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ORIGINAL SCIENTIFIC REPORT

Efficacy of Intravenous Lidocaine for Postoperative Analgesia Following Laparoscopic Surgery: A Meta-Analysis

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Abstract

Background Intravenous (IV) lidocaine has analgesic and anti-inflammatory properties. This study aims to evaluate the efficacy of IV lidocaine in controlling postoperative pain following laparoscopic surgery.

Methods A meta-analysis of randomised controlled trials (RCTs) comparing IV lidocaine versus placebo/routine treatment for postoperative analgesia following laparoscopic surgery. The primary outcome was opiate requirement at 24 h. Secondary outcomes included cumulative opiate requirement, numerical pain scores (2, 12, 24, 48 h at rest and on movement), recovery indices (nausea and vomiting, length of stay, time until diet resumption, first flatus and bowel movement) and side effects (cardiac/neurological toxicity). Subgroup analyses were performed according to operation type and to compare IV lidocaine with intraperitoneal lidocaine.

Results Fourteen RCTs with 742 patients were included. IV lidocaine was associated with a small but significant reduction in opiate requirement at 24 h compared with placebo/routine care. IV lidocaine was associated with reduced cumulative opiate requirement, reduced pain scores at rest at 2, 12 and 24 h, reduced nausea and vomiting and a shorter time until resumption of diet. The length of stay did not differ between groups. There was a low incidence of IV lidocaine-associated toxicity. In subgroup analyses, there was no difference between IV and intraperitoneal lidocaine in the measured outcomes.

Conclusions IV lidocaine has a multidimensional effect on the quality of recovery. IV lidocaine was associated with lower opiate requirements, reduced nausea and vomiting and a shorter time until resumption of diet. Whilst IV lidocaine appears safe, the optimal treatment regimen remains unknown. Statistical heterogeneity was high.

Introduction

Local anaesthetics have been administered using various routes in an attempt to provide postoperative analgesia. Local anaesthetic infiltrated locally around the operative wound does not provide durable postoperative analgesia [1]. Novel regional anaesthetic techniques including transversus abdominis plane block (TAP) are better [2];

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however, the issue of the limited duration of action of local anaesthetic exists. Wound catheters aim to provide a continuous postoperative infusion of local anaesthetic to the operative site. This group has reviewed these local anaesthetic techniques in the setting of abdominal surgery [3, 4], and more specifically colorectal surgery [5], and demonstrated a reduction in opiate requirement, nausea and vomiting and length of stay. Whilst the beneficial effect of these techniques predominantly arises from local blockade of afferent pain fibres, some therapeutic effect may arise from systemic absorption of local anaesthetics [6–8].

Intravenous (IV) use of local anaesthetics for postoperative analgesia was described over 50 years ago [9, 10]. IV lidocaine has antihyperalgesic [11] and analgesic properties and can be administered safely between 1.3 and 3 mg/kg/h [12]. The mechanism of action of IV lidocaine is debated, and may relate to sodium channel blockade of peripheral afferent pain fibres and attenuation of central excitability in the dorsal horns of the spinal cord [13–15]. IV lidocaine has anti-inflammatory properties [16] and modulates the stress response following open surgery [17].

Previous meta-analyses demonstrated that IV lidocaine reduces postoperative opiate analgesia requirements [18–21]. However, these analyses were limited by heterogeneity of the included studies (non-abdominal and both open and laparoscopic procedures). Since these initial meta-analyses were performed, a large number of high-quality randomised controlled trials (RCTs) have been published. Modern postoperative care is focused on multimodal management to enhance recovery [22]; laparoscopic surgery is a keystone of such an approach. Given the discrepancy in postoperative pain following open and laparoscopic surgery, pooling both types of surgery for meta-analysis may not be appropriate. These issues provide impetus for re-appraisal of the literature.

This study aims to determine the efficacy of IV lidocaine in laparoscopic abdominal surgery.

Methods

The study protocol was designed prospectively following PRISMA guidelines [23] and was reviewed by PROSPERO (CRD42014010300).

Literature search

A literature search was conducted on the 18th June 2014 of PubMed/Ovid Medline, Embase, Cochrane library and clinicaltrials.org. The search was limited to human studies in the English language. The detailed search strategy is presented in supplementary materials (S1.1).

Inclusion criteria

RCTs, abdominal laparoscopic surgery, adult humans (>16 years).

Exclusion criteria

Open surgery, neuraxial techniques, non-general anaesthetic, pharmacokinetic studies, irrelevant techniques and children.

Intervention

IV lidocaine administered perioperatively.

Comparator

Placebo/routine care.

Data extraction/data synthesis

Two reviewers independently reviewed full text articles meeting inclusion criteria. Data were extracted using predesigned proformas (Supplementary material S1.2), either directly or indirectly from figures using plotdigitizer (www.plotdigitizer.sourceforge.net), or if not possible the corresponding author was contacted (Supplementary material S1.3). Where parametric data were not available, the median, range, and group size were used to calculate standard deviations, with the median favoured over the mean when data were skewed [24, 25].

Primary outcomes

Opiate (morphine equivalent, milligrammes) consumption at 24 h postoperatively. Non-morphine opioids were converted to morphine equivalent doses using previously described formulae [26–28].

Secondary outcomes

- *Total cumulative opiate*
- *Pain numerical rating score* (NRS) on movement and at rest at 2, 12, 24 and 48 h postoperatively. A continuous 0–10 scale was used (0 = no pain, 10 = worst possible pain), and alternative methods (e.g. visual analogue scale, millimetres) were converted to this scale.
- *Recovery indices* Nausea and vomiting, length of stay, resumption of diet, and time until first bowel motion and first passage of flatus postoperatively.
- *Side effects* Cardiac side effects (consisting of arrhythmia, severe hypotension, or bradycardia) and

