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REVIEW ARTICLE

The impact of peri-operative intravenous lidocaine on postoperative outcome after elective colorectal surgery

A meta-analysis of randomised controlled trials

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BACKGROUND There has recently been increasing interest in the use of peri-operative intravenous lidocaine (IVL) due to its analgesic, anti-inflammatory and opioid-sparing effects. However, these potential benefits are not well established in elective colorectal surgery.

OBJECTIVES To examine the effect of peri-operative IVL infusion on postoperative outcome in patients undergoing elective colorectal surgery.

DESIGN A meta-analysis of randomised controlled trials (RCTs) comparing peri-operative IVL with placebo infusion in elective colorectal surgery. The primary outcome measure was postoperative pain scores up to 48 h. The secondary outcome measures included time to return of gastrointestinal function, postoperative morphine requirement, anastomotic leak, local anaesthetic toxicity and hospital length of stay.

DATA SOURCES PubMed, Scopus and the Cochrane Library databases were searched on 5 November 2018.

ELIGIBILITY CRITERIA Studies were included if they were RCTs evaluating the role of peri-operative IVL vs. placebo in adult patients undergoing elective colorectal surgery. Exclusion criteria were paediatric patients, noncolorectal or emergency procedures, non-RCT methodology or lack of relevant outcome measures.

RESULTS A total of 10 studies were included ($n = 508$ patients; 265 who had undergone IVL infusion, 243 who had undergone placebo infusion). IVL infusion was associated with a significant reduction in time to defecation (mean difference −12.06 h, 95% CI −17.83 to −6.29, $I^2 = 93\%$, $P = 0.0001$), hospital length of stay (mean difference −0.76 days, 95% CI −1.32 to −0.19, $I^2 = 45\%$, $P = 0.009$) and postoperative pain scores at early time points, although this difference does not meet the threshold for a clinically relevant difference. There was no difference in time to pass flatus (mean difference −5.33 h, 95% CI −11.53 to 0.88, $I^2 = 90\%$, $P = 0.09$), nor in rates of surgical site infection or anastomotic leakage.

CONCLUSION This meta-analysis provides some support for the administration of peri-operative IVL infusion in elective colorectal surgery. However, further evidence is necessary to fully elucidate its potential benefits in light of the high levels of study heterogeneity and mixed quality of methodology.

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Introduction

There has been significant interest in the potential for peri-operative intravenous lidocaine (IVL) infusion in patients undergoing abdominal surgery,[1] with increasing evidence in a range of surgical specialties, including colorectal surgery,[2] hepatobiliary surgery,[3] obstetrics[4] and gynaecology.[5] Studies have suggested that IVL conveys a postoperative benefit in terms of its analgesic, anti-inflammatory and opioid-sparing effects, resulting in reduced postoperative pain, reduced time to return of gastrointestinal function, and reduced nausea and vomiting.[6] In addition, there is

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some evidence for a beneficial effect on intra-operative parameters, including a reduction in anaesthetic requirement[7,8] and improved recovery from general anaesthesia.[9]

A Cochrane review[1] compared IVL infusion with placebo or thoracic epidural analgesia for postoperative pain and recovery in a total of 68 randomised controlled trials (RCTs) across a range of surgical specialties, including general, spinal, endocrine and cardiothoracic surgery, and gynaecology. This demonstrated an unclear effect of IVL vs. placebo on pain scores, recovery of gastrointestinal function, postoperative nausea and overall opioid requirement, and highlighted poor quality evidence. This review[1] did not seek to differentiate the benefits in individual surgical specialities such as colorectal alone, although a comparison was made between open and laparoscopic abdominal surgery. This included a range of nongastrointestinal procedures so is not directly comparable to the aims of the current meta-analysis.

Specific to the field of colorectal surgery, a recently published systematic review[10] examined the role of IVL in the setting of elective colorectal surgery and concluded that this provided limited benefit in the reduction of early postoperative pain and morphine requirement when compared with placebo, and a variable degree of improvement when compared with epidural analgesia. This has been followed by a meta-analysis within colorectal surgery, which found improved time to recovery of gastrointestinal function as well as reduced hospital length of stay.[11]

The recently published Enhanced Recovery After Surgery (ERAS) Society Recommendations for peri-operative care in elective colorectal surgery[12] have concluded that although 'the use of lidocaine infusions to reduce opioid use and nausea in colorectal surgery is now well established', the benefit in terms of reduction of postoperative ileus is unclear. Despite this, no meta-analysis has been conducted to date to assess the role of combined intra-operative and postoperative IVL in colorectal surgery specifically. In addition, substantial additional evidence has been published[2,13,14] since the previous systematic review.[10]

The aims of this meta-analysis were to examine the effect of peri-operative IVL on postoperative outcome in patients undergoing elective colorectal surgery, including postoperative pain, morphine consumption, time to return of gastrointestinal function, hospital length of stay and complications; to study the role of peri-operative lidocaine infusion in laparoscopic vs. open elective colorectal surgical procedures; to identify the optimal dosing and infusion regimen as well as duration of infusion; and to determine the incidence of local anaesthetic toxicity.

Materials and methods

Search strategy

A search of PubMed, Scopus and the Cochrane Library databases was conducted up to 5 November 2018 in order to identify full-text studies examining the impact of peri-operative IVL in elective colorectal surgery. The electronic search terms adopted were (intravenous OR infusion) AND (lidocaine OR lignocaine) AND (colon OR rectal OR colorectal OR proctectomy OR colonic), with no limitation placed on data or language for inclusion. The bibliographies of all studies that met the inclusion criteria were hand-searched for any additional suitable articles and relevant conference abstracts to ensure study inclusion was as complete as possible, and this accounts for the additional 39 manuscripts identified from other sources. The meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[15]

Selection of articles

Following the exclusion of initial studies on the basis of article title and abstract by two independent researchers (KR and HJE), the remaining full-text articles were screened in detail for inclusion. Studies were included if they were RCTs that evaluated the role of peri-operative intravenous IVL infusion vs. placebo in adult patients undergoing elective colorectal surgery. Exclusion criteria comprised paediatric patients, noncolorectal or emergency procedures, non-RCT methodology or lack of any relevant clinical outcome measures. Studies that included more than two study arms, but had IVL and placebo groups, were included and only those groups pertinent to this meta-analysis were considered. No consideration was given to how long the lidocaine infusion was continued after surgery, but to be eligible for inclusion, the infusion had to commence before the surgical incision.

