REVIEW ARTICLE

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Impact of Intravenous Lidocaine Infusion on Postoperative Analgesia and Recovery from Surgery

A Systematic Review of Randomized Controlled Trials

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Abstract

Postoperative pain continues to be inadequately managed. While opioids remain the mainstay for postoperative analgesia, their use can be associated with adverse effects, including ileus, which can prolong hospital stay. A number of studies have investigated the use of perioperative intravenous lidocaine infusion for improving postoperative analgesia and enhancing recovery of bowel function.

This systematic review was performed to determine the overall efficacy of intravenous lidocaine infusion on postoperative analgesia and recovery from surgery in patients undergoing various surgical procedures. We searched the databases of MEDLINE, CINAHL and the Cochrane Library from 1966 to December 2009. We searched for randomized controlled comparisons of lidocaine infusion with placebo in the surgical setting and reporting on post-operative analgesia and other aspects of patient recovery from surgery. The quality of all included studies was assessed using the Modified Oxford Scale.

Information on postoperative pain intensity and analgesic requirements was extracted from the trials and compared qualitatively. Other relevant data such as return of bowel function, length of hospital stay, intraoperative anaesthetic requirement and adverse effects were also compared.

Sixteen trials were included. A total of 395 patients received intravenous lidocaine with 369 controls. In open and laparoscopic abdominal surgery, as well as in ambulatory surgery patients, intravenous perioperative infusion of lidocaine resulted in significant reductions in postoperative pain intensity and opioid consumption. Pain scores were reduced at rest and with cough or movement for up to 48 hours postoperatively. Opioid consumption was reduced by up to 85% in lidocaine-treated patients when compared with controls. Infusion of lidocaine also resulted in earlier return of bowel function, allowing for earlier rehabilitation and shorter duration of hospital stay. First flatus occurred up to 23 hours earlier, while first bowel movement occurred up to 28 hours earlier in the lidocaine-treated patients. Duration of hospital stay was reduced by an average of 1.1 days in the lidocaine-treated patients. Administration of intravenous lidocaine infusion did not result in toxicity or clinically significant adverse events. Lidocaine had no impact on postoperative analgesia in patients undergoing tonsillectomy, total hip arthroplasty or coronary artery bypass surgery.

In conclusion, intravenous lidocaine infusion in the perioperative period is safe and has clear advantages in patients undergoing abdominal surgery. Patients receiving lidocaine infusion had lower pain scores, reduced postoperative analgesic requirements and decreased intraoperative anaesthetic requirements, as well as faster return of bowel function and decreased length of hospital stay. Further studies are needed to assess whether lidocaine has a beneficial effect in patients undergoing other types of surgery and to determine the optimum dose, timing and duration of infusion of lidocaine in this setting.

Opioids remain the mainstay for postoperative analgesia. However, the use of opioids can be associated with an increased incidence of postoperative complications, such as respiratory depression, sedation, postoperative nausea and vomiting (PONV), ileus and urinary retention.[1] Recent data also suggest that extensive use of opioids may be associated with hyperalgesia and allodynia.[2] Therefore, there is a continuous search for adjuvant therapies to reduce the doses of opioids and their related adverse effects, thereby improving patient recovery.

Lidocaine is an amide local anaesthetic that has analgesic, antihyperalgesic[3] and anti-inflammatory[4] properties. It has been previously shown to be an effective analgesic in a number of settings, including cancer pain,[5] chronic pain[6] and pain due to adiposis dolorosa.[7,8] These properties of lidocaine are mediated by a variety of mechanisms, including sodium channel blockade,[4] inhibition of G protein-coupled receptors[4,9] and NMDA receptors.[10,11] A number of studies have been published to assess the analgesic effect of perioperative intravenous infusion of lidocaine. We therefore performed this systemic review to assess the efficacy of perioperative intravenous infusion of lidocaine on postoperative outcomes, including pain scores, opioid consumption, opioid-related adverse effects and duration of hospital stay.