Table 1 Description of included studies

First author (year)	Operation	Design	Group	No. per group	Mean age	Sex (% female)	Intervention protocol	Postoperative infusion	Additional analgesic and anti-emetic drugs	Modified quality score	Paper's conclusions
Laparoscopic cholecystectomy											
Wu et al. [32]	Lap. cholecystectomy	RCT	IV lidocaine	25	51.8	60	Continuous IV infusion of lidocaine 3 mg/kg/h throughout procedure	No	Post-op: IM meperidine PRN, IV prochlorperazine	13	Additional effect on pain relief and synergistic effect on bowel function recovery when combined with dextromethorphan
			Control	25	51.4	56	Continuous IV infusion of saline of equivalent volume				
Lauwick et al. [33]	Lap. cholecystectomy	RCT	IV lidocaine	25	50.2	80	IV bolus of lidocaine 1.5 mg/kg and IV bolus of fentanyl 1.5 mg/kg followed by 2 mg/kg/h IV lidocaine infusion until the end of surgery	No	Intra-op: acetaminophen PR, dexamethasone IV. Ketorolac IV. Droperidol. Pre-incisional 2 % lidocaine infiltration around port-sites +10 ml of 0.25 % bupivacaine at closure	12	IV lidocaine infusion reduces opioid consumption
			Control	24	53.8	54	IV bolus of fentanyl 3 mg/kg		Post-op: Acetaminophen PO,Naproxen, PO, oxycodone PO, ondansetron IV		
Saadawy et al. [34]	Lap. cholecystectomy	RCT	IV lidocaine	40	41.2	85	IV bolus of lidocaine 2 mg/kg followed by continuous IV infusion of lidocaine 2 mg/kg/h until end of surgery	No	Intra-op: Fentanyl IV Post-op: Morphine PCA	13	IV lidocaine improved postoperative analgesia and reduced opioid requirements
			Control	40	42.1	80	IV bolus of saline 25 ml followed by continuous IV infusion of saline at 50 ml/h until end of surgery				
Yang et al. [35]	Lap. cholecystectomy	RCT	IV lidocaine	26	48.5	62	IV bolus of lidocaine 1.5 mg/kg followed by continuous IV infusion of lidocaine 2 mg/kg/h IP instillation of saline	No	Post-op: Fentanyl PCA, ramosetron IV	14	IP lidocaine and IV lidocaine significantly reduced pain and opioid consumption
			IP lidocaine	22	48.0	55	IP instillation of 3.5 mg/kg lidocaine & IV bolus of saline				
			Control	24	48.0	50	IV bolus and IP saline at equivalent volume				

Table 1 continued

First author (year)	Operation	Design	Group	No. per group	Mean age	Sex (% female)	Intervention protocol	Postoperative infusion	Additional analgesic and anti-emetic drugs	Modified quality score	Paper's conclusions
Ram et al. [45]	Lap. cholecystectomy	RCT	IV lidocaine	25	42.6	80	IV bolus of lidocaine 1.5 mg/kg followed by continuous IV infusion of lidocaine 2 mg/kg/h maintained until 1 h after surgery, IP instillation of 100 ml saline	Yes	Pre-op: metoclopramide PO, morphine IM 60 min pre-op. Post-op: Morphine PCA	14	IV lidocaine superior to IP lidocaine in providing pain relief. IV lidocaine brought return of bowel activity
			IP lidocaine	25	42.6	80	IP instillation of 100 ml of 0.2 % lidocaine. IV bolus and continuous IV infusion of saline based on volume of lidocaine that would be needed				
Laparoscopic colorectal resection											
Kaba et al. [36]	Lap. right or left colectomy	RCT	IV lidocaine	20	57	45	IV bolus of lidocaine 1.5 mg/kg followed by continuous IV infusion of lidocaine 2 mg/kg/h during procedure followed by continuous IV infusion of lidocaine 1.33 mg/kg/h postoperatively for 24 h	Yes	Pre-op: hydroxyzine PO Intra-op: droperidol, tropisetron. Sufentanil IV. Acetaminophen IV Post-op: 1st 24 h, Acetaminophen IV, Ketorolac IV, Piritramide PCA After 24 h: Acetaminophen PO, diclofenac, PO tramadol PO	14	IV lidocaine improves postoperative analgesia, fatigue, and bowel function associated with significant reduction in hospital stay
			Control	20	52	25	Equal bolus and infusion volumes of saline				
Kim et al. [37]	Lap. colorectal procedure, right hemicolectomy, left hemicolectomy, anterior resection, subtotal colectomy	RCT	IV lidocaine	32	60.9	28	IV bolus of lidocaine 1 mg/kg followed by continuous IV infusion of lidocaine 1 mg/kg/h with 90 mg ketorolac for 24 h	Yes	Post-op: NSAID and/or meperidine after ketorolac infusion stopped	14	IV lidocaine might reduce postoperative nausea and vomiting
			Control	36	60.1	36	IV bolus of saline then continuous IV infusion of 90 mg ketorolac in 240 ml saline				

Table 1 continued

First author (year)	Operation	Design	Group	No. per group	Mean age	Sex (% female)	Intervention protocol	Postoperative infusion	Additional analgesic and anti-emetic drugs	Modified quality score	Paper's conclusions
Tikuisis et al. [38]	Lap. hemicolectomy	RCT	IV lidocaine	30	57.2	40	IV bolus of lidocaine 1.5 mg/kg (maximum 100 mg) followed by continuous IV infusion of lidocaine 2 mg/kg/h during the surgical procedure. Infusion of 1 mg/kg/h IV lidocaine post-op. Followed by continuous IV infusion of lidocaine 1 mg/kg/h for 24 h after surgery	Yes	Intra-op: Fentanyl IV Post-op: Ketorolac IV, continuous IV fentanyl infusion	12	IV lidocaine infusion has beneficial effects on postoperative pain, restoration of bowel function, and length of stay
			Control	30	56	36	IV bolus of saline followed by continuous IV infusions of saline at equivalent volumes to intervention group				
Laparoscopic gynaecological procedure											
De Oliveira et al. [40]	Lap. gynaecological procedure, salpingo-oophorectomy, cystectomy, tubal ligation, diagnostic laparoscopy	RCT	IV lidocaine	31	37.2	100	IV bolus of lidocaine 1.5 mg/kg followed by continuous IV infusion of lidocaine 2 mg/kg/h maintained until end of surgery	No	Intra-op: Remifentanyl IV, ketorolac IV, ondansetron IV Post-op: Acetaminophen PO, hydromorphone IV, Ibuprofen PO, hydrocodone PO, metoclopramide IV, prochlorpaerazine IV	14	IV lidocaine improves quality of recovery. Patients had less opioid consumption
			Control	32	39.1	100	Equal bolus and infusion volumes of saline				
Grady et al. [39]	Lap. gynaecological procedure, bilateral tubal ligation, diagnostic laparoscopy, lap. salpingectomy-oophorectomy, lap. laser treatment of adhesions, Lap. ovarian cystec	RCT	IV lidocaine	24	31	100	IV bolus of lidocaine 1.0 mg/kg followed by continuous IV infusion of lidocaine 2 mg/kg/h maintained until 15 min before wound closure	No	Pre-op: Fentanyl IV Intra-op: Fentanyl IV Post-op: Fentanyl, meperidine, oxycodone, oxycodone-acetaminophen, hydrocodone-acetaminophen, hydromorphone, ketorolac ondansatron	12	IV lidocaine may improve postoperative pain and shorten time to return of bowel function
			Control	21	31	100	IV bolus of lidocaine 1.0 mg/kg followed by continuous IV infusion of saline at same rate as above				