Data extraction

Study data were extracted from the included RCTs by one author (KER) and checked by another (HJE). The primary outcome measure was postoperative pain scores up to 48 h [at rest and movement scored on the visual analogue scale (VAS)]. In line with the previous Cochrane meta-analysis[1] and reflecting the International Association for the Study of Pain (IASP) recommendations, we have considered a 1-cm difference in VAS (on a 0 to 10 cm scale) as a clinically, rather than just statistically, significant difference. Secondary outcome measures included time to return of gastrointestinal function, both in terms of flatus and defecation, postoperative morphine requirement, incidence of prolonged ileus, surgical site infection, anastomotic leak, signs of local anaesthetic toxicity and overall hospital length of stay. In addition, data were collated on patient baseline demographics[(age, sex, American Society of Anesthesiologists' (ASA) physical status], operative variables (operating time, estimated blood loss, nature of colorectal resection and indication for surgery) and details of the lidocaine infusion (dose, starting point, duration postoperatively and any bolus dose administered) as well as the details of the placebo administered. The studies included were stratified according to whether the patients underwent open or laparoscopic resection. If the data necessary for meta-analysis of continuous variables were not

available, the corresponding author was approached to provide the raw data, and if a response was not received, the technique described by Hozo *et al.*[16] was employed to estimate the mean and standard deviation from the median and interquartile range [IQR].

Where results were available only in graphical format and the authors did not respond to the request for raw data, data were extracted in either direct or indirect form using plotdigitizer (www.plotdigitizer.sourceforge.net). Where opioid drugs other than morphine were provided by the study, previously described conversion methods were used to standardise all opiates to an equivalent morphine dose.[17] Risk of bias was assessed using the Cochrane Collaboration tool,[18] which focuses upon random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias) and selective reporting (reporting bias).

Statistical analysis

Statistical analysis was performed using RevMan 5.3[18] (Cochrane, London, UK). Dichotomous variables were analysed using the Mantel–Haenszel random effects model and quoted as a risk ratio with 95% CIs. Continuous variables were analysed using the inverse-variance random effects model and quoted as a mean difference with 95% CI. Data were used to construct forest plots, with a P value less than 0.05 on two-tailed testing indicating a statistically significant difference. Study heterogeneity and inconsistency were assessed using the I^2 statistic,[19] with 25% or less representing low heterogeneity, 25 to 50% as moderate and more than 50% high heterogeneity.

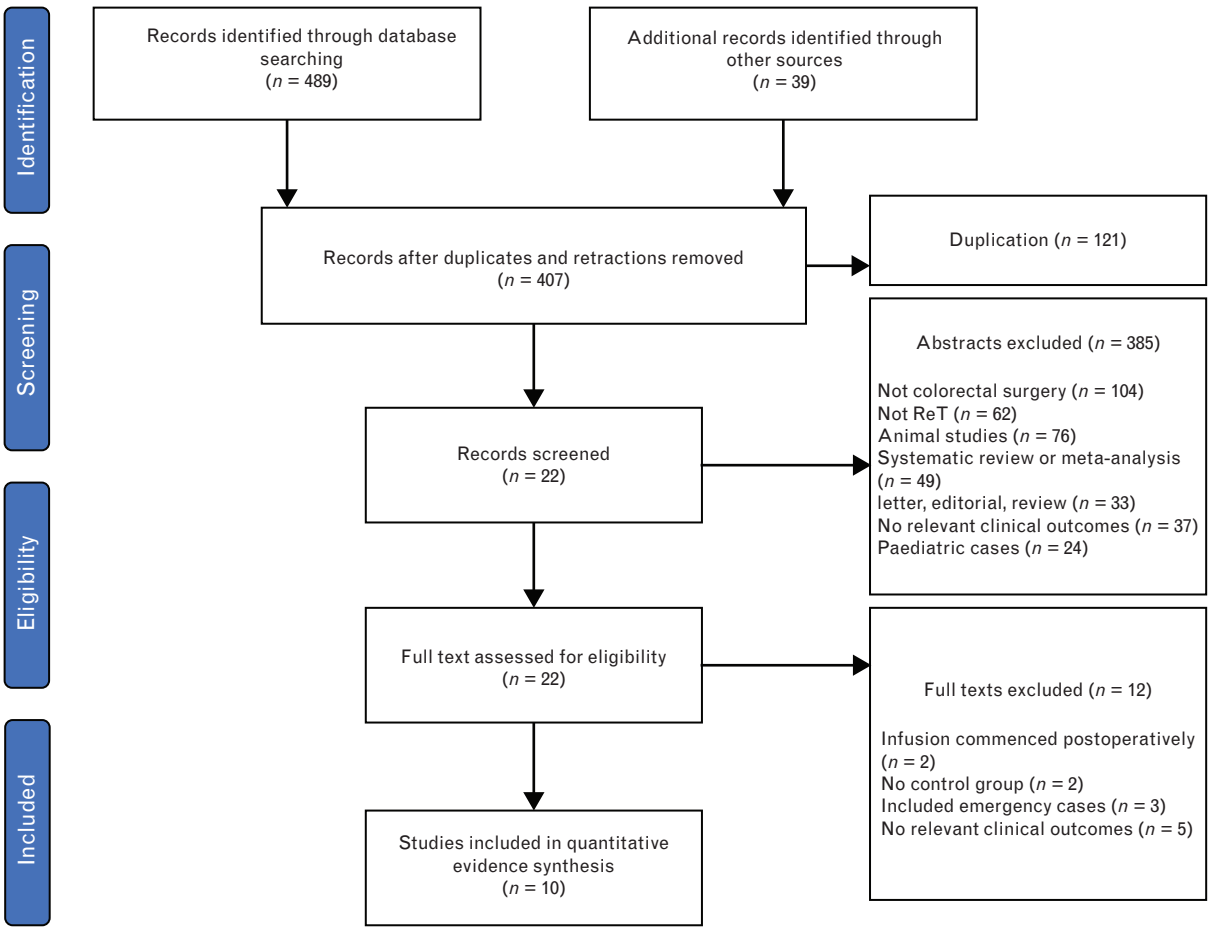
Protocol registration

The protocol for this meta-analysis was registered with the PROSPERO database (www.crd.york.ac.uk/prospero) - registration no. CRD42018115916.

