comparison: lidocaine vs control (placebo/untreated), outcome: PONV 'late' (0–24 h, −48 h, −72 h). (A) Forest plot with subgroup analysis 'open abdominal surgery', 'laparoscopic abdominal surgery', and 'other surgery'. Trials appraised as high risk of bias for at least one domain or as unclear risk of bias for all domains were excluded from the analysis. (B) Funnel plot of all trials. (C–F) Trial sequential analysis (TSA) was used to demonstrate or reject an anticipated relative risk reduction (RRR) of 20% and an incidence in the control arm of 30% (clinical relevant estimate), an alpha of 5%, and a beta of 10%. The heterogeneity-adjusted (H: D^2=25%) required information size (IS) is 3069 patients (vertical blue line). Details to the graphical presentation of TSA are explained within the Methods. TSA revealed absence of evidence for the anticipated intervention effect for all subgroups and the pooled meta-analysis (C–F: Number of participants does not reach the IS and the Z-curve (green) does not cross the monitoring boundary (blue)).

the corresponding monitoring boundaries for the surgical subgroups and the pooled meta-analysis.

Trial sequential analysis for pain 'early' (assumptions: α=5%, ß=10%, MD=−1.0, SD=2.0, Heterogeneity correction: D^2=25%) revealed a required information size of 449 participants. Therefore, TSA of the pooled meta-analysis (999 patients of low risk of bias studies) showed firm evidence for the anticipated intervention effect (Fig. 3F). Further, TSA revealed firm evidence for the anticipated intervention effect for the subgroups open abdominal surgery (Fig. 3C) and laparoscopic abdominal surgery (Fig. 3D). TSA also pointed out that the lack of significance

in the subgroup other surgery was because of the underlying equivalency between intervention and control (Fig. 3E).

Trial sequential analysis for 'postoperative opioid consumption' (assumptions: α=5%, ß=10%, MD=−8.97, SD=25.12, Heterogeneity correction: D^2=25%) revealed a required information size of 880 participants. TSA of the pooled meta-analysis (1208 patients of low risk of bias studies) demonstrated firm evidence for the anticipated intervention effect (Fig. 4F). TSA revealed firm evidence for the anticipated intervention effect for the subgroup laparoscopic abdominal surgery (Fig. 4D) and absence of evidence for the subgroups open abdominal surgery (Fig. 4C) and other surgery (Fig. 4E).

Trial sequential analysis for 'PONV late' (assumptions: α=5%, ß=10%, MD=−1.0, SD=2.0, Heterogeneity correction: D^2=25%) pointed up a required information size of 3069 participants. The analysis revealed absence of evidence for the anticipated intervention effect for all subgroups and the pooled meta-analysis (886 patients of low risk of bias studies) (Fig. 5C-F).

TSA using the empirical estimates and the appropriate between-trial heterogeneities of the meta-analyses (web-Appendix, supporting information 8) largely confirmed the TSA results obtained by using the clinically relevant estimates supporting reliability of the analyses.

Discussion

Summary of evidence

This review demonstrates that patients undergoing any elective surgery under general anaesthesia who have received perioperative i.v. lidocaine have slightly lower pain scores at 1–4 h (MD −0.84, 95% CI −1.10 to −0.59) and at 24 h (MD −0.34, 95% CI −0.57 to −0.11) after surgery compared with those receiving a control treatment, despite having received the same postoperative access to opioid analgesia. At 48 h after surgery there was no benefit with respect to pain relief associated with this intervention. Subgroup analysis suggested that best benefit in terms of the level of pain reduction and the duration of pain relief is for patients undergoing laparoscopic abdominal surgery (MD −1.14, 95% CI −1.51−−0.78) followed by open abdominal surgery (MD −0.72, 95% CI −0.96 to −0.47). Furthermore we showed that opioid requirements (MD −5.36 mg, 95% CI −7.12 to −3.59) and opioid-related side-effects (PON/PONV: RR 0.82, 95% CI 0.70 to 0.97) during the postoperative phase, were lower among patients who received i.v. lidocaine.