Table 1 continued

First author (year)	Operation	Design	Group	No. per group	Mean age	Sex (% female)	Intervention protocol	Postoperative infusion	Additional analgesic and anti-emetic drugs	Modified quality score	Paper's conclusions
Laparoscopic urological procedure											
Lauwick et al. [41]	Lap. prostatectomy	RCT	IV lidocaine	20	60	0	IV bolus of lidocaine 1.5 mg/kg followed by continuous IV infusion of lidocaine 2 mg/kg/h until surgery end, Postoperative continuous IV infusion of lidocaine 1 mg/kg/h for 24 h	Yes	Intra-op: Fentanyl IV, dexamethasone IV, ketorolac IV. droperidol. bupivicaine 0.25 % infiltrated around trocar ports Post-op: Morphine PCA, acetaminophen, naproxen, oxycodone once morphine stopped, ondansatron IV	13	IV lidocaine attenuated deterioration in functional walking capacity, and had opioid sparing effects.
			Control	20	59	0	IV bolus of saline followed by continuous IV infusion of saline 6 ml/kg/h until end of surgery, Postoperative continuous IV infusion of saline of equivalent volumes to intervention group				
Wuethrich et al. [42]	Lap. renal surgery, pyeloplasty, adrenalectomy, partial nephrectomy, nephrectomy	RCT	IV lidocaine	32	50.6	50	IV bolus of lidocaine 1.5 mg/kg followed by continuous IV infusion of 2 mg/kg/h. At the end of surgery, dose reduced to 1.3 mg/kg/h for 24 h	Yes	Intra-op: Fentanyl Post-op: Morphine PCA for 24 h, SC morphine for second 24 h IV, acetaminophen, metamizol IV 6 hourly for the next 48 h	14	IV lidocaine did not influence length of the stay, opioid consumption or return of bowel function
			Control	32	52.3	53	IV bolus of saline then continuous IV infusion of saline at equivalent volumes to intervention group				

Table 1 continued

First author (year)	Operation	Design	Group	No. per group	Mean age	Sex (% female)	Intervention protocol	Postoperative infusion	Additional analgesic and anti-emetic drugs	Modified quality score	Paper's conclusions
Other Laparoscopic gastrointestinal surgery											
Kim et al. [43]	Lap. appendicectomy	RCT	IV lidocaine	22	38.5	59	IV bolus of lidocaine 1.5 mg/kg followed by continuous IV infusion of lidocaine 2 mg/kg/h maintained until end of procedure, IP instillation of saline	No	Post-op: Fentanyl PCA	14	IV lidocaine is as effective as IP instillation for reducing pain and fentanyl consumption
			IP lidocaine	25	32	44	IP instillation of lidocaine 3.5 mg/kg at pneumoperitoneum, IV bolus of saline followed by continuous IV infusion of saline until end of procedure				
			Control	21	32	52	Equal bolus, infusion and instillation volumes of saline				
Kim et al. [44]	Lap.-assisted distal gastrectomy	RCT	IV lidocaine	17	59	35	IV bolus of lidocaine 1.5 mg/kg followed by continuous IV infusion of lidocaine 2 mg/kg/h	No	Post-op: Fentanyl PCA	13	IV lidocaine showed reduction in fentanyl use & pain with more favourable outcomes
			Control	17	62	41	Equal bolus and infusion volumes of saline				

RCT randomised controlled trial, *IV* intravenous, *PRN* as required, *IM* intramuscular, *PR* per rectum, *PO* oral, *PCA* patient-controlled analgesia, *NSAID* non-steroidal anti-inflammatory drug, *SC* subcutaneous, *IP* intraperitoneal)

