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Perioperative intravenous lidocaine infusion for postoperative pain control: a meta-analysis of randomized controlled trials

Perfusion intraveineuse périopératoire de lidocaïne pour le contrôle de la douleur postopératoire: une méta-analyse d'études randomisées contrôlées

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Abstract

Introduction *Various strategies have been proposed for postoperative pain control. Among those, intravenous lidocaine infusion (IVLI) has gained in interest. However, its clinical benefit remains unclear. This systematic review is an evaluation of the analgesic efficacy and safety of IVLI during general anesthesia.*

Methods *A systematic search was performed using MEDLINE, EMBASE, Cochrane, and SCOPUS databases, likewise, grey literature. The review included all randomized controlled trials that used a placebo or any comparator and evaluated IVLI during general anesthesia for any type of surgery. Primary outcomes were pain control and opioid requirement. Secondary outcomes were mortality, length of stay, ileus recovery time, nausea/vomiting, and adverse events. Random effects models were used and heterogeneity was assessed using the I^2 index.*

Results *From 5,472 citations retrieved, 29 studies involving a total of 1,754 patients met eligibility. At six hours postoperatively, intravenous lidocaine infusion reduced pain at rest (weighted mean difference [WMD] −8.70, 95% confidence intervals [CI] −16.19 to −1.21), during cough (WMD −11.19, 95% CI −17.73 to −4.65), and during movement (WMD −9.56, 95% CI −17.31 to −1.80). Intravenous lidocaine infusion also reduced opioid requirement (morphine) (WMD −8.44 mg, 95% CI −11.32 to −5.56), time to first flatus (WMD −7.62 hr, 95% CI −10.78 to −4.45), time to first feces (WMD −10.71 hr, 95% CI −16.14 to −5.28), nausea/vomiting (risk ratios = 0.71, 95% CI 0.57-0.90), and hospital length of stay (WMD −0.17 days, 95% CI −0.41 to 0.07). Abdominal surgery was strongly associated with benefit. For the 12 studies that systematically screened adverse events, the*

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incidence of cardiac and neurologic adverse events was comparable. Eight studies observed toxic plasma levels.

Discussion *Perioperative IVLI reduced postoperative pain and opioid requirement, as well as ileus recovery time, hospital length of stay, and nausea/vomiting. Intravenous lidocaine infusion was effective mainly in abdominal surgery populations. Considering that toxic levels were detected and that adverse events were not systematically screened for in most studies, dose and safety of IVLI should be established before recommending its use.*

Résumé

Introduction *Plusieurs stratégies ont été proposées pour le contrôle de la douleur postopératoire. Parmi ces stratégies, la lidocaïne par voie intraveineuse suscite un intérêt croissant. Toutefois, ses avantages cliniques demeurent peu clairs. Cette revue méthodique est une évaluation de l'efficacité analgésique et de l'innocuité de la lidocaïne par voie intraveineuse pendant l'anesthésie générale.*

Méthode *Une recherche méthodique a été réalisée dans les bases de données MEDLINE, EMBASE, Cochrane et SCOPUS ainsi que dans la littérature grise. Cette revue a tenu compte de toutes les études randomisées contrôlées ayant utilisé un placebo ou un traitement de référence et évalué la lidocaïne par voie intraveineuse pendant l'anesthésie générale, quel que soit le type de chirurgie. Les principaux critères d'évaluation étaient le contrôle de la douleur et le besoin en opioïdes. Les critères d'évaluation secondaires étaient la mortalité, la durée d'hospitalisation, le temps de récupération du transit intestinal, les nausées et vomissements et les événements indésirables. Des modèles à effets aléatoires ont été utilisés et l'hétérogénéité a été évaluée à l'aide de l'indice I^2.*

Résultats *Des 5472 citations extraites, 29 études auxquelles un total de 1754 patients ont participé répondaient à nos critères de sélection. Six heures après l'opération, la lidocaïne par voie intraveineuse a réduit la douleur au repos (différence moyenne pondérée [DMP] −8,70, intervalles de confiance [IC] 95 % −16,19 à −1,21), pendant les épisodes de toux (DMP −11,19, IC 95 % −17,73 à −4,65), et en mouvement (DMP −9,56, IC 95 % −17,31 à −1,80). La lidocaïne par voie intraveineuse a également réduit le besoin en opioïdes (morphine) (DMP −8,44 mg, IC 95 % CI −11,32 à −5,56), le temps jusqu'à la première flatuosité (DMP −7,62 h, IC 95 % −10,78 à −4,45), le temps jusqu'à la première selle (DMP −10,71 h, IC 95 % −16,14 à −5,28), les nausées et vomissements (risques relatifs = 0,71, IC 95 % 0,57-0,90) et la durée d'hospitalisation (DMP −0,17 jours, IC 95 % −0,41 à 0,07). La chirurgie abdominale a été fortement associée aux bienfaits de la lidocaïne par voie intraveineuse. Dans les 12 études ayant méthodiquement rendu compte*

des événements indésirables, l'incidence d'événements indésirables cardiaques et neurologiques était comparable. Huit études ont fait état de taux plasmatiques toxiques.

Discussion *La lidocaïne par voie intraveineuse périopératoire a réduit la douleur postopératoire et le besoin d'opioïdes, ainsi que le temps de récupération du transit intestinal, la durée d'hospitalisation et les nausées et vomissements. La lidocaïne par voie intraveineuse a été particulièrement efficace chez les patients subissant une chirurgie abdominale. Étant donné que des niveaux toxiques ont été observés dans la plupart des études sans pour autant qu'une association avec les événements indésirables puisse être établie, la posologie et l'innocuité de la lidocaïne par voie intraveineuse devrait être déterminée avant de recommander son utilisation.*

Postoperative pain control is a major concern in anesthesia, especially in the emerging field of fast-track surgery.[1,2] Anesthesiologists can choose among different interventions for postoperative pain control, but there is little evidence that different pain intervention strategies impact clinically important postoperative outcomes.[3]

Many years ago, intravenous infusion of lidocaine (IVLI) was proposed as an anesthesia adjuvant, but this approach has gained in interest in the medical literature only recently.[4] Lidocaine has been described as having analgesic,[5] anti-hyperalgesic,[6] and anti-inflammatory[5,7] properties. Two systematic reviews evaluating the effect of IVLI for pain relief in patients with chronic neuropathic pain or burn injury showed a potential benefit. However, its effect on postoperative outcomes is not well understood.[8,9] Recently, two systematic reviews evaluated the effect of perioperative use of IVLI as an adjuvant to general anesthesia. However, one review was limited to abdominal surgery and did not include an evaluation of potential side effects of IVLI,[10] while the other review included only a small number of studies due to a limited search strategy.[11]

Thus, we undertook a systematic review of randomized controlled trials to evaluate the efficacy and safety of perioperative IVLI on postoperative outcomes in all types of surgery requiring general anesthesia.

Methods

Search strategy

We electronically searched Ovid Medline (1950 - July 2010, Week 1), Embase (1974 - July 2010, Week 1), the Cochrane Central Register of Controlled Trials, and the Scopus database. No restrictions were used in language or type of publication. To identify relevant grey literature, we

used the OpenSIGLE repository and three public search engines, i.e., Google Scholar, Intute, and the Trip databases. The search strategy was developed for Medline and adapted for each database using the same keywords. The keywords and MESH (EMTREE) terms used were divided in two main categories: 1) groups of keywords for lidocaine and 2) groups of keywords for surgery/anesthesia. We also used specific filters in Medline[12] and Embase[13] to limit our search to randomized control trials (RCTs). This search strategy was designed and peer-reviewed by co-investigators prior to its execution. The complete search strategy used in Medline is presented in the Appendix. We reviewed the bibliographies of all included studies to identify additional relevant publications.

Study selection

We included RCTs that evaluated the efficacy on postoperative outcomes of administering IVLI in adults ($\geq$18 yr old) during general anesthesia. We included all comparator groups, including placebo and usual care.

Data abstraction

We developed a standardized data abstraction form. Following pilot testing of the form, data were abstracted independently by two investigators (L.V. and D.C.), and disagreements were resolved by consensus or by a third party (A.F.T.). Citations from the grey literature were adjudicated by a single reviewer (L.V.). If important data were missing or were ambiguous, corresponding authors were contacted to obtain additional information.