Results

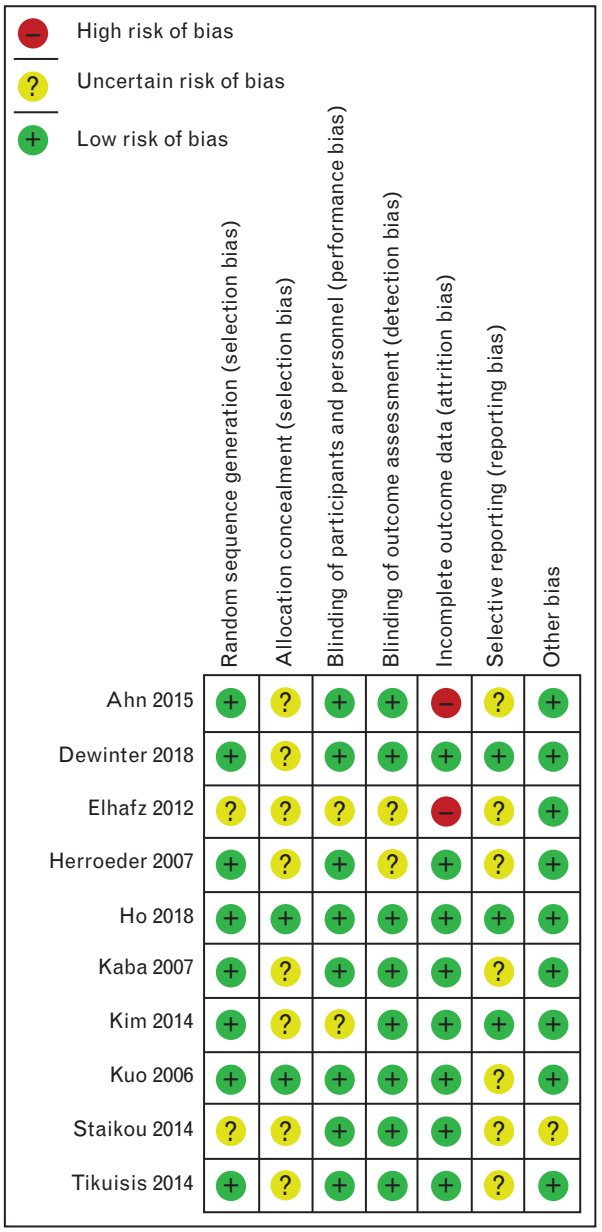
The initial literature search identified a total of 489 potentially eligible full-text articles, of which a total of 10 studies were included in the meta-analysis[2,13,20–27] (Fig. 1). Two studies initially identified as potentially eligible were excluded subsequently because the

Fig. 1



PRISMA diagram of studies considered for inclusion from the initial literature search.

Fig. 2



Risk of bias assessment of the included studies.

lidocaine infusion was not commenced until after the completion of surgery.[14,28] Overall, the risk of bias within the included studies was moderate and the quality of the studies was similarly moderate (Fig. 2). In the assessment of publication bias, markers of imprecision and inconsistency (as estimated from the sample size and CI of the effect sizes), and the quality of evidence was low to moderate, in keeping with the recent Cochrane meta-analysis[1] on a similar topic.

There was a total of 610 participants in the 10 RCTs included within the meta-analysis. However, several studies[2,23,24,27] included study groups such as neuraxial techniques and continuous wound infusions, which did not fall within the remit of the meta-analysis, and these groups were excluded. Therefore, a total of 265 participants received a peri-operative IVL infusion and 243 received a placebo infusion. In six studies, the surgery was performed laparoscopically,[2,20–22,24,26] and in four via an open technique.[13,23,25,27] Baseline patient demographics are shown in Supplementary Digital Content Table 1, http://links.lww.com/EJA/A277 and details of the interventions are given in Supplementary Digital Content Table 2, http://links.lww.com/EJA/A277.

Although postoperative pain scores at rest were significantly lower in the IVL group, there were no differences in pain scores on coughing when the IVL and placebo groups were compared. However, when the *clinically* relevant difference in VAS-rated pain scores as employed by the previous Cochrane meta-analysis and reflecting the IASP threshold were used, there were no clinically relevant differences in pain scores between patients receiving peri-operative IVL or placebo.

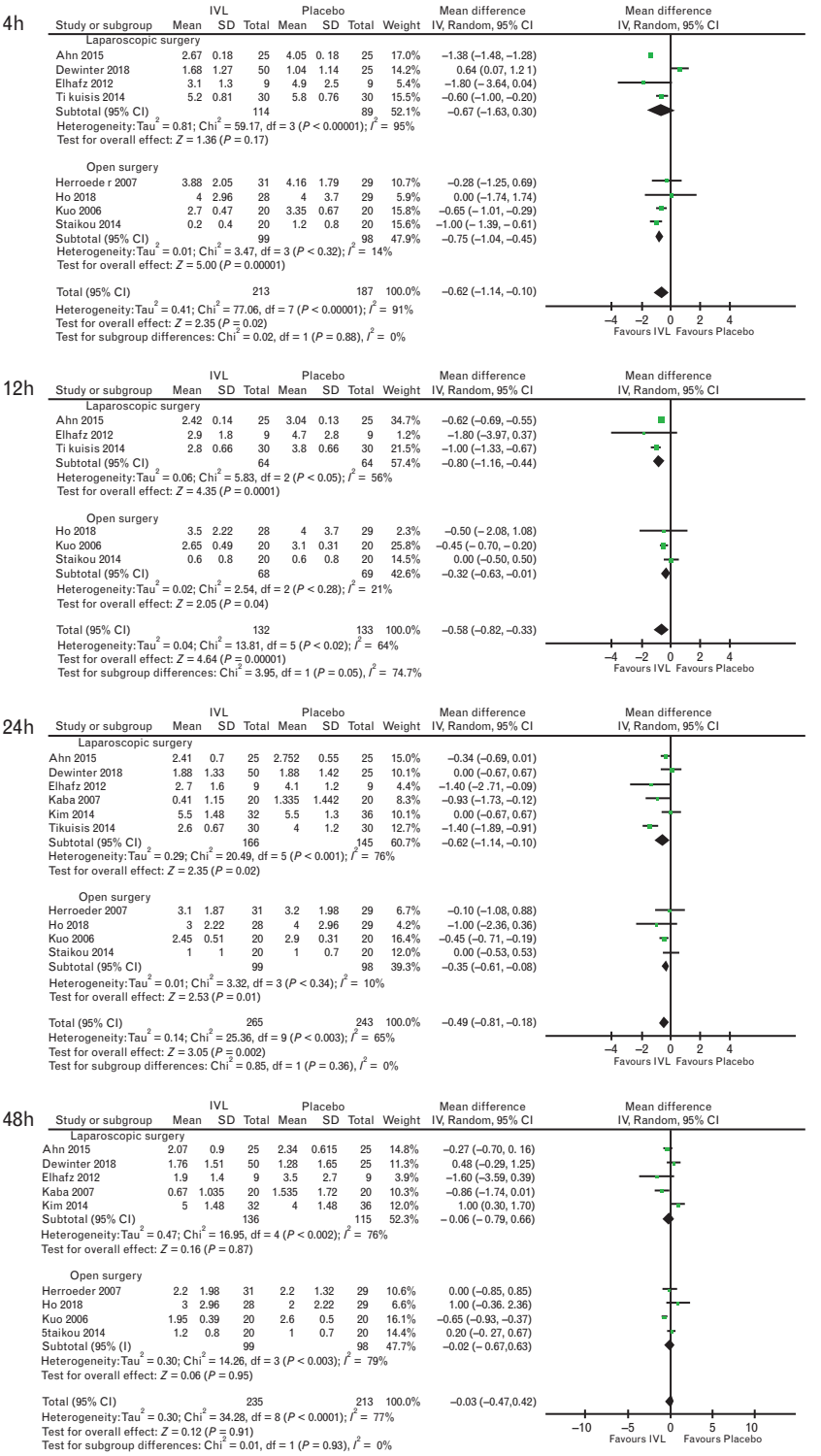
Pain scores at rest were analysed at 4, 12, 24 and 48 h postoperatively. A total of eight studies[2,13,20,22–25,27] considered VAS pain scores at 4 h postoperatively, four in the laparoscopic group[2,20,22,24] and four in the open group.[13,23,25,27] Overall, IVL was associated with a significantly lower VAS pain score at rest (−0.62, 95% CI −1.14 to −0.10, $P = 0.02$, $I^2 = 91\%$; Fig. 3), and in those undergoing open surgery (−0.75, 95% CI −1.04 to −0.45, $P < 0.00001$, $I^2 = 14\%$). However, no significant difference was seen in patients undergoing laparoscopic surgery (−0.67, 95% CI −1.63 to 0.30, $P = 0.17$, $I^2 = 95\%$).