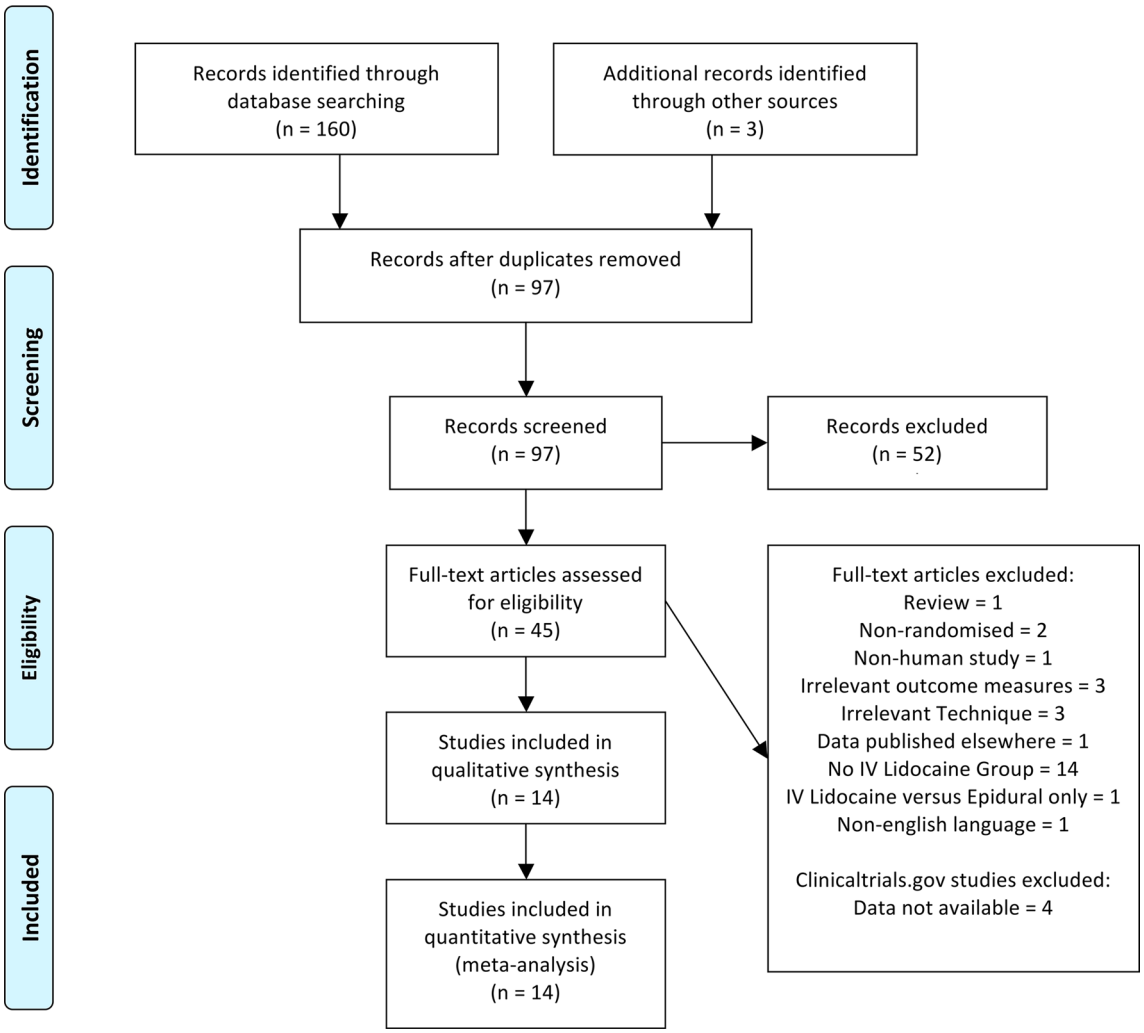

Fig. 1 PRISMA flow diagram detailing literature search

neurological side effects (consisting of numbness, metallic taste, dizziness, visual disturbance, or headaches)

Subgroup analyses

Pre-defined subgroup analyses were performed according to laparoscopic surgery type; (i) cholecystectomy (ii) colonic resection (iii) gynaecological (iv) urological and (v) other gastrointestinal surgery. Secondary analyses compared IV lidocaine to intraperitoneal (IP) lidocaine. A further post hoc analysis compared studies using an intra-operative only regimen of IV lidocaine compared with studies that used both intraoperative and a continuous postoperative infusion. Lastly, a subgroup comparison of low-quality (bias assessment score <10) and high-quality studies was performed.

Bias and quality assessment

Each of the included studies was assessed for quality and potential bias using a modified fifteen-point scale adapted from criteria described by Chalmers and Jadad et al. [29, 30] (Supplementary material S1.1).

Statistical analysis

Continuous variables were analysed using the mean weighted difference (WMD). A random effects model was selected on the basis of radial plots produced for the primary outcome (Supplementary materials S2.1). Dichotomous data were analysed using pooled odds ratios. The statistical significance was set at $p < 0.05$. Heterogeneity was assessed using t^2, χ^2 and I^2 corrected by the DerSimionan–Laird method and classified as low