1. Literature Search and Data Extraction

We searched the databases of MEDLINE, CINAHL and the Cochrane Library from 1966 to December 2009 for studies assessing the

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impact of perioperative intravenous infusion of lidocaine on pain outcomes and patient recovery. The following terms were used for the search: 'lidocaine', 'intravenous', 'pain', 'postoperative' and 'surgery'. Bibliographies of retrieved articles were also screened for additional studies. The quality of all included studies were assessed using the Modified Oxford Scale.[12]

We designed a data collection form and extracted data from the included studies on (i) type of surgery; (ii) number of patients and groups included; (iii) lidocaine regimens (timing and duration); (iv) intraoperative anaesthetic requirements; (v) pain scores; (vi) analgesic consumption; (vii) return of bowel function; (viii) adverse effects; and (ix) duration of hospital stay.

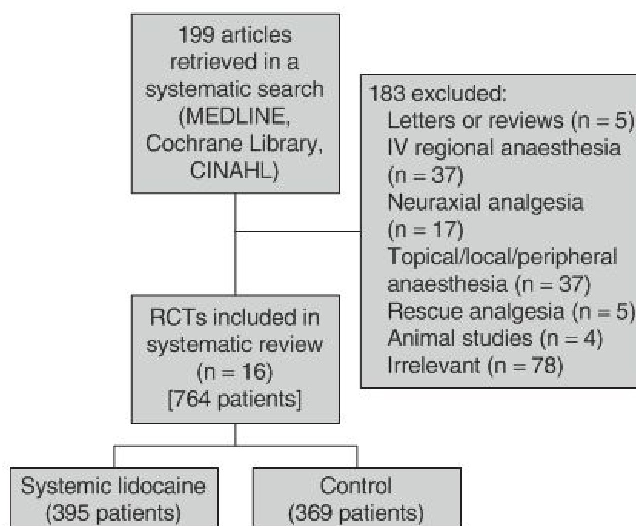

Fig. 1. Flow chart of systematic literature search. **IV** = intravenous; **RCTs** = randomized controlled trials.

2. Results

Of 199 articles retrieved by electronic searching, 183 were excluded for the following reasons: 5 were letters or literature reviews, 37 were studies on intravenous regional anaesthesia, 17 were studies involving neuraxial lidocaine, 37 were studies on topical, local or peripheral nerve blocks, 5 were studies using lidocaine as a rescue analgesic, 4 were animal studies and 78 were not relevant to our study criteria (figure 1). The 16 selected randomized controlled trials (RCTs) included a total of 764 patients: 395 received lidocaine with 369 controls.

Of the 16 included studies, 12 were in abdominal surgery, of which 8 were open[13-20] and 4 were laparoscopic,[21-24] 1 was in orthopaedic surgery,[25] 1 was in cardiac surgery,[26] 1 was in tonsillectomies[27] and 1 included a variety of ambulatory surgeries.[28] The minimum Modified Oxford Scale score of an included trial was 2 and the maximum was 7.

2.1 Abdominal Surgery

2.1.1 Open Abdominal Surgery

In patients undergoing open abdominal surgeries, lidocaine infusion was given as an initial intravenous bolus dose of 100 mg[13,14] or 1.5–2 mg/kg prior to induction or incision,[15-18,20] followed by an infusion of lidocaine at a rate of 1.5–3 mg/kg/hour[16-18,20] or 2–3 mg/minute.[13-15] Infusions were stopped at the end of surgery[17,20] or continued for up to 24 hours postoperatively.[13-16,18,19] Harvey et al.[19] used a lidocaine infusion at 1 mg/minute without a bolus dose, which was started immediately postoperatively for 24 hours (table I).

Pain scores were reported in seven of the eight studies, of which five showed a significant reduction in pain scores.[13,15-17,20] There was also a trend towards lower pain scores in the two studies that did not report a statistically significant reduction in pain scores.[18,19] In the first of these, a study by Herroeder et al.[18] on colorectal patients, there were no significant differences in pain scores, at rest or during cough, between the two groups, although there was a tendency towards lower visual analogue scale (VAS) scores in the lidocaine group than in the placebo group from 0 to 156 hours postoperatively. Similarly, the trial by Harvey et al.[19] reported no significant difference in VAS scores; however, a trend toward lower VAS scores was noted at 24 hours after surgery in the lidocaine group (table I).