Pain at 12 h postoperatively was considered in six studies,[13,20,22–24,27] including 265 patients, with three studies in patients undergoing laparoscopic surgery[20,22,24] and three studies in those undergoing open surgery.[13,23,27] IVL was associated with a significant reduction in pain scores at rest in the overall group (mean difference −0.58, 95% CI −0.82 to −0.33, $P < 0.00001$, $I^2 = 64\%$; Fig. 3), as well as the laparoscopic group (mean difference −0.80, 95% CI −1.16 to −0.44, $P < 0.0001$, $I^2 = 66\%$) and open group (mean difference −0.32, 95% CI −0.63 to −0.01, $P = 0.04$, $I^2 = 21\%$).

Pain scores at rest at 24 h postoperatively were considered by all studies included within the meta-analysis.[2,13,20–27] IVL was again associated with a significant reduction in pain scores in the overall (mean difference −0.49, 95% CI −0.81 to −0.18, $P = 0.002$, $I^2 = 65\%$; Fig. 3), laparoscopic (mean difference −0.62, 95% CI −1.14 to −0.10, $P = 0.02$, $I^2 = 76\%$) and open surgical groups (mean difference −0.35, 95% CI −0.61 to −0.08, $P = 0.01$, $I^2 = 10\%$).

A total of nine studies[2,13,20,22–27] considered the impact of IVL on pain scores at rest at 48 h postoperatively in 448 patients. There were no significant differences in pain

Fig. 3



Pain at rest

Forest plot comparing visual analogue scale pain scores at rest at 4, 12, 24 and 48 h postoperatively for patients receiving intravenous lidocaine vs. placebo, for both laparoscopic and open surgery.

scores between the IVL and placebo groups in any analysis (Fig. 3).

A total of six studies considered VAS pain score on coughing at 4 h postoperatively,[2,22–25,27] three including patients undergoing laparoscopic surgery[2,22,24] and three with patients undergoing open surgery.[23,25,27] There was no significant difference in the VAS pain score on coughing between those receiving IVL and placebo, either overall (mean difference −0.50, 95% CI −1.02 to 0.03, $P = 0.07$, $I^2 = 72\%$) or in those undergoing open (mean difference −0.89, 95% CI −1.85 to 0.07, $P = 0.07$, $I^2 = 75\%$) or laparoscopic procedures (mean difference −0.21, 95% CI −1.02 to 0.60, $P = 0.61$, $I^2 = 72\%$; Fig. 4).

In terms of VAS on coughing at 12 h postoperatively, four studies included data on this variable including 158 patients,[22–24,27] of which two were in open[23,27]and two in laparoscopic[22,24] studies (Fig. 4). Overall, IVL was associated with a significant reduction in postoperative pain on coughing at 12 h vs. placebo (mean difference −0.69, 95% CI −0.97 to −0.41, $P < 0.00001$, $I^2 = 0\%$). This was mirrored when only laparoscopic (mean difference −0.93, 95% CI −1.39 to −0.46, $P = 0.0001$, $I^2 = 0\%$) and open studies (mean difference −0.55, 95% CI −0.90 to −0.20, $P = 0.002$, $I^2 = 0\%$) were included.

Seven studies (333 patients)[2,22–27] included data on VAS pain score on coughing at 24 h postoperatively, of which four studies[2,22,24,26] were conducted in laparoscopic surgery and three studies in open surgery.[23,25,27] IVL was associated with no significant difference in pain on coughing at 24 h postoperatively vs. placebo, both overall and in either open or laparoscopic groups (Fig. 4).

VAS score on coughing at 48 h postoperatively was considered in six studies,[2,23–27] three in laparoscopic surgery[2,24,26] and three in open procedures.[23,25,27] At 48 h postoperatively, IVL did not significantly affect VAS-rated pain on coughing in any of the groups (Fig. 4).

The time to passage of flatus was considered in eight studies[2,13,21,23–27] including a total of 398 patients. Overall, IVL infusion was not associated with a significant difference in the time to passage of flatus (mean difference −5.33 h, 95% CI −11.53 to 0.88, $P = 0.09$, $I^2 = 90\%$; Fig. 5). When the four studies in laparoscopic surgery were considered, an IVL infusion ($n = 201$) was not associated with any difference in the time to passage of flatus (mean difference −3.78 h, 95% CI −12.88 to 5.32, $P = 0.42$, $I^2 = 87\%$). However, in patients undergoing open surgery (four studies; $n = 197$), IVL was associated with a significant reduction in the time to passage of flatus of 8.4 h (95% CI −13.7 to −3.1, $P = 0.002$, $I^2 = 31\%$).

Time to defecation was examined in seven studies including a total of 378 patients. Overall, the use of IVL was associated with a significant reduction in time to defecation (mean difference −12.06 h, 95% CI −17.83 to −6.29, $P = 0.0001$, $I^2 = 93\%$; Fig. 5). When the five studies involving laparoscopic surgery were considered ($n = 261$), IVL was associated with a significant reduction in the time to defecation (mean difference −12.33 h, 95% CI −18.63 to −6.03, $P = 0.0001$, $I^2 = 96\%$). However, no difference was seen in patients undergoing open surgery (mean difference −11.04 h, 95% CI −23.56 to 1.48, $P = 0.08$, $I^2 = 0\%$), although this was based upon data from two studies alone including a total of 107 patients.

The incidence of prolonged postoperative ileus was considered in four studies,[2,21,22,25] of which three were conducted in patients undergoing laparoscopic surgery[2,21,22] and one in open surgery.[25] Overall, the use of IVL was not associated with any difference in the incidence of prolonged postoperative ileus in either group (Fig. 5).