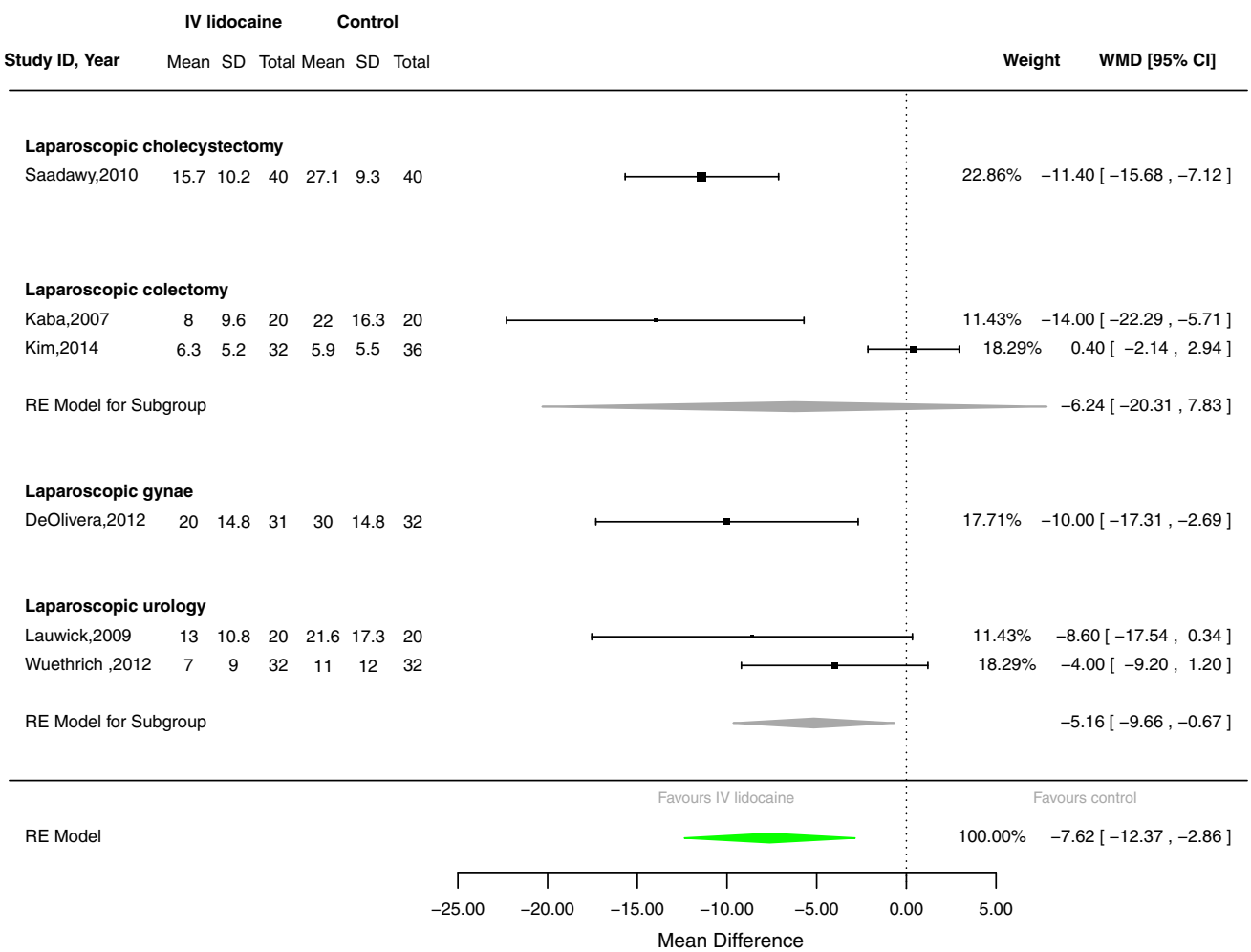

Fig. 2 Forest plot detailing 24-h postoperative opiate consumption (in milligrammes, morphine equivalent dose) (*WMD* Weighted mean difference, *RE* Random effects, *IV* Intravenous, *SD* Standard deviation)

($I^2 < 33$ %), medium (I^2 33–66 %) and high ($I^2 > 66$ %). Sensitivity analyses were performed with and without derived data. Funnel plots were used to assess publication bias, and a weighted regression test with multiplicative dispersion was performed to assess funnel plot asymmetry.

Data were analysed using the metafor package [31] in R (version 3.1.1, R statistical programming 2014).

Results

Fourteen RCTs with a total of 742 patients were included (Table 1) [32–45]. Figure 1 is a PRISMA flow diagram outlining the literature search. All results are presented in Supplementary materials (S2).

Primary outcome

Opiate consumption at 24 hours postoperatively

Significantly lower opiate requirements (morphine equivalent dose) were demonstrated in patients receiving IV lidocaine versus control (6 studies, 355 patients, $I^2 = 78.70$ %, WMD −7.62 mg, CI −12.37 and −2.86, $p = 0.002$) (Fig. 2) [34, 36, 37, 40–42]. This finding was replicated in the urology subgroup (2 studies, 104 patients, $I^2 = 0$ %, WMD −5.16 mg, CI −9.66 to −0.67, $p = 0.02$) [41, 42] but not the colorectal subgroup ($p = 0.4$) [36, 37]. The same result was seen in sensitivity analyses (4 studies, 252 patients, $I^2 = 83.12$ %, WMD −5.99 mg, CI −11.67 to −0.31, $p = 0.04$) [34, 37, 41, 42].

Secondary outcomes

Cumulative opiate consumption postoperatively

The cumulative opiate consumption was lower in the IV lidocaine group compared with control (8 studies, 430 patients, $I^2 = 86.67$ %, WMD 5.93 mg, CI −11.07 to −0.79, $p = 0.02$) (Fig. 3) [32–34, 37, 39, 41, 42]. The result was unchanged following sensitivity analysis. Reduced cumulative opiate use was seen in the laparoscopic cholecystectomy group (3 studies, 179 patients, $I^2 = 0$ %, WMD −6.08 mg, CI −7.96 to −4.21, $p < 0.0001$) [32–34].

Pain scores

Pain scores at rest

There were significantly lower pain scores at rest in the IV lidocaine group at 2 h (8 studies, 430 patients, $I^2 = 98.18$ %, WMD −1.14, CI −1.87 to −0.41, $p = 0.002$) [32–35, 38, 42–44], 12 h (6 studies, 317 patients, $I^2 = 97.46$ %, WMD −1.09, CI −1.67 to −0.51, $p = 0.0002$) [32, 34, 35, 38, 43, 44], 24 h (10 studies, 538 patients, $I^2 = 92.81$ %, WMD −0.42, CI −0.76 to −0.08, $p = 0.02$) [32–35, 37, 38, 41–44] but not 48 h (7 studies, 349 patients, $I^2 = 93.02$ %, WMD 0.15, CI −0.28 to 0.58,