Outcome measures and data collected

Our primary outcomes were pain control, as assessed by visual analog scales or the equivalent, and the use of opioids. Secondary outcomes were mortality, postanesthesia care unit (PACU) and hospital length of stay, ileus recovery time (as defined by time to first flatus and/or feces), incidence of nausea or vomiting, the use of volatile anesthetics, and adverse events.

For each selected study, we collected the following population characteristics: age, sex, weight, American Society of Anesthesiologists physical status, type and length of surgery, chronic use of opioids, and factors potentially affecting lidocaine metabolism (i.e., hepatic disease and chronic use of propanolol). The study intervention characteristics collected were bolus dose, infusion rate, length of infusion, timing of infusion, total dose, and mean plasma lidocaine concentration. We also noted relevant co-interventions, such as local or regional anesthesia, including opioids or other anesthetic agents. Recorded

adverse events included plasma lidocaine concentration >5 µg·mL^{-1} allergic reaction, neurological events (seizure, coma, tinnitus, numbness of the tongue, restlessness, vertigo, drowsiness, and apnea), or cardiovascular side effects (hypotension, arrhythmias). When data were not mutually exclusive for a specific adverse event, the highest incidence was used for analysis.

Data synthesis

Pain scores were analyzed at six, 12, 24, 48, and 72 hr following surgery. When data from one of these specific time periods were not available, data from the closest time interval were used. In one study, patients were randomized into four groups: two groups received IVLI, but with a different co-intervention, and two groups received the same comparator.[14] Morphine equivalence was calculated for opioids when means $\pm$ standard deviations were reported. The following equivalents were considered: 10 mg of morphine = 100 µg of fentanyl iv,[15] 75 mg of meperidine im,[15,16] 15 mg of piritramide iv,[17] or 10 µg of sufentanil iv.[18]

Risk of bias assessment

The methodological quality of the included studies was evaluated by two reviewers (L.V. and D.C.) using an adaptation of the scale used by the Cochrane Collaboration[19,20] and the Jadad scale.[21] The Cochrane Risk-of-Bias assessment tool allows a qualitative evaluation of the probability of bias (low, high, unclear) in five different potential sources of bias.

Statistical analysis

Data were analyzed with Review Manager, version 5.0 (RevMan, The Cochrane Collaboration, Oxford, United Kingdom) using random effects models. Continuous data are expressed as weighted mean difference (WMD) with 95% confidence intervals, while dichotomous data are presented as risk ratios (RR). Heterogeneity was evaluated using the I^2 index.[22] Sensitivity analyses were performed to identify potential sources of heterogeneity based on the following subgroups determined a priori: methodological quality (Jadad score $\geq$3 vs <3, placebo or other comparator, blinding), type of surgery (cardiac, abdominal, open, or laparoscopic), intervention regimen (bolus prior to infusion, infusion rate $\geq$3 mg·kg^{-1}·hr^{-1}, infusion prolonged after surgery, infusion during outcome measurement), and source of sponsorship.

We conducted the study and prepared the manuscript following the guidelines from the PRISMA statement for systematic reviews and meta-analyses (www.prisma-statement.org).

Results

Literature search

We extracted 5,072 records, excluding duplicates, from the four main databases searched (Embase, Medline, Cochrane, and Scopus) (Fig. 1), and from those we selected 32 citations for inclusion. Three studies were excluded because none of the outcomes of interest were evaluated. Searching the grey literature through OpenSIGLE and the three public search engines did not identify additional studies. Thus, 29 studies enrolling a total of 1,754 patients were ultimately included in this systematic review.

Description of included studies

All studies were written in English except one in German[23] and one in Spanish.[24] Seven studies originated in the USA,[25-31] one in Belgium,[32] two in Taiwan,[14,33] three in Germany,[23,34,35] one in New Zealand,[36] three in Sweden,[37-39] two in China,[40,41] one in France,[42] three in Canada,[43-45] one in Mexico,[24] two in Saudi Arabia,[46,47] one in Israel,[48] one in the Republic of Korea[49] and one in Finland.[50] Studies were conducted in patients undergoing abdominal, cardiac, thoracic, orthopedic, or urologic

surgery (Table 1). Source of sponsorship was not mentioned in 11 studies,[23-27,29,42,45-48] while other studies received grants from foundations, national councils, or universities. No study reported industry sponsorship. Descriptions of the 29 studies are summarized in Table 1.

Risk of bias assessment

Twelve studies (46%) had a low risk of bias according to the five potential sources of bias considered in the Cochrane Risk-of-Bias assessment tool (Table 2). Two studies had a high risk of bias, as they were not blinded.[28,50] In contrast, 23 (79%) studies with a score $\geq$ 3 using the Jadad scale were considered of high methodological quality.[51] Twenty-six (90%) studies were placebo-controlled blinded studies.[14,23-27,29-43,45-49]

Primary outcomes

Postoperative pain

Postoperative pain was evaluated in 19 studies and at different time periods, from one minute to 96 hr following surgery. Most studies presented mean pain

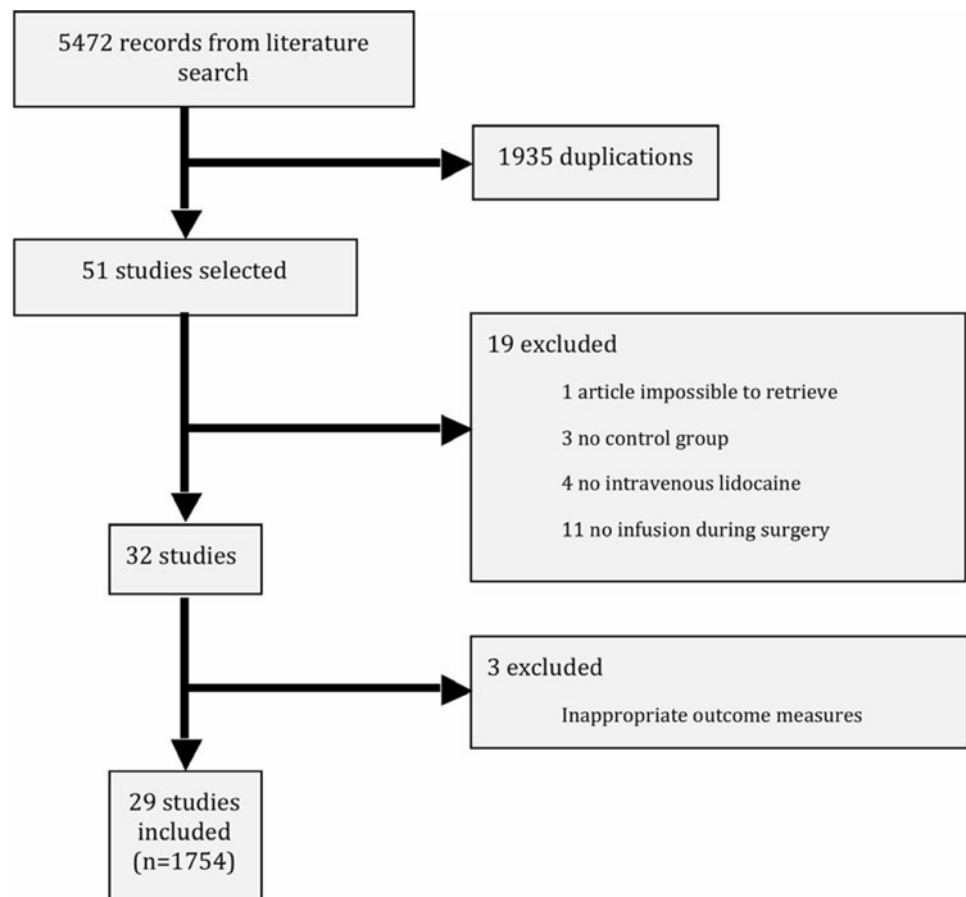**Fig. 1** Results of the search strategy