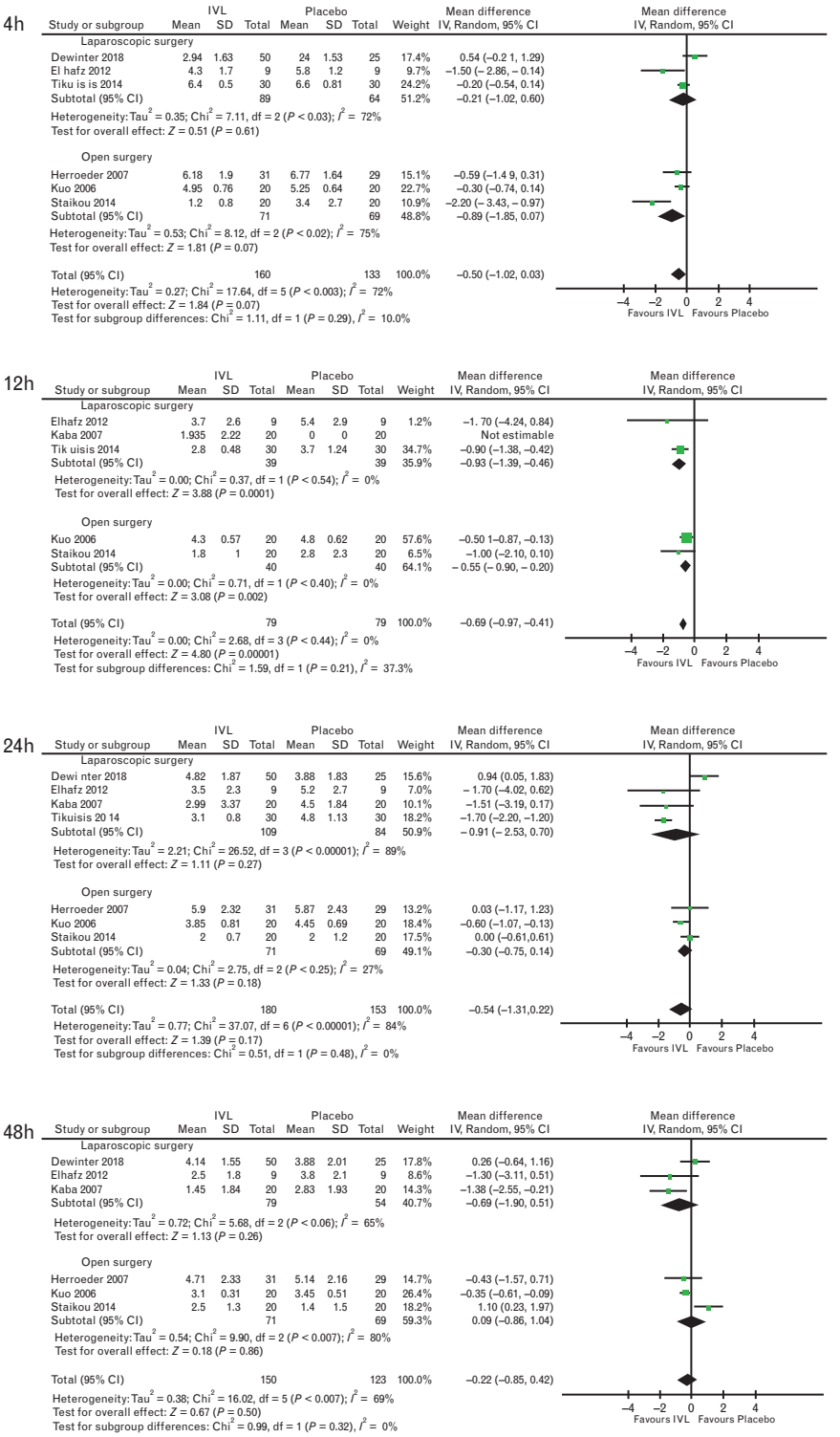
A total of five studies considered the time to tolerance of oral intake,[2,20–22,25] of which four studies were conducted in laparoscopic surgery (253 patients) and one in open procedures (60 patients) (Fig. 6). Overall, the use of IVL was not associated with a significant difference in time to tolerance of enteral intake (mean difference −3.02 h, 95% CI −6.06 to 0.01, $P = 0.05$), and in just those undergoing laparoscopy (mean difference −1.96 h, 95% CI −4.97 to 1.04, $P = 0.20$). No meta-analysis was conducted on those undergoing open surgery, as this only considered data from a single study.

The most common variable considered was the overall postoperative morphine requirement, which was considered in a total of seven studies,[13,20,21,23,25–27] three of which were conducted in laparoscopic surgery[20,21,26] and four in open surgery.[13,23,25,27] Overall, there was no difference in the postoperative morphine requirement between those receiving IVL and placebo (mean difference −8.86 mg, 95% CI −21.87 to 4.15, $P = 0.18$, $I^2 = 97\%$; Fig. 6), nor in those undergoing laparoscopic (mean difference −3.31 mg, 95% CI −15.01 to 8.39, $P = 0.58$, $I^2 = 76\%$) or open surgery alone (mean difference −13.79 mg, 95% CI −35.75 to 8.18, $P = 0.22$, $I^2 = 98\%$).

Hospital LOS was reported in eight studies included within the meta-analysis,[2,13,20–22,25–27] including 450 patients, of whom 293 underwent laparoscopic surgery (five RCTs) and 157 underwent open surgery (three RCTs). Overall, the use of IVL was associated with a significantly shorter hospital LOS (mean difference −0.76 days, 95% CI −1.32 to −0.19, $P = 0.009$, $I^2 = 45\%$; Fig. 6), as well as when analysis was undertaken of those undergoing laparoscopic surgery (mean difference −0.83 days, 95% CI −1.58 to −0.09, $P = 0.03$, $I^2 = 32\%$). However, no significant difference was seen when those undergoing open surgery were considered (mean difference −0.73, 95% CI −1.65 to 0.18, $P = 0.12$, $I^2 = 52\%$).