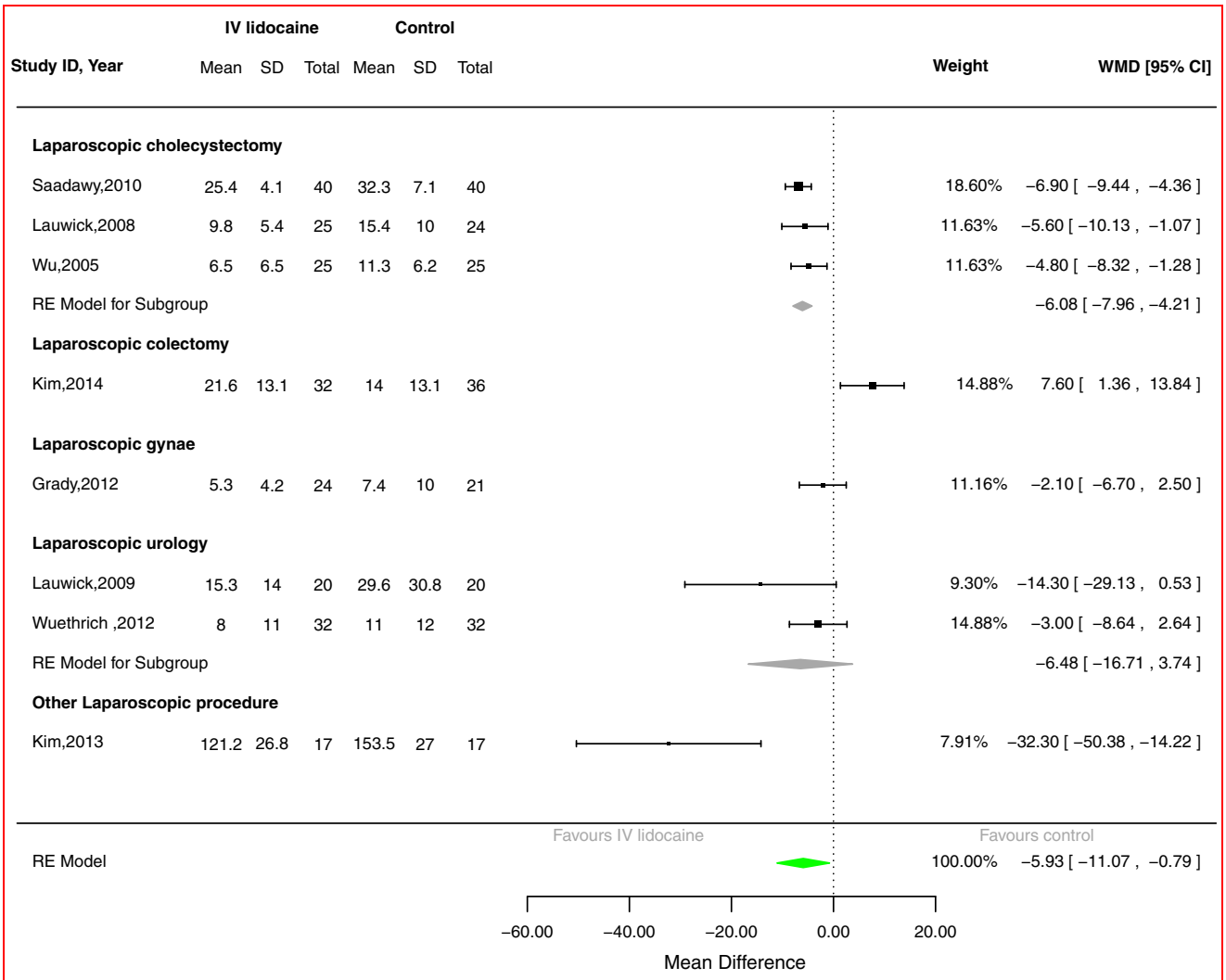

Fig. 3 Cumulative opiate consumption (in milligrammes, morphine equivalent dose) forest plot (*WMD* Weighted mean difference)

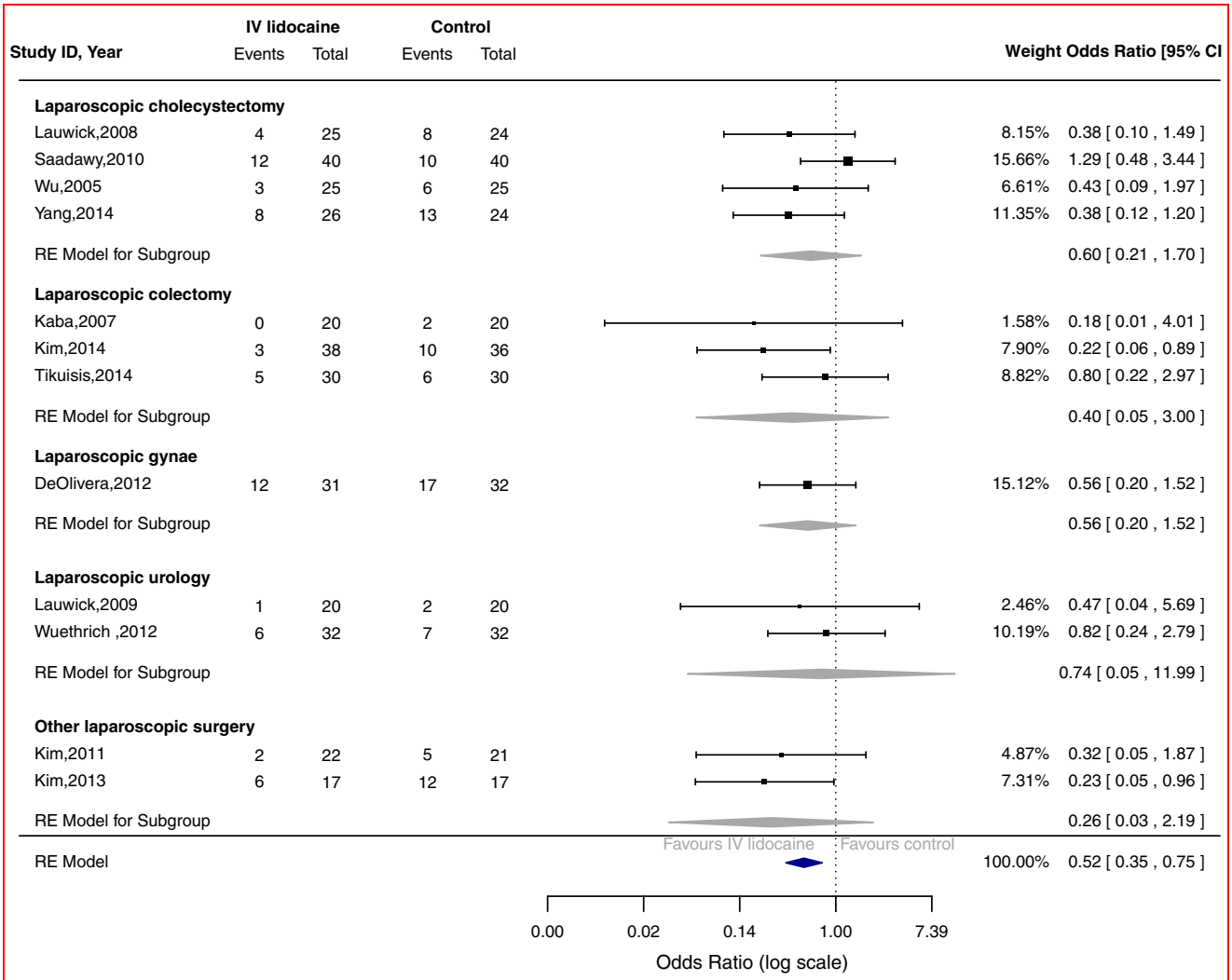

Fig. 4 Nausea and vomiting forest plot

$p = 0.5$) [32, 35, 37, 41–44]. In subgroup analyses, the other laparoscopic GI surgery subgroup demonstrated lower pain scores in the IV lidocaine group at all time points [43, 44]. In the urology subgroup, IV lidocaine was associated with elevated pain scores at 48 h (2 studies, 104 patients, $I^2 = 0$ %, WMD 0.92, CI 0.42–1.41, $p = 0.0003$) [41, 42].