Strength of evidence for the outcomes pain and postoperative opioid requirements was limited by inconsistency. At the same time, conclusiveness was strengthened by analysis of methodological study quality and lack of risk of bias across studies for those outcomes. Especially trial sequential analysis results revealed that we can be confident (at least in terms of the required information size) of the positive effects lidocaine has on the reduction of postoperative pain, in patients undergoing abdominal and laparoscopic abdominal surgery and on reduction of opioid requirements in patients undergoing laparoscopic abdominal surgery. TSA indicated further that lidocaine has no beneficial effect on early postoperative pain in the mixed subgroup 'other surgery'. The selective benefit of this intervention for abdominal surgery patients may be as a result of lidocaine-related effects on the specific inflammatory environment of the abdominal region. However, this is rather a speculative hypothesis which has to be proved in future trials and primary research. The results for PONV 'late' should be treated with caution as we could identify funnel plot asymmetry and an underpowered patient population size (TSA results) underlying this meta-analysis to reach firm evidence.

Positive effects of systemic lidocaine were also recognized for reduction of postoperative ileus and functional gastrointestinal recovery (time to first flatus and bowel movement/sounds). For the outcome 'time to first defecation', there is currently no evidence of positive effect detectable. In general, evidence is limited for outcomes concerning gastrointestinal recovery because of imprecision.

We also found limited evidence of effect for length of hospital stay, postoperative nausea (early time points after surgery), intraoperative opioid consumption, and postoperative opioid requirements (early time points after surgery). There was no evidence of treatment effect found for the reduction of postoperative vomiting because of the intervention, which may be dependent on the limited event rate.

In terms of risk of surgical complications such as postoperative infection, urinary retention, bleeding, anastomotic leak, thromboembolic disease, and wound healing disturbances, there was currently no evidence for either benefit or harm. However, the body of evidence is limited by imprecision as a result of the small number of studies reporting surgical complications.

This review illustrates that there are no major adverse events as a result of systemic lidocaine administration in the perioperative setting, detectable on the basis of 45 small randomized, controlled trials reviewed. However, this assumption is based only on a sample of small studies without a systematic screening for adverse events. Therefore, current data are certainly underpowered to assess most (rare) potential serious side-effects.

The second comparison analysed in this review was lidocaine i.v. vs thoracic epidural analgesia. For this comparison, we were able to identify two studies. As a result of the low number of identified studies analysing the effect of systemic lidocaine compared with TEA the summarized effects of each outcome for this comparison were only of very low evidence. In general, we were not able to identify any evidence of effect, neither positive nor negative, in terms of postoperative pain, functional gastrointestinal recovery, ileus, length of hospital stay, and PONV.

At the time of submission of our protocol, there were three systematic reviews addressing similar questions[62–65] and one article was published as a referenced review to the original of McCarthy and colleagues[65] In 2012 another meta-analysis was published which analyses perioperative systemic lidocaine for postoperative analgesia and recovery after abdominal surgery.[66] It is reassuring that existing systematic reviews with comparable or slightly different research questions have found more or less similar results and consequently concluded that this intervention should be considered in appropriate patients. However, the more up-to-date search, the greater number of included trials, and the broader range of included surgery types improved the precision and the external validity of the present review. In addition, the present review has analysed publication bias, TSA, and inconsistency for the outcomes 'pain early', 'postoperative opioid requirements', and 'PONV late' and provides sufficient background information to the study's details.

Limitations

A major limitation of this review was the large and unexplained heterogeneity between studies which limited the quality of

evidence for most of the outcomes because of inconsistency. The preplanned subgroup analysis according to different surgical procedures was of limited success to explain the heterogeneity. Only for the subgroup, open abdominal surgery of the outcomes pain 'early' and postoperative opioid consumption heterogeneity could be decreased significantly.

Another limitation was the small trial sizes of the included studies, as small trials tend to over- or underestimate the underlying treatment effect. In combination with publication bias (preferred publication of positive results) the pooled intervention effect can be dramatically overestimated. However, in the current meta-analysis publication bias seem not to play a role for most of the outcomes (symmetric funnel plots). Nevertheless, evidence was limited by indirectness of effect estimates. As small trials also tend to have limited heterogeneity in their patient population and/or implemented intervention (low within-study clinical heterogeneity) the estimated treatment effects of meta-analyses including solely small trials possess lower external validity and generalizability.

So far, at least, it is unclear, which is the best dose for an administered bolus of lidocaine and for the following continuous infusion of lidocaine. This is also valid for the length of administration of lidocaine infusion. Subgroup analysis comparing different treatment regimens (dosing of lidocaine and different timing of administration) presented in the Cochrane review have not revealed conclusive results.[1]

Finally, assumptions regarding the most appropriate dosing, timing (including the duration of administration) and the type of surgery resulted from indirect comparisons based on different clinical trials with varying clinical settings. For this reason, clinical trials investigating a dose-response and multiple surgical categories within one trial (e.g. as a clinical trials with factorial design), would be warranted to further elucidate and gain insights into these issues based on direct comparisons.