Table 1 Description of included studies

Studies	N	Population Groups	Age	Surgery	Intervention Bolus	Intervention Infusion	Total dose	Duration of infusion	Outcomes measured (main outcome underlined)	Follow-up period
Knight et al. (1980)[28]	40	Lidocaine (n = 20)	NM	CABG and valve surgery	6 mg·kg⁻¹	up to 21 mg·kg⁻¹	1,373 ± 903.4 mg	NA	HD during surgery, PLC	End of surgery
		Morphine (n = 20)	NM		0.5–1 mg·kg⁻¹	up to 2 mg·kg⁻¹	121 ± 53.7 mg	NA		
Kasten et al. (1982)[29]	20	Lidocaine (n = 10)	58.1 ± 6.3	CABG	3 mg·kg⁻¹	0.05 mg·kg⁻¹·min⁻¹	851 ± 160 mg	NA	HD during surgery PLC	30 min PO
		Saline (n = 10)	55.1 ± 6.0		Same volume	Same volume	0			
Cassuto et al. (1985)[38]	20	Lidocaine (n = 10)	44 (30–67)*	Cholecystectomy	100 mg	2 mg·min⁻¹	3,190 mg (3,130–3,280) mg	105 min (75–150)* + 24 hr PO	POP, meperidine consumption, PLC, HD, No/Vo	48 hr PO
		Saline (n = 10)	55 (34–68)*		Same volume	Same volume	0	112 min (68–150)* + 24 hr PO		
Wallin et al. (1987)[39]	38	Lidocaine (n = 18)	54 ± 8.5	Cholecystectomy	100 mg	2 mg·min⁻¹	3,260 ± 51 mg	30 min preop + 110 ± 25.5 min + 24 hr PO	Autonomic response during surgery, meperidine consumption, HD, AE, No/Vo	2 days PO
		Saline (n = 20)	49 ± 8.9		Same volume	Same volume	0	Same + 102 ± 35.8 min		
Rimbäck et al. (1990)[37]	30	Lidocaine (n = 15)	55 ± 11.6	Elective cholecystectomy	100 mg	3 mg·min⁻¹	4,747 ± 81.3 mg	109 ± 27.1 min + 24 hr PO	PO colonic inhibition, bowel function, HD, POP, No/Vo, AE	3 days PO
		Saline (n = 15)	51 ± 11.6		Same volume	Same volume	0	104 ± 31.0 min + 24 hr PO		
Striebel et al. (1992)[23]	42	Lidocaine (n = 20)	32.2 ± 10.7	Tonsillectomy	1.5 mg·kg⁻¹	2 mg·kg⁻¹·hr⁻¹ for 6 hr then 0.5 mg·kg⁻¹·hr⁻¹ for 18 hr	724.5 ± 240.8 mg	24 hr	POP, analgesic consumption, PLC, AE	24 hr PO
		Saline (n = 20)	31.1 ± 10.6		Same volume	Same volume	0	Same		
Insler et al. (1995)[26]	100	Lidocaine (n = 44)	62.7	CABG	1.5 mg·kg⁻¹	0.03 mg·kg⁻¹·min⁻¹	NA	Surgery + 48 hr PO OR ICU discharge earlier	POP, PO sedation, HD, time to extubation, ICU-LOS, hr-LOS, myocardial infarction, PLC	Hospital discharge
		Placebo (n = 45)			Same volume	Same volume	NA	Same		
Groudine et al. (1998)[27]	40	Lidocaine (n = 18)	Mean 64.7 Range (47–74)	Radical retropubic prostatectomy	1.5 mg·kg⁻¹	2 or 3 mg·kg⁻¹·hr⁻¹	NA	NA + 1 hr PO	PO bowel function, H-LOS, analgesic consumption, POP, PLC	Hospital discharge
		Saline (n = 20)			Same volume	Same volume	0	NA + 1 hr PO		
Rinne et al. (1998)[50]	100	Lidocaine (n = 50)	60 ± 8	CABG	1 mg·kg⁻¹	20 µg·kg⁻¹·min⁻¹	NA	20 hr	Cardioprotection, cardiac function and HD, PLC	3 days PO
		No infusion (n = 50)	61 ± 8		0	0	0	0		
Mitchell et al. (1999)[36]	65	Lidocaine (n = 28)	56.9 ± 8.9	Left heart valve surgery	1 mg·kg⁻¹	240 mg × 1 hr, 120 mg × 1 hr, 60 mg·hr⁻¹	NA	48 hr	Cerebral protection, neuropsychologic tests, PLC, HD, ICU-LOS, ventilation, hepatic function, renal dysfunction, H-LOS	6 months PO
		Dextrose 5% (n = 27)	54.4 ± 9.7		Same volume	Same volume	Same	Same		

Table 1 continued

Studies	N	Groups	Surgery	Age	Bolus	Infusion	Total dose	Duration of infusion	Outcomes measured (main outcome underlined)	Follow-up period
									Population			Intervention					
Wang et al. (2002)[41]	118	Lidocaine (n = 43)	CABG	57.8 ± 9.7	1.5 mg·kg⁻¹ + 4 mg·kg⁻¹ (priming of CPB)	4 mg·min⁻¹	994.7 ± 236.8 mg	149.4 ± 59.2 min	PO cognitive dysfunction, ICU-LOS, ICU ventilation, ICU intubation, HD, H-LOS, transfusion, PLC	9 days PO
		Saline (n = 45)		59.3 ± 9.4	Same volume	Same volume	0	132.2 ± 53.0 min		
Koppert et al. (2004)[34]	43	Lidocaine (n = 20)	Major abdominal surgery	58 ± 12	1.5 mg·kg⁻¹	1.5 mg·kg⁻¹·hr⁻¹	816.5 ± 238.1 mg	6.2 ± 2.1 hr	POP, morphine consumption, PLC, bowel function	Hospital discharge
		Saline (n = 20)		56 ± 12	Same volume	Same volume	0	6.2 ± 1.9 hr		
Wu et al. (2005)[14]	100	DM IM + saline iv (n = 25)	Laparoscopic cholecystectomy	52.4 ± 10.2	0	DM 40 mg (20 mg CMP) IM 30 min pre-incision	0	Infusion 30 min before incision + 81.8 ± 8.6 min	POP, meperidine consumption, AE, bowel function	48 hr PO
		CMP IM + lidocaine iv (n = 25)		51.8 ± 7.2	0	CMP 20 mg IM lidocaine 3 mg·kg⁻¹·hr⁻¹	344.2 ± 28.1 mg	Infusion 30 min before incision + 81.4 ± 9.1 min		
		CMP IM, saline iv (n = 25)		51.4 ± 8.4	0	CMP 20 mg IM saline 3 mg·kg⁻¹·hr⁻¹	0	Infusion 30 min before incision + 81.0 ± 8.4 min		
		DM IM + Lidocaine iv (n = 25)		50.9 ± 9.6	0	DM 40 mg (20 mg CMP) IM Lidocaine 3 mg·kg⁻¹·hr⁻¹	334.2 ± 25.5 mg	Infusion 30 min before incision + 81.2 ± 8.5 min		
Kuo et al. (2006)[33]	60	Lidocaine iv, saline epidural (n = 20)	Colorectal surgery	63 (50–75)	2 mg·kg⁻¹	3 mg·kg⁻¹·hr⁻¹	700.5 ± 41.2 mg	30 min preop 157.8 ± 13.4 min	Immune response, POP, bowel function, analgesic consumption, bowel function, H-LOS, No/Vo	Hospital discharge
		Saline iv and saline epidural (n = 20)		62 (46–85)	Same volume	Same volume		30 min preop + 150.8 ± 11.5 min		
Kaba et al. (2007)[32]	45	Lidocaine (n = 20)	Laparoscopic colectomy	57 ± 17	1.5 mg·kg⁻¹	2 mg·kg⁻¹·hr⁻¹	3,007.1 ± 120.6 mg	169 ± 47 min + 24 hr PO	Acute rehabilitation. POP, piritramide consumption. PO fatigue score, bowel function, H-LOS. No/Vo, Biochemical markers, immune response, PLC, HD	Hospital discharge
		Saline (n = 20)		52 ± 13	Same volume	Same volume	0	170 ± 48 min + 24 hr PO		
Herroeder et al. (2007)[35]	66	Lidocaine (n = 31)	Colorectal surgery	56.1 ± 11.8	1.5 mg·kg⁻¹	2 mg·min⁻¹	982.5 ± 119.0 mg	194.3 ± 59.48 min + 4 hr PO	H-LOS, PACU-LOS, bowel function, POP, opioid consumption, immune response, PLC	Hospital discharge
		Saline (n = 29)		56.9 ± 12.0	Same volume	Same volume	0	210.5 ± 96.29 min + 4 hr PO		
Martin et al. (2008)[42]	60	Lidocaine (n = 28)	Hip arthroplasty	64 ± 9	1.5 mg·kg⁻¹	1.5 mg·kg⁻¹·hr⁻¹	NM	30 min before incision and 1 hr PO	Morphine consumption, POP, opioid consumption, hip flexion angle, pressure pain perception, PLC, H-LOS	3 months PO
		Saline (n = 30)		6 ± 13	Same volume	Same volume	NM	Same		