Pain scores on movement

There were significantly lower pain scores on movement in the IV lidocaine group at 12 h (3 studies, 190 patients, $I^2 = 92.42$ %, WMD −1.15, CI −1.97 to −0.32, $p = 0.006$) [32, 34, 38], but not at 2 h (4 studies, 254 patients, $I^2 = 93.40$ %, WMD −0.81, CI −2.05 to 0.42, $p = 0.2$) [32, 34, 38, 42], 24 h (6 studies, 343 patients, $I^2 = 89.44$ %, WMD −0.69, CI −1.39 to 0.01, $p = 0.05$) [32–34, 38, 41, 42] or 48 h (3 studies, 154 patients, $I^2 = 0$, WMD −0.04, CI −0.46 to 0.54, $p = 0.88$) [32, 41, 42]. Pain on movement was significantly lower with IV lidocaine in the laparoscopic cholecystectomy subgroups at 24 and 48 h.

Recovery indices

IV lidocaine was associated with a significantly reduced incidence of nausea and vomiting (12 studies, 647 participants, $I^2 = 0$ %, OR = 0.52, CI 0.35 to 0.75, $p = 0.003$) compared with control (Fig. 4) [32–38, 40–44]. This difference was seen only in pooled analysis and not in individual subgroups. There was no difference in length of stay between study groups (9 studies, 453 participants, $I^2 = 98.91$ %, WMD 0.27 h, CI −11.67 to 12.21, $p = 1.0$) (Fig. 5) [33, 35, 37–39, 41–44] and was similar in all subgroups.

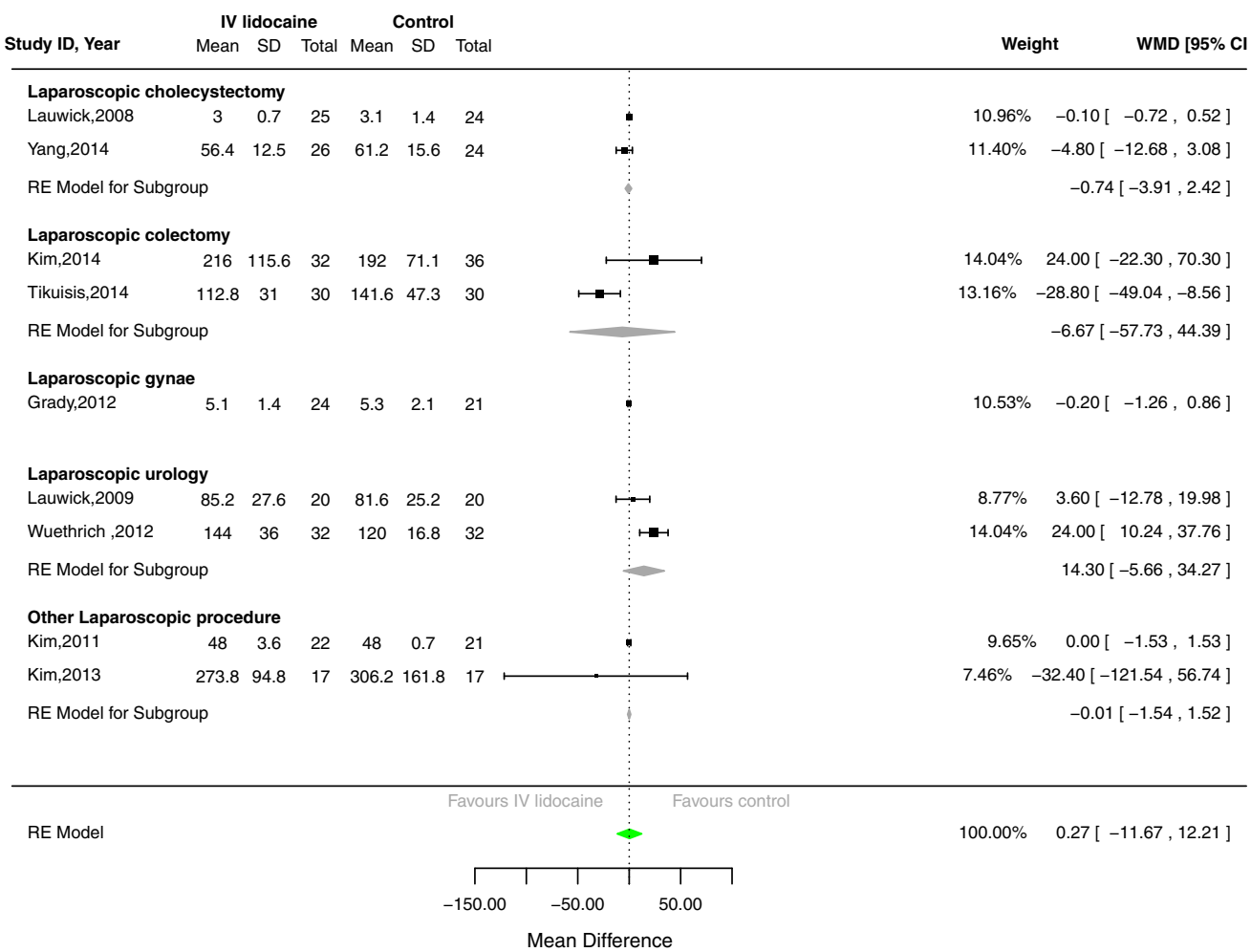

Fig. 5 Length of stay (in hours) forest plot (*WMD* Weighted mean difference)

Diet resumption was quicker in the IV lidocaine group (6 studies, 295 patients, $I^2 = 93.79$ %, WMD −6.20 h, CI −12.37 to −0.03, $p = 0.049$) [35, 37, 38, 41, 43, 44]. Diet resumption was shorter in the colorectal surgery subgroup (2 studies, 128 patients, $I^2 = 0.00$ %, WMD −6.01 h, CI −6.92 to −5.10, $p < 0.001$) [37, 38].

There was no difference in time until first bowel movement (7 studies, 360 patients, $I^2 = 84.48$ %, WMD −3.06 h, CI −9.81 to 3.68, $p = 0.37$) [36–39, 41–43] or time until flatus (8 studies, 437 patients, $I^2 = 89.00$ %, WMD −2.24 h, CI −6.17 to 1.69, $p = 0.26$) [32, 34–37, 39, 41, 42] between groups.