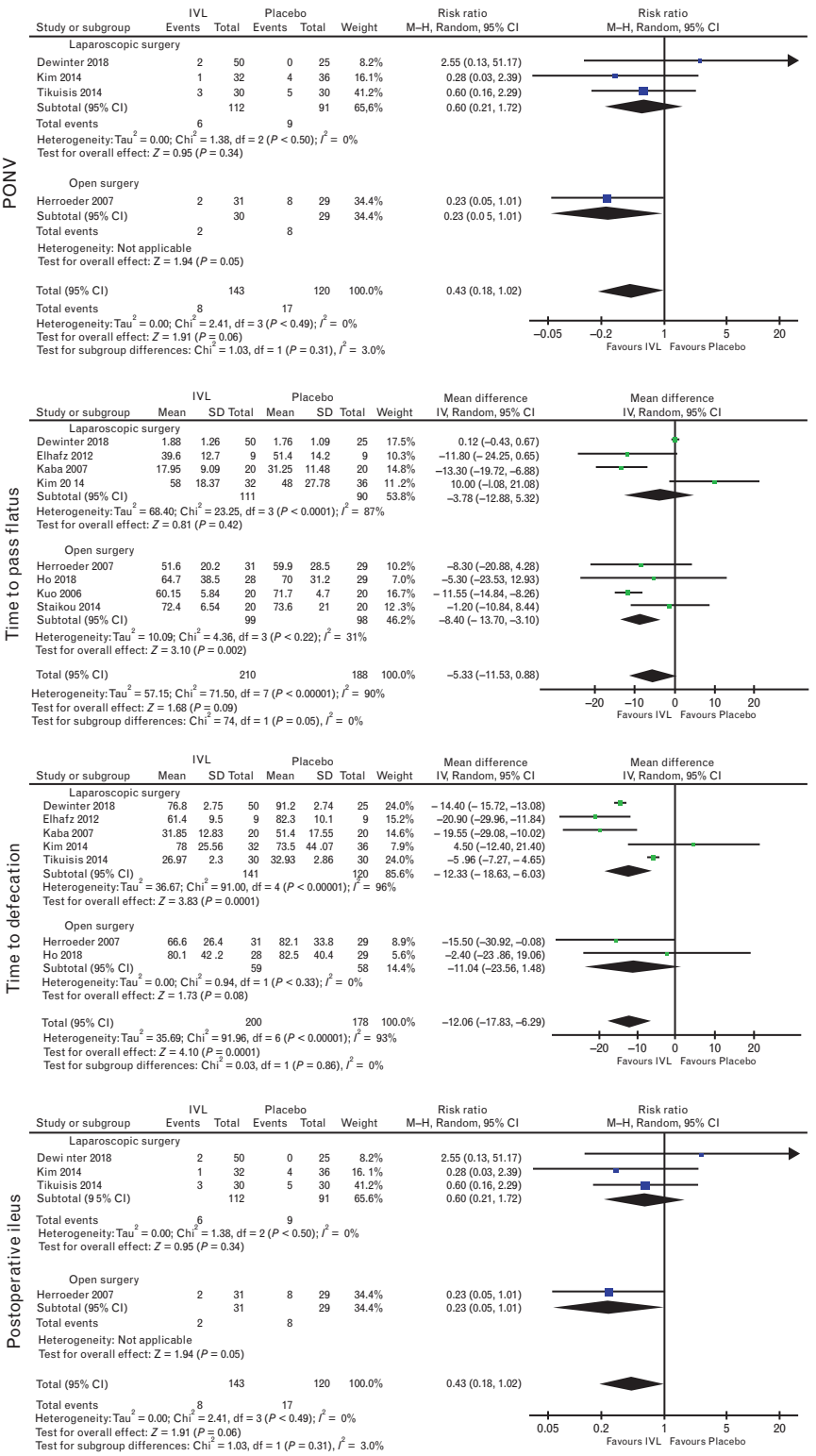
Only two studies[21,22] included data on the incidence of surgical site infection ($n = 128$). IVL was not associated with any difference in the incidence of surgical site

Fig. 4



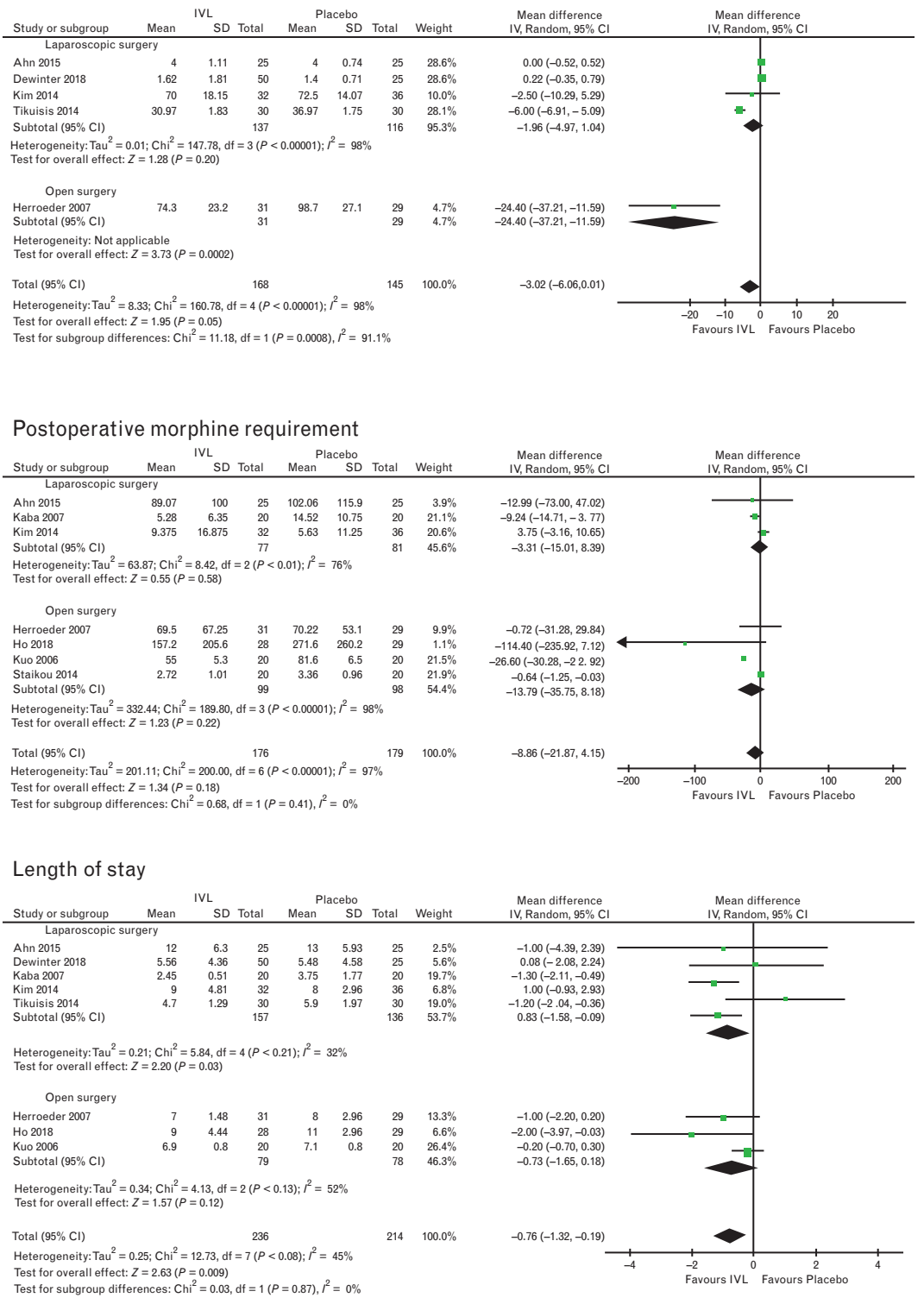
Forest plot comparing visual analogue scale pain scores on coughing at 4, 12, 24 and 48 h postoperatively for patients receiving intravenous lidocaine vs. placebo, for both laparoscopic and open surgery.

Fig. 5



Forest plot comparing incidence of postoperative nausea and vomiting, time to pass flatus (h), time to defaecation (h) and incidence of postoperative ileus for patients receiving intravenous lidocaine vs. placebo, for both laparoscopic and open surgery.

Fig. 6



Forest plot comparing comparing time to tolerance of diet, overall postoperative morphine requirement and hospital length of stay in patients receiving intravenous lidocaine vs. placebo, for both laparoscopic and open surgery.

infection vs. placebo (risk ratio 1.06, 95% CI 0.11 to 10.19, $P = 0.96$, $I^2 = 2\%$). Four studies considered the incidence of anastomotic leakage,[2,21,22,25] three in patients undergoing laparoscopic surgery[2,21,22] and just one in open surgery.[25] Both overall and in those undergoing laparoscopic surgery, the use of IVL was not associated with any difference in the incidence of anastomotic leak. Due to a lack of data, no meta-analysis was performed in those undergoing open surgery.