Table 1 continued

Studies	N	Population			Intervention		Total dose	Duration of infusion	Outcomes measured (main outcome underlined)	Follow-up period
		Groups	Surgery	Age	Bolus	Infusion				
Lauwick et al. (2008)[44]	50	Lidocaine (n = 25)	Endocholecystectomy	50.2 ± 15.5	1.5 mg·kg⁻¹	2 mg·kg⁻¹·hr⁻¹	234.15 ± 48.3 mg	60 (50–65)* min	Fentanyl consumption in PACU, No in PACU, POP, PACU-LOS	24 hr after hospital discharge
		No infusion (n = 24)		53.8 ± 16.4	nothing	nothing	0	70 (57.5–80)* min		
El-Tahan et al. (2009)[46]	90	Lidocaine (n = 45)	Cesarian Delivery	28.1 ± 4.2	1.5 mg·kg⁻¹	1.5 mg·kg⁻¹·hr⁻¹	363.7 ± 10.4 mg	30 min before incision and 1 hr PO surgery: 43.2 ± 5.5 min	Surgical stress response and neonatal outcome, uterine tone, PLC, AE	24 hr PO
		Saline (n = 45)		26.5 ± 4.6	Same volume	Same volume	0	30 min before incision and 1 hr PO surgery: 40.8 ± 6.6 min		
Mathew et al. (2009)[30]	277	Lidocaine (n = 88)	CABG and valve surgery	61.7 ± 11.9	1 mg·kg⁻¹	4 mg·min⁻¹ × 1 hr, 2 mg·min⁻¹ × 1 hr, 1 mg·min⁻¹ × 46 hr	3,206.1 ± 18.7 mg	48 hr	PO cognitive function, PLC, immune response, AE	1 yr PO
		Saline (n = 94)		61.4 ± 13.9	Same volume	Same volume	0	Same		
Lauwick et al. (2009)[43]	40	Lidocaine (n = 20)	Laparoscopic prostatectomy	60 ± 6	1.5 mg·kg⁻¹	2 mg·kg⁻¹·hr⁻¹ for the surgery, then 1 mg·kg⁻¹·hr⁻¹ for 24 hr	2,705.8 ± 444.3 mg	322.5 (283.5–349.0)* min	Functional walking capacity, morphine consumption, PO bowel function, POP	Hospital discharge
		Saline (n = 20)		59 ± 8	Same volume	Same volume	0	300.0 (272.5–322.5)* min		
Juàrez-Pichardo et al. (2009)[24]	45	Lidocaine (n = 15)	Laparoscopic cholecystectomy	‘	1 mg·kg⁻¹	25 µg·kg⁻¹·min⁻¹	251.3 ± 63.2 mg	103 ± 36 min	PO, HD, PO sedation, POP	100 min PO
		Placebo (n = 15)		42 ± 12	Same volume	Same volume	0	NM		
Yardeni et al. (2009)[48]	65	Lidocaine (n = 30)	Abdominal hysterectomy	55.9 ± 5.6	2 mg·kg⁻¹	1.5 mg·kg⁻¹·hr⁻¹	259.9 ± 11 mg	109 ± 8.43 min	POP, analgesia consumption, immune response	72 hr PO
		Saline (n = 30)		53.4 ± 8.2	Same volume	Same volume	0	106 ± 14.6 min		
McKay et al. (2009)[31]	67	Lidocaine (n = 29)	Ambulatory surgery	43 ± 15	1.5 mg·kg⁻¹	2 mg·kg⁻¹·hr⁻¹	517 ± 203 mg	NM	PACU-LOS, POP, PO opioid consumption, No/Vo, PLC	24 hr after hospital discharge
		Saline (n = 27)		46 ± 15	Same volume	Same volume	0	NM		
Cui et al. (2010)[40]	45	Lidocaine (n = 20)	Thoracic surgery	54 ± 9	0	33 µg·kg⁻¹·min⁻¹	411.8 ± 85.8 mg	192 ± 40 min	Morphine consumption and POP in PACU and ward, propofol effect-site concentration, PO sedation/agitation, PLC, AE	7 days PO
		Saline (n = 20)		51 ± 10	0	Same volume	0	204 ± 41 min		
Saadawy et al. (2010)[47]	120	Lidocaine (n = 40)	Laparoscopic cholecystectomy	41.2 ± 8.4	2 mg·kg⁻¹	2 mg·kg⁻¹·hr⁻¹	374.1 ± 42.1 mg	80.3 ± 15.8 min	Morphine consumption in first 24 hr, POP, quality of sleep PO bowel function, PLC, AE	24 hr PO
		Saline (n = 40)		42.1 ± 8.5	25 mL	50 mL·hr⁻¹	0	79.5 ± 16.8 min		
Bryson et al. (2010)[45]	93	Lidocaine (n = 44)	Abdominal hysterectomy	46.3 ± 5.7	1.5 mg·kg⁻¹	3 mg·kg⁻¹·hr⁻¹	475.2 ± 102.4 mg	105.0 ± 29.1 min	H-LOS, functional recovery, bowel function, opioid consumption, quality of recovery	7 days PO
		Saline (n = 46)		45.4 ± 6.4	Same volume	Same volume	0	108.0 ± 35.4 min		
Kim et al. (2010)[49]	99	Lidocaine (n = NA)	CABG	NA	1.5 mg·kg⁻¹	2 mg·kg⁻¹·hr⁻¹	NA	NA	Myocardial injury, AE	72 hr PO
		Saline (n = NA)		NA	Same volume	Same volume	NA	NA		

Table 1 continued

Studies	N	Population			Intervention				Outcomes measured (main outcome underlined)	Follow-up period
		Groups	Surgery	Age	Bolus	Infusion	Total dose	Duration of infusion		
Swenson et al. (2010)[25]	45	Lidocaine (n = 22)	Open colon resection	52 (40–62)*	<1.5 mg·kg⁻¹	First 11 patients: 2 or 3 mg·min⁻¹ Last 11 patients: 1 or 2 mg·kg⁻¹·hr⁻¹	NA	4,194 ± 1,694 min	POP and PO bowel function, PLC, AE, opioid consumption, H-LOS	Hospital discharge
		Epidural (n = 20)		49 (36–54)*	0	Epidural Bupivacaine 0.125% + hydromorphone 6 µg·mL⁻¹ at 10 mL·hr⁻¹	0	5,496 ± 2,463 min		

*Data presented as median and 25–75% interquartile range

CABG Coronary artery bypass graft; PLC plasma lidocaine concentration; H-LOS hospital length of stay; PACU-LOS postanesthesia care unit length of stay; ICU-LOS intensive care unit length of stay; HD hemodynamic; POP postoperative pain; PO postoperative; VAS visual analogue scale; AE adverse events; N/Vo nausea/vomiting; IM intramuscular; DM dextromethorphan; CMP chlorpheniramine maleate; NM no mention; CPB cardiopulmonary bypass; NA not available

scores,[14,24,26,31-33,35,38,40,42,45,47,48] while five studies presented median pain score.[23,25,34,43,44] The data from the studies reporting medians could not be included in the pooled analyses. One study[27] evaluated pain with an adapted scale that could not be pooled with other data. Eighteen studies[14,23-27,31-35,38,42-45,47,48] evaluated pain scores at rest, seven during cough,[14,32,33,35,43,47,48] and five during movement.[32,34,42,43,45] One study[31] evaluated pain 24 hr after the surgery during rest and activity together and therefore was not included in our analyses.

Postoperative pain at rest

Following surgery, the WMD between groups for pain control at rest was statistically significant at six hours (nine studies, $n = 579$, WMD −8.70, 95% CI −16.19 to −1.21; $I^2 = 89\%$) and at 12 hr (six studies, $n = 389$, WMD −6.52, 95% CI −12.12 to −0.91; $I^2 = 79\%$) but not at 24, 48, or 72 hr (Fig. 2). Although a statistically significant difference was not observed between groups after 12 hr, a trend towards improved pain control at rest was observed among patients who received IVLI during the perioperative period. Sensitivity analyses showed that the benefit at 12 hr and prior and the observed trend after 12 hr may be explained by abdominal surgeries (Fig. 3).