Five of eight trials that involved open intra-abdominal surgery reported a significant reduction in total analgesic consumption in the post-operative period up to 48–72 hours.[13-17] These reductions ranged from 33% to 35% when the lidocaine infusion was maintained for 0–1 hour postoperatively,[16,17] and up to 83% compared

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Table I. Included studies with quality score, patient (pt) groups, lidocaine (L) regimens, pain scores and analgesic requirements

Study (year)	Quality score R/CA/DB/F	No. of pts	Dose and duration of L infusion	Duration of study (h)	Type of surgery	Postop analgesic requirement	Pain scores
McKay et al.[28] (2009)	2/0/1/0	56 L (29) C (27)	1.5 mg/kg + 2 mg/kg/h after induction until 1 h after arrival in PACU	24	Various outpt surgeries	50% reduction in morphine requirement in PACU in the L group ($p < 0.02$). No difference in opioid consumption after discharge from PACU	VAS scores were significantly lower at rest in PACU in the L group ($p = 0.043$). No difference in VAS scores at 24 h
Yardeni et al.[20] (2009)	1/0/1/0	65 L (32) C (33)	2 mg/kg + 1.5 mg/kg/h 20 min before surgery until end of surgery	72	Transabdominal hysterectomy	No difference in pt-controlled epidural analgesia total volume or boluses received between groups at any timepoint	VAS scores were significantly lower at rest and with coughing, respectively, at 4 h ($p = 0.029$ and $p = 0.0001$) and 8 h ($p = 0.011$ and $p = 0.048$) after surgery in the L group. No difference in VAS scores from 12 to 72 h
Harvey et al.[19] (2009)	2/1/2/1	22 L (11) C (11)	1 mg/min postop for 24 h	24	Elective small bowel and colorectal surgery	No difference in morphine consumption at 6, 18 or 24 h	No difference at 6 h ($p = 0.24$) or 18 h ($p = 0.26$) with trend toward significance in the L group at 24 h ($p = 0.08$)
Lauwick et al.[23] (2009)	2/1/2/0	40 L (20) C (20)	1.5 mg/kg + 2 mg/kg/h at induction until end of surgery and 1 mg/kg/min postop for 24 h	72	Laparoscopic prostatectomy	No difference in morphine consumption on postop d 1 ($p > 0.05$). On postop d 2, 70% of pts in the L group vs 30% of pts in the C group did not use PCA morphine ($p = 0.011$). Total morphine consumption at 48 h trends towards significance ($p = 0.05$) with a 49% reduction in the L group	No difference in VAS scores at any timepoints
Lauwick et al.[24] (2008)	2/1/2/2	49 L (25) C (24)	1.5 mg/kg + 2 mg/kg/h before induction until end of surgery	24	Laparoscopic cholecystectomy	36% reduction in fentanyl consumption in PACU with L ($p = 0.018$). No difference at 24 h	No difference in PACU and at 24 h
Martin et al.[25] (2008)	2/1/2/1	58 L (28) C (30)	1.5 mg/kg + 1.5 mg/kg/h after induction until 1 h postop	48	Total hip arthroplasty	No difference in morphine consumption in PACU, at 24 h and at 48 h	No difference at rest and on movement at 24 h, 48 h and 3 mo
Herroeder et al.[18] (2007)	2/1/2/2	60 L (31) C (29)	1.5 mg/kg + 2 mg/min after intubation until 4 h postop	156	Colorectal surgery	No difference in overall piritramide consumption from 0 to 156 h	No difference at rest and with coughing from 0 to 156 h, but a trend toward lower VAS scores in the L group