Six studies examined the incidence of local anaesthetic toxicity in IVL vs. placebo including 300 patients,[2,13,20,22,24,27] with four studies[2,20,22,24] conducted on patients undergoing laparoscopic surgery and two in those undergoing open procedures.[13,27] Only one study[2] had any incidence of local anaesthetic toxicity, with all other studies reporting no events, hence a meta-analysis was not conducted on this outcome. There was only one case of local anaesthetic toxicity, which was mild in nature, with a metallic taste and tinnitus.

Discussion

This meta-analysis of 10 RCTs examining the impact of IVL vs. placebo in elective colorectal surgery has demonstrated that IVL is associated with a statistically significant reduction in VAS pain scores at rest at early time points (4, 12 and 24 h) and pain scores on coughing at 12 h only. However, when these are interpreted in light of the IASP threshold for a clinically significant difference in VAS-rated pain scales, these cannot be interpreted as clinically significant results. In addition, there was a significant reduction in time to defecation and hospital LOS in those who underwent IVL infusion vs. placebo. No difference was seen in the time to passage of flatus, pain at rest at 48 h postoperatively, pain on coughing at 4, 24 and 48 h postoperatively, overall morphine consumption or complication rates (Supplementary Digital Content Table 3, http://links.lww.com/EJA/A277). However, the results should be interpreted with some caution in respect of the time to first flatus and hospital length of stay, as these differences are almost entirely the result of one or two studies (Kuo *et al.*[27] for the time to first flatus and Kaba *et al.*[26] and Tikuisis *et al.*[22] for the hospital LOS). This renders the conclusion potentially weaker and further evidence is needed to provide a more definitive answer. When studies in laparoscopic surgery were analysed, the benefits of peri-operative IVL were more pronounced. IVL was associated with a significant reduction in time to defecation, pain at rest, and at 12 and 24 h, pain on coughing at 12 h and overall hospital LOS, but no difference in pain scores at any other time point, time to return of flatus, morphine requirement or surgical complications. However, again, the differences in pain score cannot be considered clinically significant. When open surgery studies were considered, IVL was associated with a significant reduction in time to flatus but not faeces, pain at rest at early time points (4, 12 and 24 h) and on coughing at 12 h only, but there was no difference in the hospital LOS or morphine requirement.

The details of the lidocaine infusion differed greatly between studies included within this meta-analysis. In terms of commencement of the IVL infusion, one study commenced 30 min before the start of surgery,[27] five studies commenced before induction of anaesthesia,[20,22,23,25,26] one started at the time of induction[2] and three commenced after induction or at the time of skin incision.[13,21,24] In addition, there was a degree of variability in the dosage of lidocaine. In terms of the lidocaine bolus, all but one study[24] administered a bolus before commencing the infusion, with the most common dosage being 1.5 mg kg^{-1}, which was used in seven studies,[2,13,20,22,23,25,26] with one study[27] administering 2 mg kg^{-1}, and one[21] 1 mg kg^{-1}. This was also reflected in differing doses for the IVL infusion, with the most common rate of 2 mg kg^{-1} h^{-1} being administered in four studies,[20,22,23,25] followed by 1 mg kg^{-1} h^{-1} in two studies,[13,21] 3 mg kg^{-1} h^{-1} in one study[27] and 1.5 mg kg^{-1} h^{-1} in one study.[2] One study administered a weight-dependent rate of infusion,[24] and one study reduced the infusion rate between intra-operative and postoperative stages.[26]

There was also variability in the infusion duration; three studies administered the infusion only intra-operatively,[20,23,27] and three commenced intra-operatively and continued for 24 h.[21,22,26] Two studies discontinued the infusion at 4 h postoperatively,[2,25] one after 48 h[13] and one[24] on return of gastrointestinal function or at day 5, whichever was sooner. The level of heterogeneity between different infusions is a potentially significant source of bias. There are insufficient data for the individual regimens to separately analyse these and draw meaningful conclusions. There were significant levels of heterogeneity observed in the meta-analyses. Overall, 10 of the 14 analyses demonstrated high levels of heterogeneity, with a similar level in the analyses concerning laparoscopic surgery ($n = 10/15$). This was lower when studies of open surgery alone were analysed ($n = 5/12$), but this remains a significant confounder.

One previous systematic review[10] has examined the impact of IVL in elective colorectal surgery, which included five RCTs comparing IVL and placebo. That demonstrated that IVL provided limited benefit in the reduction of early postoperative pain and morphine consumption. No meta-analysis of the available data was conducted, and since its publication, two further RCTs[2,13] have been published that are included in the current meta-analysis. In addition, a meta-analysis of nine RCTs[11] has recently been published focusing on the time to return of gastrointestinal function following IVL in patients undergoing colorectal surgery. That meta-analysis did not include two RCTs,[2,20] which were potentially eligible, and also included one RCT which administered

the lidocaine in the postoperative setting only,[28] which the current meta-analysis excluded due to the potential heterogeneity that this causes. The findings of the current meta-analysis mirror these previous studies in their observation of a statistically significant improvement in early postoperative pain and time to return of gastrointestinal function in those receiving IVL. However, the current meta-analysis did not find any difference in morphine consumption rates, contrary to the previous systematic review. In addition, no conclusions were drawn regarding the relative effectiveness of IVL in open vs. laparoscopic surgery by the previous systematic review.

A recently updated meta-analysis[1,29] examined the role of IVL in all branches of surgery which included a total of 68 RCTs, finding IVL to be associated with a statistically significant benefit in terms of pain scores. However, this did not meet the threshold for a clinically relevant difference. A significant difference was also seen in gastrointestinal recovery, hospital length of stay and opioid requirement. This Cochrane review[1] and a recently published commentary article[30] make note of the significant level of heterogeneity introduced by including studies conducted in a range of surgical specialties, which is avoided in the current meta-analysis. There is also significant variability in the details of the IVL infusion, which are also relevant to the current meta-analysis and are due to a lack of standardisation in the literature.

Conclusion

This meta-analysis provides support for the administration of peri-operative IVL in elective colorectal surgery, in terms of earlier return of gastrointestinal function and reduced hospital LOS, with no difference in complication rates or apparent issues surrounding local anaesthetic toxicity. The pain scores at early time points were significantly lower in those receiving the IVL infusion, although this did not meet the threshold for a clinically relevant difference. This meta-analysis supports the use of peri-operative IVL infusion as a good choice for analgesia, particularly in laparoscopic colorectal surgery, with benefits most pronounced in the first 24 h following surgery, which may help promote early mobilisation and nutrition, key components of enhanced recovery pathways. There remains the option to give regular multimodal analgesia alongside IVL in the postoperative setting, thus reserving opioid analgesia for breakthrough pain alone. Further research is needed to explore whether the anti-inflammatory and natural killer cell effects result in improved oncological outcomes. In addition, further evidence would be beneficial in light of the high levels of study heterogeneity as well as to understand the optimal dosage and timing of the IVL infusion in order to standardise further studies and maximise the potential benefits of its administration.