Implication for practice

The described effects on postoperative pain scores were most obvious and evident in the immediate postoperative period (~0.8 NRS points), defined as one to four h postoperatively for the purpose of this review. The effect was less pronounced and evident at intermediate time points (defined as 24 h) with only approximately half of the effect (~0.3 NRS points) and the effect was not significant in the late postoperative period (48 h).

The resulting clinical question and implication is whether these effects are worth the efforts associated with this intervention.

To address this question it is useful to bear in mind that under conditions of clinical trials and meta-analyses,[67–69] and clinical audits,[6 70] the benefit of neuraxial techniques (e.g. epidural analgesia) over an opioid-based patient-controlled analgesia - although usually considered superior in terms of pain relief - is in the range of 1–2 points on a 0 to 10 visual analogue scale depending on the specified pain outcome. In this light, the perioperative administration of i.v. lidocaine could be seen as clinically relevant in terms of superior pain relief, at least for the early postoperative period, in patients undergoing laparoscopic abdominal surgery (MD −1.14, 95% CI −1.51 to −0.78).

We think that lidocaine has the potential to be an alternative to epidural analgesia (at least in specific populations of patients) especially because of the beneficial, even if small, impact on a multiplicity of clinical and patient relevant outcomes, such as gastrointestinal recovery, PONV, and opioid consumption during postoperative recovery in patients undergoing abdominal surgery.

As far as the clinical applicability of these results are concerned it is reassuring that this intervention did not produce relevant clinical side-effects in the investigated cohort of participants despite the encouraging effects of lidocaine administration in the administered doses (~1.5 mg kg^{-1} of body weight as bolus and ~2 mg kg^{-1} h^{-1} as continuous infusion) . However, we cannot make any conclusions regarding the tolerability in patients with compromised liver or renal function.

Thus, the effects of a relatively simple intervention such as the administration of i.v. lidocaine should be considered relevant and worthwhile to be discussed with patients if the site of the surgical procedure (abdominal and laparoscopic abdominal surgeries) or the expected pain level is appropriate.

The described effects may be considered especially relevant if conditions are prevalent that worsen the risk-to-benefit ratio of more invasive treatments, such as (thoracic) epidural analgesia or peripheral regional analgesia techniques. Such conditions include hereditary or acquired coagulation disorders and treatment with anticoagulants, resulting in absolute or relative contraindications to perform central neuraxial blocks. This may also include conditions with less precisely defined risk (e.g. patients receiving low molecular weight heparin) (LMWH), in the presence of additional drugs interfering with coagulation (e.g. acetylsalicylic acid); or LMWH plus the presence of renal or liver diseases. Further, it may be of value in cases that turn out to be a major surgical procedure but are not planned as such (e.g. conversion form diagnostic laparoscopy to major laparoscopic or even open abdominal procedure).

Conclusions

There is limited evidence that this intervention, when compared with placebo, has an impact on pain scores, especially in the early postoperative phase. There is also limited evidence that this has further impact on other relevant clinical outcomes, such as gastrointestinal recovery, postoperative nausea, and opioid requirements. The analyses revealed that i.v. lidocaine is especially useful as adjuvant during general anaesthesia, for patients undergoing abdominal surgery, because of its beneficial impact on multiple outcomes during postoperative recovery. So far there is a scarcity of studies that have systematically assessed the incidence of adverse effects; the optimal dose; timing (including the duration of the administration); and the effects when compared with epidural anaesthesia, which limit conclusions on those particular points.

Authors' contributions

Study design/planning: S.W., J.J., N.L.P., P.K.
Study conduct: S.W., J.J., N.L.P., A.S., M.W.H., K.H., L.H.J.E., D.M.P., P.K.
Data analysis: S.W., J.J., N.L.P., A.S., M.W.H., K.H., L.H.J.E., D.M.P., A.A., P.K.
Writing paper: S.W., J.J., N.L.P., A.S., M.W.H., K.H., L.H.J.E., D.M.P., A.A., P.K.
Revising paper: all authors

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helping with the translation of Spanish articles during the search process.

Declaration of interest

M.W.H.: is working in this research area and has participated in a clinical study that is relevant for this systematic review (Herroeder 2007). Critical appraisal and data extraction was done by J.J and S.W. K.H.: is working in this research area and has participated in a clinical study that is relevant for this systematic review (Herroeder 2007).

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