Pain during cough

After surgery, the WMDs for pain control during cough were statistically significant among the IVLI and control groups at six hours (seven studies, $n = 410$, WMD −11.19, 95% CI −17.73 to −4.65; $I^2 = 84\%$), 12 hr (four studies, $n = 280$, WMD −7.44, 95% CI −14.24 to −0.63; $I^2 = 84\%$), and 24 hr (six studies, $n = 380$, WMD −6.94, 95% CI −12.87 to −1.01; $I^2 = 78\%$) favouring pain reduction for IVLI groups (Fig. 2). However, despite a clear trend in pain reduction, the WMDs were not statistically different at 48 or 72 hr. All studies were performed in abdominal surgery populations, except one[40] that evaluated pain during cough at six hours after thoracic surgery. Sensitivity analyses showed consistent findings.

Pain during movement

Pain during movement after surgery was decreased significantly with IVLI at six hours (two studies, $n = 130$, WMD −9.56, 95% CI −17.31 to −1.80; $I^2 = 45\%$) (Fig. 2). No difference was observed at 24 or 72 hr. The only study that assessed pain during movement 12 hr after surgery observed no difference between groups.[32] In abdominal surgery only, pain during movement was not significantly reduced by IVLI (Fig. 3).

Table 2 Risk of bias and methodological quality assessment of included studies

Study	Rating based on Cochrane risk of bias tool							Jadad scale			
	Sequence generation	Allocation concealment	Blinding	Incomplete outcome date	Selective outcome reporting	Other bias	Summary	Total	Randomization	Blinding	Attrition information (withdrawal and drop out)
Knight et al. (1980)[28]	Unclear	Unclear	High	Unclear	Low	Unclear	High	1	1	0	0
Kasten et al. (1986)[29]	Unclear	Low	Low	Unclear	Low	Low	Unclear	3	1	2	0
Cassuto et al. (1985)[38]	Unclear	Unclear	Low	Unclear	Low	Low	Unclear	2	1	1	0
Wallin et al. (1987)[39]	Unclear	Unclear	Low	Unclear	Low	Low	Unclear	2	1	1	0
Rimback et al. (1990)[37]	Unclear	Unclear	Low	Unclear	Low	Low	Unclear	2	1	1	0
Striebel et al. (1992)[23]	Unclear	Unclear	Unclear	Low	Low	Unclear	Unclear	3	1	1	1
Insler et al. (1995)[26]	Low	Low	Low	Low	Low	Low	Low	5	2	2	1
Groudine et al. (1998)[27]	Low	Unclear	Low	Low	Low	Low	Unclear	4	2	1	1
Rinne et al. (1998)[50]	Unclear	Unclear	High	Low	Low	Unclear	High	2	1	0	1
Mitchell et al. (1999)[36]	Unclear	Unclear	Low	Low	Low	Low	Unclear	4	1	2	1
Wang et al. (2002)[41]	Unclear	Unclear	Low	Low	Low	Low	Unclear	3	1	1	1
Koppert et al. (2004)[34]	Low	Low	Low	Low	Low	Low	Low	5	2	2	1
Wu et al. (2005)[14]	Low	Low	Low	Low	Low	Low	Low	5	2	2	1
Kuo et al. (2006)[33]	Low	Unclear	Low	Unclear	Low	Low	Unclear	4	2	2	0
Kaba et al. (2007)[32]	Low	Low	Low	Low	Low	Low	Low	5	2	2	1
Herroeder et al. (2007)[35]	Low	Low	Low	Low	Low	Low	Low	5	2	2	1
Martin et al. (2008)[42]	Low	Low	Low	Low	Low	Low	Low	5	2	2	1
Lauwick et al. (2008)[44]	Low	Low	Low	Low	Low	Low	Low	5	2	2	1
El-Tahan et al. (2009)[46]	Low	Low	Low	Low	Low	Low	Low	5	2	2	1
Mathew et al. (2009)[30]	Low	Low	Low	Low	Low	Low	Low	5	2	2	1
Lauwick et al. (2009)[43]	Low	Low	Unclear	Low	Low	Low	Unclear	3	2	0	1
Juàrez-Pichardo et al. (2009)[24]	Low	Low	Low	Low	Low	Low	Low	5	2	2	1
Yardeni et al. (2009)[48]	Unclear	Low	Unclear	Low	Low	Unclear	Unclear	3	1	1	1
McKay et al. (2009)[31]	Low	Unclear	Unclear	Unclear	Low	Unclear	Unclear	3	2	1	0
Cui et al. (2010)[40]	Low	Low	Low	Low	Low	Low	Low	5	2	2	1
Saadawy et al. (2010)[47]	Low	Low	Low	Low	Unclear	Low	Unclear	5	2	2	1
Bryson et al. (2010)[45]	Low	Low	Low	Low	Low	Low	Low	5	2	2	1
Kim et al. (2010)[49]	NA	NA	Unclear	NA	NA	NA	Unclear	NA	1	1	NA
Swenson et al. (2010)[25]	Low	Low	Low	Unclear	Low	Unclear	Unclear	5	2	2	1

NA Not available

Morphine equivalent administration during the postoperative period

Seventeen studies described the administration of analgesic agents during the postoperative period (from PACU to eight days following surgery). Morphine equivalent administration could be calculated for 12 of these studies.[14,26,27,31,34,35,37-39,44,45,47] The mean morphine dose received in the control group was 46.4 mg. A reduction in morphine of 8.4 mg was observed in the IVLI group compared with the control group (12 studies, $n = 690$, WMD −8.44, 95% CI −11.32 to −5.56; $I^2 = 18\%$). This reduction was explained mainly by the type of surgery (abdominal *vs* non-abdominal) (Fig. 3). In the four studies presenting median opioid doses, two studies observed results consistent with these findings[32,40] while two studies observed contradicting results.[25,42]