Side effects

In studies that reported IV lidocaine associated side effects, there was one reported cardiac side effect in the IV lidocaine group (arrhythmia, 8 studies, 486 patients) and no neurological side effects [32, 34, 35, 37–40, 42].

Intravenous versus intraperitoneal lidocaine

IV was compared with intraperitoneal lidocaine in three trials including 145 patients [35, 43, 45]. There was no difference between analgesic modalities in any of the measured outcomes.

Discussion

IV lidocaine was associated with reduced 24 h and cumulative opiate consumption compared with placebo/routine treatment. IV lidocaine also demonstrated lower pain scores at rest at 2, 12 and 24 h and on movement at 12 h. IV lidocaine was associated with less nausea and vomiting, and a shorter time until resumption of diet. The other recovery indices were not different between groups. The incidence of IV lidocaine-associated cardiac and neurological side effects was low.

The reduction in opiate consumption in the IV lidocaine group is significant for two reasons. Firstly opiate requirement is a surrogate marker for pain, indicating IV lidocaine is an effective analgesic adjunct with opiates. Secondly, by minimising opiate use, opiate-related side effects may be reduced. Although not all nausea and vomiting can be ascribed to opiates, nausea and vomiting was significantly reduced in the IV lidocaine group, and it may be inferred that the time until resumption of diet was also shorter as a result.

IV lidocaine was also associated with a reduction in pain scores. This reduction in pain scores was most evident at rest and these effects were confined to the first 24 h postoperatively, although this may be influenced by the duration of infusion. In almost all measured outcomes, the difference in pain score was less than the 1.3 point reduction deemed clinically significant [46]. However, the demonstrable reduction in opiate consumption, together with less emesis and quicker resumption of diet indicate that IV lidocaine provides an improved quality of recovery.

A significant strength of this meta-analysis is the attempt to be more procedure-specific by including only laparoscopic surgery. Previous meta-analyses included open and laparoscopic as well as non-abdominal operations [21], although subgroup analysis was attempted to analyse separate operations (although only including 1–3 studies per subgroup) [19]. There is evidence to suggest differing analgesic efficacy in the context of different surgical procedures [47]. It has been postulated that IV lidocaine is the most effective following major open operations as a result of its anti-inflammatory effect [12]. In contrast to this view, the present meta-analysis has demonstrated IV lidocaine to be effective for less invasive laparoscopic procedures. Whilst some subgroups included relatively similar operations (laparoscopic cholecystectomy), other subgroups consisted of very different operations (urology subgroup included laparoscopic prostatectomy and nephrectomy, Table 1). The extent of IP dissection is likely to lead to differing levels of pain [48–50]. The size and location of the specimen extraction incision will also vary according with each operation. This heterogeneity in operation type also manifests statistically, with almost all of the reported continuous outcomes demonstrating high levels of statistical heterogeneity ($I^2 > 66$ %). Inter-study differences in postoperative adjunct analgesic and anti-emetic regimens may additionally contribute to heterogeneity seen in the present meta-analysis (Table 1).

An early meta-analysis [18] demonstrated a shorter length of stay associated with IV lidocaine in open and laparoscopic surgery combined. This has not been replicated by a more recent meta-analysis and this study [19]. Length of stay as an outcome should be treated with caution in pooled analyses as data are likely to have a skewed distribution and are affected by local factors, culture and practice. Following abdominal surgery the time until resumption of diet serves as a good indication of gut function. Resumption of diet was significantly faster in the IV lidocaine group, notably in the colorectal surgery subgroup where gastrointestinal paralysis is often the major barrier to recovery and discharge. There were non-significant trends towards a shorter time to first flatus and bowel movement in the IV lidocaine group.

The IV lidocaine dose range used in the included studies was a bolus of 1–2 mg/kg (median 1.5 mg/kg) followed by an intraoperative infusion of 1–3 mg/kg/h (median 2 mg/kg/h) and 1–1.3 mg/kg/h (median 1 mg/kg/h) in those studies that continued the infusion in the postoperative period. Most studies based on their doses of IV lidocaine on previously published regimens. The intraperitoneal dose of lidocaine was 3.5 mg/kg. The bolus IV dose for treatment of ventricular arrhythmias is 1.5 mg/kg [51, 52]. Plasma concentrations of lidocaine are generally considered to be safe below 5 μg/ml and can cause cardiac toxicity between 5 and 10 μg/ml [53]. The plasma levels of lidocaine measured in one included study were all lower than the threshold safety level of 5 μg/ml (mean of 2.4 μg/ml (SD 0.6, max 4.0 μg/ml) at termination of surgery and 2.7 μg/ml (SD 1.1, max 4.6 μg/ml) at the end of 24 h infusion) [36]. Other studies have shown similar doses of IV lidocaine are associated with plasma concentrations less than 5 μg/ml threshold [54, 55]. Importantly IV lidocaine appears to be a safe treatment modality. There was only one reported instance of cardiac arrhythmia, although one other study reported witnessed arrhythmias on cardiac monitoring with no clinical sequelae [32]. There were no reported neurological side effects in any study.

Intraperitoneal instillation of local anaesthetic was first described as an alternative local anaesthetic route in 1951 [56], and has re-emerged following the increasing utilisation of laparoscopic surgery. The mechanism of action of intraperitoneal local anaesthetic is disputed with some suggesting that analgesic effects result from systematic absorption of LA through the peritoneum [57, 58]. In the present study, there was no difference between intraperitoneal and IV lidocaine in the measured outcomes; however, the number of studies was small.

The optimal perioperative treatment protocol for IV lidocaine is currently unknown. The present meta-analysis sought to compare intraoperative infusion only with a postoperative infusion continued into the postoperative period. This could not be adequately addressed on the basis of the current literature as a result of the different operation profiles between the two subgroups. RCTs that employed a continuous postoperative infusion predominantly consisted of major surgery, whereas those within the intraoperative infusion group consisted mostly of day case surgery where

a continuous postoperative infusion is not likely to be appropriate.

Conclusion

This present study confirms the analgesic and opiate sparing attributes of IV lidocaine following laparoscopic surgery. Reduced nausea and vomiting and more rapid return to food intake emphasise that the overall quality of recovery may be improved with IV lidocaine. The optimal dose and duration of lidocaine infusion need to be tested in carefully designed prospective clinical studies.

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Conflict of interests No conflicts of interest to declare.

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