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References

1 Weibel S, Jelting Y, Pace NL, *et al.* Continuous intravenous peri-operative lidocaine infusion for postoperative pain and recovery in adults. *Cochrane Database Syst Rev* 2018; **6**:CD009642.
2 Dewinter G, Coppens S, Van de Velde M, *et al.* Quadratus lumborum block versus peri-operative intravenous lidocaine for postoperative pain control in patients undergoing laparoscopic colorectal surgery: a prospective, randomized, double-blind controlled clinical trial. *Ann Surg* 2018; **268**: 769–775.
3 Zhao JB, Li YL, Wang YM, *et al.* Intravenous lidocaine infusion for pain control after laparoscopic cholecystectomy: a meta-analysis of randomized controlled trials. *Medicine (Baltimore)* 2018; **97**:e9771.
4 Gholipour Baradari A, Firouzian A, Hasanzadeh Kiabi F, *et al.* Bolus administration of intravenous lidocaine reduces pain after an elective caesarean section: findings from a randomised, double-blind, placebo-controlled trial. *J Obstet Gynaecol* 2017; **37**:566–570.
5 Samimi S, Taheri A, Davari Tanha F. Comparison between intraperitoneal and intravenous lidocaine for postoperative analgesia after elective abdominal hysterectomy, a double-blind placebo controlled study. *J Family Reprod Health* 2015; **9**:193–198.
6 Dunn LK, Durieux ME. Peri-operative use of intravenous lidocaine. *Anesthesiology* 2017; **126**:729–737.
7 Weinberg L, Jang J, Rachbuch C, *et al.* The effects of intravenous lignocaine on depth of anaesthesia and intraoperative haemodynamics during open radical prostatectomy. *BMC Res Notes* 2017; **10**:248.
8 Sloan TB, Mongan P, Lyda C, Koht A. Lidocaine infusion adjunct to total intravenous anesthesia reduces the total dose of propofol during intraoperative neurophysiological monitoring. *J Clin Monit Comput* 2014; **28**:139–147.
9 Nakhli MS, Kahloul M, Guizani T, *et al.* Intravenous lidocaine as adjuvant to general anesthesia in renal surgery. *Libyan J Med* 2018; **13**:1433418.
10 MacFater WS, Rahiri JL, Lauti M, *et al.* Intravenous lignocaine in colorectal surgery: a systematic review. *ANZ J Surg* 2017; **87**:879–885.
11 Cooke C, Kennedy ED, Foo I, *et al.* Meta-analysis of the effect of peri-operative intravenous lidocaine on return of gastrointestinal function after colorectal surgery. *Tech Coloproctol* 2019; **23**:15–24.
12 Gustafsson UO, Scott MJ, Hubner M, *et al.* Guidelines for peri-operative care in elective colorectal surgery: enhanced recovery after surgery (ERAS®) Society recommendations: 2018. *World J Surg* 2019; **43**: 659–695.
13 Ho MLJ, Kerr SJ, Stevens J. Intravenous lidocaine infusions for 48 h in open colorectal surgery: a prospective, randomized, double-blinded, placebo-controlled trial. *Korean J Anesthesiol* 2018; **71**:57–65.
14 Beaussier M, Parc Y, Guechot J, *et al.* Ropivacaine preperitoneal wound infusion for pain relief and prevention of incisional hyperalgesia after laparoscopic colorectal surgery: a randomized, triple-arm, double-blind controlled evaluation vs intravenous lidocaine infusion, the catch study. *Colorectal Dis* 2018; **20**:509–519.
15 Moher D, Liberati A, Tetzlaff J, *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* 2010; **8**:336–341.
16 Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 2005; **5**:13.
17 Pereira J, Lawlor P, Vigano A, *et al.* Equianalgesic dose ratios for opioids. A critical review and proposals for long-term dosing. *J Pain Symptom Manage* 2001; **22**:672–687.
18 Cochrane Collaboration. *Review manager (revman). Version 5.3.* Copenhagen: The Cochrane Collaboration: The Nordic Cochrane Centre; 2014.
19 Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**:1539–1558.

20 Ahn E, Kang H, Choi GJ, *et al.* Intravenous lidocaine for effective pain relief after a laparoscopic colectomy: a prospective, randomized, double-blind, placebo-controlled study. *Int Surg* 2015; **100**: 394–401.
21 Kim HO, Lee SR, Choi WJ, Kim H. Early oral feeding following laparoscopic colorectal cancer surgery. *ANZ J Surg* 2014; **84**:539–544.
22 Tikuisis R, Miliauskas P, Samalavicius NE, *et al.* Intravenous lidocaine for postoperative pain relief after hand-assisted laparoscopic colon surgery: a randomized, placebo-controlled clinical trial. *Tech Coloproctol* 2014; **18**:373–380.
23 Staikou C, Avramidou A, Ayiomamitis GD, *et al.* Effects of intravenous versus epidural lidocaine infusion on pain intensity and bowel function after major large bowel surgery: a double-blind randomized controlled trial. *J Gastrointest Surg* 2014; **18**:2155–2162.
24 Elhafz AA, Elgebaly AS, Bassuoni AS, El Dabaa AA. Is lidocaine patch as effective as intravenous lidocaine in pain and illus reduction after laparoscopic colorectal surgery? A randomized clinical trial. *Anesth Essays Res* 2012; **6**:40–146.
25 Herroeder S, Pecher S, Schonherr ME, *et al.* Systemic lidocaine shortens length of hospital stay after colorectal surgery: a double-blinded, randomized, placebo-controlled trial. *Ann Surg* 2007; **246**:192–200.
26 Kaba A, Laurent SR, Detroz BJ, *et al.* Intravenous lidocaine infusion facilitates acute rehabilitation after laparoscopic colectomy. *Anesthesiology* 2007; **106**:11–18.
27 Kuo CP, Jao SW, Chen KM, *et al.* Comparison of the effects of thoracic epidural analgesia and i.v. Infusion with lidocaine on cytokine response, postoperative pain and bowel function in patients undergoing colonic surgery. *Br J Anaesth* 2006; **97**:640–646.
28 Harvey KP, Adair JD, Isho M, Robinson R. Can intravenous lidocaine decrease postsurgical ileus and shorten hospital stay in elective bowel surgery? A pilot study and literature review. *Am J Surg* 2009; **198**:231–236.
29 Kranke P, Jokinen J, Pace NL, *et al.* Continuous intravenous peri-operative lidocaine infusion for postoperative pain and recovery. *Cochrane Database Syst Rev* 2015; **7**:CD009642.
30 Paterson HM. Continuous intravenous lidocaine infusion for postoperative pain and recovery in adults. *Tech Coloproctol* 2019; **23**:69–71.