Secondary outcomes

Mortality

Six studies presented mortality data.[26,28,30,36,41,50] Mortality in the IVLI group (0.4%) was not significantly different from that in the control group (0.5%) (six studies, $n = 611$, RR: 0.87, 95% CI 0.42-1.80; $I^2 = 0\%$).
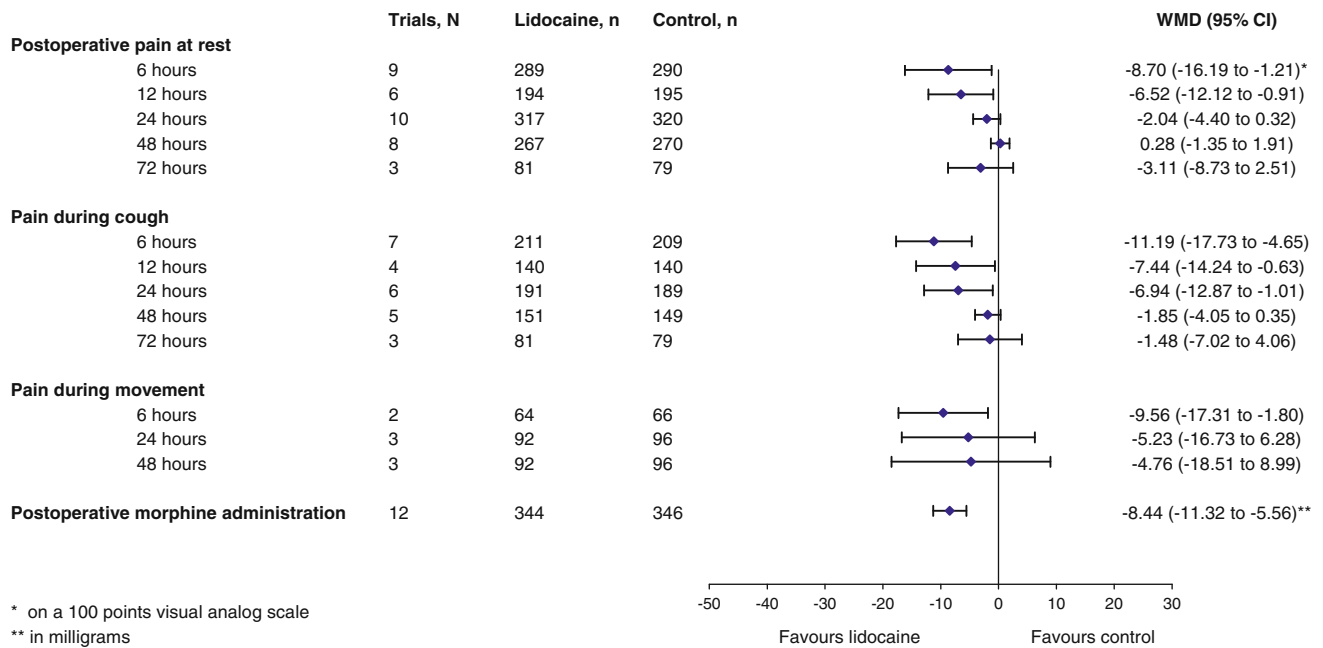
	Trials, N	Lidocaine, n	Control, n	WMD (95% CI)
Postoperative pain at rest				
6 hours	9	289	290	-8.70 (-16.19 to -1.21)*
12 hours	6	194	195	-6.52 (-12.12 to -0.91)
24 hours	10	317	320	-2.04 (-4.40 to 0.32)
48 hours	8	267	270	0.28 (-1.35 to 1.91)
72 hours	3	81	79	-3.11 (-8.73 to 2.51)
Pain during cough				
6 hours	7	211	209	-11.19 (-17.73 to -4.65)
12 hours	4	140	140	-7.44 (-14.24 to -0.63)
24 hours	6	191	189	-6.94 (-12.87 to -1.01)
48 hours	5	151	149	-1.85 (-4.05 to 0.35)
72 hours	3	81	79	-1.48 (-7.02 to 4.06)
Pain during movement				
6 hours	2	64	66	-9.56 (-17.31 to -1.80)
24 hours	3	92	96	-5.23 (-16.73 to 6.28)
48 hours	3	92	96	-4.76 (-18.51 to 8.99)
Postoperative morphine administration	12	344	346	-8.44 (-11.32 to -5.56)**

* on a 100 points visual analog scale
** in milligrams

Favours lidocaine   Favours control

Fig. 2 Postoperative pain and opioid requirement

	Trials, N	Lidocaine, n	Control, n	WMD (95% CI)
Postoperative pain at rest				
6 hours				
Abdominal surgery	7	215	215	-11.21 (-21.10 to -1.31)*
Non abdominal surgery	1	44	45	3.50 (-3.83 to 10.83)
12 hours				
Abdominal surgery	5	150	150	-7.75 (-14.68 to -0.83)
Non abdominal surgery	1	44	45	-2.00 (-8.30 to 4.30)
24 hours				
Abdominal surgery	8	245	245	-4.44 (-9,22 to 0.33)
Non abdominal surgery	2	72	75	0.81 (-4.20 to 5.83)
48 hours				
Abdominal surgery	6	195	195	-0.02 (-1.78 to 1.74)
Non abdominal surgery	2	72	75	2.12 (-2.25 to 6.48)
Postoperative pain during cough				
6 hours				
Abdominal surgery	6	191	189	-11.25 (-18.62 to -3.87)
Non abdominal surgery	1	20	20	-11.10 (-20.73 to -1.47)
Pain during movement				
24 hours				
Abdominal surgery	2	64	66	-9.69 (-26.27 to 6.90)
Non abdominal surgery	1	28	30	3.00 (-8.32 to 14.32)
48 hours				
Abdominal surgery	2	64	66	-9.40 (-32.90 to 14.09)
Non abdominal surgery	1	28	39	3.00 (-7.04 to 13.04)
Postoperative morphine administration				
Abdominal surgery	10	271	274	-8.72 (-12.22 to -5.23)**
Non abdominal surgery	1	44	45	-6.90 (-37.29 to 23.49)

* on a 100 points visual analog scale
** in milligrams
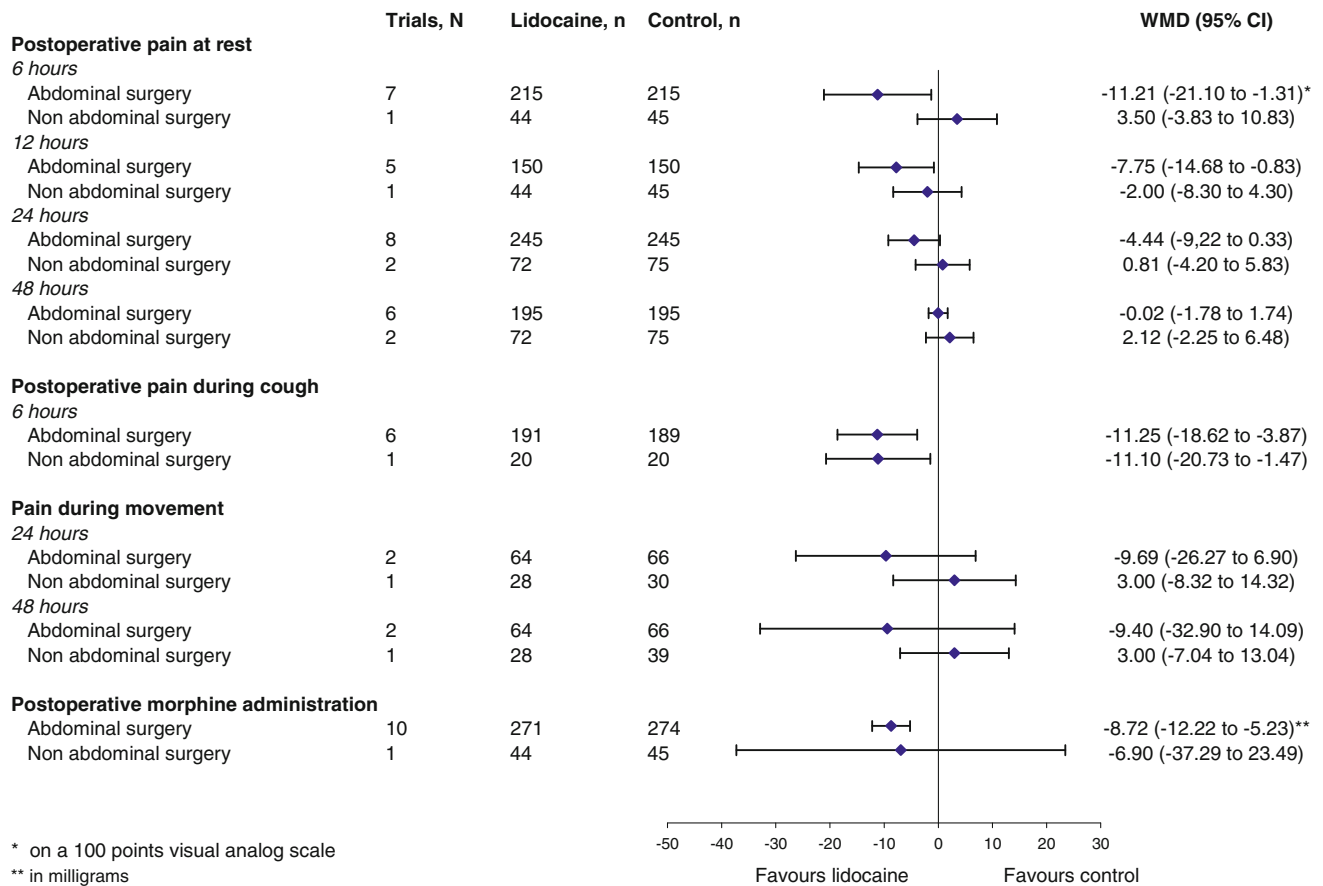
Favours lidocaine   Favours control

Fig. 3 Sensitivity analyses by type of surgery

Nausea or vomiting

Thirteen studies assessed the incidence of postoperative nausea or vomiting[25,31-34,37,38,40,43-47] (Table 3). Pooled results showed that the incidence was significantly lower in patients who received IVLI (25%) than in those who did not (35%) (12 studies, $n = 617$, RR: 0.71, 95% CI 0.57-0.90; $I^2 = 0\%$).

Length of stay

The length of stay in the PACU was evaluated in only two studies.[31,35] A comparable length of stay was observed in the IVLI groups and control groups in both studies.

Pooled results of hospital length of stay from nine studies showed a statistically significant reduction of about four hours for patients who received IVLI (nine studies, $n = 539$, WMD -0.17 day, 95% CI -0.41 to 0.07; $I^2 = 8\%$). Among studies reporting median length of stay, two studies observed a significant difference between groups in terms of hospital length of stay: two days (interquartile range [IQR] 2-3 days) and seven days (IQR 6-8 days) for the IVLI groups and three days (IQR 3-4 days) and eight days (IQR 7-11 days) for the control groups, respectively.[32,35] However, in three other studies, no difference was observed between groups.[25,30,44]

Bowel function

Only studies conducted in abdominal surgery populations evaluated bowel function. Nine studies presented data on the time to first flatus,[14,25,27,32,33,35,37,43,47] while seven studies presented data on time to first feces[25,27,32,34,35,37,43] (Table 3).

Time to first flatus

Pooled analysis demonstrated a significant reduction of approximately eight hours in favour of IVLI (seven studies, $n = 388$, WMD -7.62 hr, 95% CI -10.78 to -4.45; $I^2 = 59\%$). All studies were conducted in cases of abdominal surgery, but statistical heterogeneity was explained by the type of abdominal surgery (open *vs* laparoscopic) (open surgery: four studies, $n = 168$, WMD -11.41 hr, 95% CI -14.36 to -8.45; $I^2 = 0\%$ *vs* laparoscopic surgery: three studies, $n = 220$, WMD -5.12 hr, 95% CI -6.65 to -3.59; $I^2 = 0\%$). One additional study[32] also showed a median reduction in time to first flatus in the IVLI group (17 hr, IQR 11-24 hr) compared with the control group (28 hr, IQR 25-33 hr), while another study showed no statistical difference among groups.[25]

Time to first feces

In the IVLI group, a statistically significant reduction of approximately 14 hr in the time to first feces was observed in the pooled analysis of studies[27,35,37,43] (four studies, $n = 168$, WMD -10.71 hr, 95% CI -16.14 to -5.28; $I^2 = 0\%$). Data from three additional studies could not be pooled because mean times were not provided or could not be calculated.[25,32,34] However, the median time to first feces in two of the studies was comparable with the results of the pooled WMD, and the third study showed no statistical differences between groups.[25]

Administration of volatile agents

The need for volatile agents during surgery was reported in six studies.[14,29,32,33,44,47] In four of the studies, a reduction in the administration of volatile agents during surgery was observed.[14,32,33,47]

Adverse events

Among the 29 studies included in this systematic review, 20 reported adverse events (Table 4). Nineteen studies calculated plasma lidocaine levels.[23,25-32,34-36,38,40-42,46,47,50] A plasma concentration of >5 μg·mL^{-1} of lidocaine was observed in eight studies,[25,26,28,29,35,36,41,50] six in cardiac surgery[26,28,29,36,41,50] and two in abdominal surgery.[25,35] Only three studies reported the number of patients involved (three patients in total).[25,26,35] There was no association between the toxic levels of lidocaine and the dose received. Among the 20 studies presenting data on adverse events, 12 studies systematically looked for cardiovascular and/or neurological adverse events.[14,25,33,34,37-40,42,45-47] Overall, the incidence of adverse events between the IVLI and the control groups was comparable.

Discussion

In this study, we observed a significant difference in pain control at rest, during cough, or during movement with the use of IVLI in surgical patients under general anesthesia. This difference was associated mainly with studies conducted in abdominal surgery populations. Accordingly, we showed that opioid use was lower among patients who received IVLI. Again, this effect was observed primarily in patients undergoing abdominal surgery. Perioperative IVLI was associated with a shorter hospital length of stay, decreased incidence of nausea or vomiting, and faster return of bowel function, with no impact on hospital mortality. The incidence of adverse events was not well-documented, but a few studies reported critical levels of lidocaine, an observation that requires further investigation.

Table 3 Incidence of nausea/vomiting and return of bowel function

Study	Group	Number of patients with nausea or vomiting	Bowel function	
			Time to first flatus (hr)	Time to first feces (hr)
Cassuto et al. (1985)[38]	Lidocaine (n = 10)	6	NA	NA
	Control (n = 10)	8	NA	NA
Rimback et al. (1990)[37]	Lidocaine (n = 15)	8	38.0 ± 27.7	73.0 ± 38.7
	Control (n = 15)	9	43.0 ± 19.4	93.0 ± 38.7
Striebel et al. (1992)[23]	Lidocaine (n = 20)	0	NA	NA
	Control (n = 20)	0	NA	NA
Groudine et al. (1998)[27]	Lidocaine (n = 18)	NA	28.5 ± 13.4	61.8 ± 13.2
	Control (n = 20)	NA	42.1 ± 16	73.9 ± 16.3
Koppert et al. (2004)[34]	Lidocaine (n = 20)	9	NA	79 (66–84)*
	Control (n = 20)	12	NA	85 (68–96)*
Wu et al. (2005)[14]	Lidocaine + DM (n = 25)	NA	13.4 ± 2.1 Mean 17.8 ± 1.9	NA
	Lidocaine + CMP (n = 25)	NA	22.1 ± 1.6	NA
	Control (CMP) (n = 25)	NA	22.9 ± 1.8 Mean 22.6 ± 1.7	NA
	Control (DM) (n = 25)	NA	22.2 ± 1.5	NA
Kuo et al. (2006)[33]	Lidocaine (n = 20)	5	60.2 ± 5.8	NA
	Control (n = 20)	9	71.7 ± 4.7	NA
Kaba et al. (2007)[32]	Lidocaine (n = 20)	1	17 (11–24)*	28 (25–33)*
	Control (n = 20)	4	28 (24–37)*	51 (41–70)*
Herroeder et al. (2007)[35]	Lidocaine (n = 31)	NA	51 ± 20	66.6 ± 26.4
	Control (n = 29)	NA	60.5 ± 29	82.1 ± 33.8
Lauwick et al. (2008)[44]	Lidocaine (n = 25)	4	NA	NA
	Control (n = 24)	8	NA	NA
El-Tahan et al. (2009)[46]	Lidocaine (n = 45)	5	NA	NA
	Control (n = 45)	7	NA	NA
Lauwick et al. (2009)[43]	Lidocaine (n = 20)	1	30.3 ± 12.7	53.7 ± 12.3
	Control (n = 20)	2	36.3 ± 9.2	61.6 ± 12.4
McKay et al. (2009)[31]	Lidocaine (n = 29)	10	NA	NA
	Control (n = 27)	13	NA	NA
Cui et al. (2010)[40]	Lidocaine (n = 20)	†	NA	NA
	Control (n = 20)	†	NA	NA
Saadawy et al. (2010)[47]	Lidocaine (n = 40)	12	5.7 ± 2.7	NA
	Control (n = 40)	10	10.8 ± 4.6	NA
Bryson et al. (2010)[45]	Lidocaine (n = 44)	11	NA	NA
	Control (n = 46)	23	NA	NA
Swenson et al. (2010)[25]	Lidocaine (n = 22)	4	64.8 (45.6–84)*	69.6 (55.2–86.4)*
	Control (n = 20)	4	38.4 (28.8–81.6)*	72.0 (40.8–108.0)*

DM Dextromethorphan; *CMP* chlorpheniramine maleate; *NA* not available

* Data presented as medians and interquartile ranges

† Similar incidence but number of patients not provided

Comparison with previous studies

The significant difference in the quality of pain control observed in studies involving patients who underwent abdominal surgery was also observed in two recent meta-analyses performed in this patient subgroup.[10,11] However, one of these studies was limited to a specific surgical population and a specific period of evaluation (24 hr) following surgery.[10] On the contrary, our study evaluated the quality of pain control at five different time periods over the first 72 hr following surgery. In addition, our study was more exhaustive and methodologically rigorous and used a

Table 4 Reported adverse events

Study	Cardiovascular				Neurological										Allergic reaction	
	Arrhythmia		Hypotension		Light-headedness		Seizure		Drowsiness		Tinnitus		Numbness of the tongue			
	Lidocaine	Control	Lidocaine	Control	Lidocaine	Control	Lidocaine	Control	Lidocaine	Control	Lidocaine	Control	Lidocaine	Control	Lidocaine	Control
Knight et al. 1980[28]	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Kasten et al. 1986[29]	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Cassuto et al. 1985[38]	0	0	NM*	NM*	1	1	NM	NM	0	0	0	0	0	0	NM	NM
Wallin et al. 1987[39]	0	0	NM	NM	0	0	NM	NM	2	0	0	0	0	0	NM	NM
Rimback et al. 1990[37]	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0
Striebel et al. 1992[23]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Insler et al. 1995[26]	1	2	NM*	NM*	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Groudine et al. 1998[27]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Rinne et al. 1998[50]	1	1	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	0	0
Mitchell et al. 1999[36]	7	9	11	10	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	0	0
Wang et al. 2002[41]	NM	NM	26	22	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Koppert et al. 2004[34]	NM	NM	NM	NM	NM*	NM*	NM	NM	4	7	NM	NM	0	0	NM	NM
Wu et al. 2005[4]	2	0	NM	NM	0	0	NM	NM	0	0	0	0	0	0	0	0
Kuo et al. 2006[33]	3	0	2	2	0	0	0	0	0	0	0	0	0	0	0	0
Kaba et al. 2007[32]	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Herroeder et al. 2007[35]	0	0	6	5	0	0	0	0	0	0	0	0	0	0	0	0
Martin et al. 2008[42]	NM	NM	NM	NM	0	0	NM	NM	0	0	NM	NM	0	0	0	0
Lauwick et al. 2008[44]	NM	NM	0	0	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	0	0
El-Tahan et al. 2009[46]	0	0	NM	NM	0	0	0	0	0	0	NM	NM	0	0	0	0
Mathew et al. 2009[30]	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Lauwick et al. 2009[43]	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	0	0
Juárez-Pichardo et al. 2009[24]	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Yardeni et al. 2009[48]	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
McKay et al. 2009[31]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Saadawy et al. 2010[47]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Bryson et al. 2010[45]	0	0	0	0	†	‡	0	0	0	0	†	‡	0	0	0	0
Kim et al. 2010[49]	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Swenson et al. 2010[25]	3	1	NM	NM	1	1	0	0	1	0	NM	NM	1	0	0	0

NM No mention

* Number of patients not mentioned but similar incidence or no significant statistical difference observed between groups

† 11 patients with light-headedness or tinnitus in the intravenous lidocaine infusion group

‡ 21 patients with light-headedness or tinnitus in control group; One patient with dizziness and visual disturbance

thorough search strategy, which led to the screening of more than 5,472 citations to include 29 studies and more than 1,754 patients. In comparison, only eight studies ($n = 360$) and 16 studies ($n = 764$) were identified for inclusion in the previous meta-analyses, respectively.[10,11] In addition, studies conducted in children were included in one of these systematic reviews, a population where the biodisponibility and effect of the drug could be different.[11] Moreover, the standard error of mean, which several studies used as a measure of dispersion of the different outcomes, was interpreted as a standard deviation in these two meta-analyses. This interpretation would have wrongly increased the precision of the outcome measure of the included studies and, thus, the point estimate of the pooled analysis. In our study, we calculated the appropriate standard deviations before conducting the pooled analyses. This approach allowed a broader description of the effect of IVLI on pain control over a clinically significant period. Moreover, rather than focusing on only a specific subgroup of patients, we conducted a series of sensitivity analyses, including stratification by the type of surgery, allowing a more exhaustive comprehension of the potential effect of IVLI. We also conducted a systematic evaluation of potential side effects of IVLI during the perioperative setting.

It remains unknown why patients undergoing abdominal surgery may particularly benefit from IVLI. One explanation might be differences in pain mechanisms; visceral pain from abdominal surgery might be triggered by mechanisms other than non-visceral pain, such as bone and cartilage trauma in orthopedic or cardiac surgeries. Part of the discomfort and pain following abdominal surgery might also be related to postoperative ileus and nausea/vomiting. Indeed, the reduction observed in the time to bowel function recovery as well as the decreased incidence of nausea/vomiting might explain why the improvement in pain control was observed mainly in studies based on abdominal surgery.

Limitations and strength

The main limitation of our study is related to the methodological quality of the included RCTs. First, our findings were based on small-sized single-centre RCTs. Despite the use of two different instruments to assess the potential risk of bias and methodological quality of included studies,[19,21] RCTs that are considered to have a low risk of bias or to be of high-methodological quality could have some important design flaws not detected by methodological evaluations. For example, some studies considered to be double-blinded did not mention if data collectors were blinded to the treatment regimen.[26,29,36-39,41] Second, pooled analyses were limited by data availability in studies meeting inclusion criteria (i.e., fewer studies evaluated pain during cough or movement as opposed to at rest). Therefore, a type II error cannot be excluded in certain analyses. In addition, only median values were presented in several studies and, therefore, could not be included in the pooled analyses since the mean values could not be estimated.[23,25,32,34,35,42,44] Furthermore, not all planned sensitivity analyses could be performed due to insufficient available data, despite efforts made to obtain these data by contacting the corresponding authors of the studies. Thus, the observed statistical heterogeneity in certain analyses could not always be explained. Moreover, despite the fact that sensitivity analyses did not reveal a statistically significant influence as a result of dose regimen and duration of therapy, we cannot exclude the possibility of a clinically important impact on the efficacy and safety of IVLI. Indeed, the included studies made no mention of having conducted a dose-response study prior to establishing their protocol, and they made no reference regarding the need to establish the ideal dose prior to conducting the RCT. The use of non-optimal dosage regimens of IVLI in some of the included studies might have had an impact on the results observed and, thus, on the results of our meta-analysis.

The main strength of our study stands in its design aimed at presenting an exhaustive evaluation of the effect of IVLI use during the perioperative period. First, the search was systematic, including grey literature and a manual search of the references of included studies and conference proceedings. Moreover, by targeting a broad population of surgical patients, we were able to provide a clear description of both the potentially beneficial and harmful effects of this analgesic modality. In addition, sensitivity analyses determined a priori enabled us to assess sources of heterogeneity when present, and also to identify the subpopulation of patients that could potentially benefit from the therapy. Our study provides an accurate and comprehensive understanding of the effects of IVLI on perioperative outcomes, including safety issues.

In summary, IVLI as an anesthesia adjuvant during general anesthesia has the potential to improve postoperative analgesia and the efficiency of care, mainly in the context of abdominal surgeries. However, the safety of IVLI cannot be confirmed considering its association with potentially serious adverse events and the scarcity of studies that have systematically assessed the incidence of adverse events, including toxic plasmatic levels of lidocaine. Thus, before its use can be recommended, further research is required, especially where it pertains to an optimal dosage regimen and the safety of this intervention.

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Conflict of interest   None declared.

Appendix

Search strategy for Medline

1. Clinical trial:.pt. (462496)
2. Animals/(4297276)
3. Humans/(10548308)
4. 2 not (2 and 3) (3233613)
5. 1 not 4 (457386)
6. Lidocaine/or Anesthetics, Local/or Local anesthetic*.mp. (36784)
7. lidocaine.mp. (22522)
8. xylocaine.mp. (856)
9. 6 or 7 or 8 (39995)
10. Anesthes*.mp. [mp = title, original title, abstract, name of substance word, subject heading word] (182287)
11. Anesthesia, Conduction/or Anesthesiology/or Anesthesia, General/(46074)
12. Intraoperative*.mp. or Intraoperative Care/or Intraoperative Period/(85683)
13. Perioperative Care/or Perioperative*.mp. (38536)
14. Postoperative*.mp. or Postoperative Care/or Pain, Postoperative/or Postoperative Period/(465147)
15. Surgical Procedures, Operative/or Operative Procedure*.mp. (53134)
16. Surgical Procedure*.mp. (191032)
17. Surger*.mp. (575864)
18. Surgery/(27904)
19. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (1131018)
20. 5 and 9 and 19 (4374)
21. local anesthesia.mp. or Anesthesia, Local/(17264)
22. 20 not 21 (3313)
23. Anesthesia, Spinal/or regional anesth*.mp. (11040)
24. 22 not 23 (2637)
25. Peripheral Nerves/or Nerve Block/or peripheral nerve block.mp. (28815)
26. 24 not 25 (2116)
27. limit 26 to (humans and "all adult (19 plus years)") (1621)

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