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Table I. Contd

Study (year)	Quality score R/CA/DB/F	No. of pts	Dose and duration of L infusion	Duration of study (h)	Type of surgery	Postop analgesic requirement	Pain scores
Kaba et al.[22] (2007)	2/1/2/1	40 L (20) C (20)	1.5 mg/kg + 2 mg/kg/h just before induction until end of surgery + 1.33 mg/kg/h postop for 24 h	48	Laparoscopic colectomy	Total dose of intraop sufentanil was less in the L group ($p = 0.008$). 64% reduction in piritramide consumption from 0 to 24 h ($p = 0.005$)	No difference at rest. Reduced VAS pain scores on movement ($p = 0.02$) and coughing ($p = 0.01$) for 48 h
Kuo et al.[17] (2006)	2/0/2/1	60 E (20) L (20) C (20)	E: 2 mg/kg + 3 mg/kg/h IV L: 2 mg/kg + 3 mg/kg/h 30 min before surgery until end of surgery	72	Colon cancer surgery	33% reduction in total PCEA consumption at 0–72 h in the IV L group when compared with the C group ($p < 0.01$)	VAS scores at rest, 2 h and 4 h, and during coughing at 12 h were significantly lower in the IV L and E groups compared with the C group ($p < 0.001$)
Wu et al.[21] (2005)	2/1/2/0	100 DM+L (25) L (25) DM (25) C (25)	IV L: 3 mg/kg/h + IM DM 40 mg (DM+L) IV L + IM CPM 20 mg (L) 30 min before surgery until end of surgery	48	Laparoscopic cholecystectomy	Pethidine consumption was significantly less over 48 h for the DM+L, DM and L groups compared with the C group ($p < 0.001$). 42% reduction in total pethidine consumption 0–48 h in the IV L group compared with the C group ($p < 0.001$)	VAS scores were significantly lower at rest at 1 and 2 h and during cough at 1, 2, 4 and 12 h for the L group compared with the C group ($p < 0.05$). The combined therapy group, DM+L had lower VAS scores at rest compared with either single-treatment group (DM or L) for 4 h ($p < 0.05$), and for 24 h with coughing ($p < 0.05$)
Koppert et al.[16] (2004)	2/1/2/1	40 L (20) C (20)	1.5 mg/kg + 1.5 mg/kg/h 30 min before skin incision until 1 h postop	72	Major abdominal surgery (prostatectomy, cystectomy, nephrectomy, colectomy and lymph node dissections)	35% reduction in overall morphine consumption 0–72 h ($p < 0.05$)	No difference in VAS scores at rest. VAS scores were significantly lower on movement at 48 and 72 h ($p < 0.01$)
Groudine et al.[15] (1998)	1/0/2/1	40 L (20) C (20)	1.5 mg/kg + 3 mg/min if >70 kg OR 2 mg/min if <70 kg after intubation until 1 h postop	72	Radical retropubic prostatectomy	50% reduction in morphine requirement in PACU in the L group ($p < 0.05$). No difference in opioid consumption after discharge from PACU	66% reduction in total pain score index in the L group (4.7 ± 4) compared with the C group (13.3 ± 7.7) [$p < 0.0001$]
Insler et al.[26] (1995)	1/1/1/1	89 L (44) C (45)	1.5 mg/kg + 30 μg/kg/min after induction until 48 h postop	96	Coronary artery bypass grafting	No difference in overall fentanyl consumption from 0 to 96 h	No difference in VAS scores between groups at 4–96 h. No data on VAS reported before 4 h

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Table I. Contd

Study (year)	Quality score R/CA/DB/F	No. of pts	Dose and duration of L infusion	Duration of study (h)	Type of surgery	Postop analgesic requirement	Pain scores
Striebel and Klettke[27] (1992)	1/0/2/0	40 L (20) C (20)	1.5 mg/kg 30 min before surgery + 2 mg/kg/h for 6 h and 0.5 mg/kg/h for 18 h	24	Tonsillectomy	No difference in postop pethidine consumption	No difference in VAS scores between groups
Rimback et al.[14] (1990)	1/0/1/0	30 L (15) C (15)	100 mg + 3 mg/min just before induction until 24 h postop	72	Cholecystectomy	36% reduction in pethidine consumption on postop d 1, and 83% reduction on postop d 2 in the L group compared with the C group ($p<0.05$)	NR
Cassuto et al.[13] (1985)	1/0/1/0	20 L (10) C (10)	100 mg + 2 mg/min 30 min before incision until 24 h postop	48	Cholecystectomy	Significant reduction in pethidine requirement at 24 and 48 h in the L group ($p<0.02$ and $p<0.01$, respectively) compared with the C group (75% reduction at 24 h, 85% reduction at 48 h)	Significantly lower cumulative pain scores in the L group for 24 h ($p<0.001$)

C = control group; **CA** = concealment of allocation; **DB** = double-blinding; **DM** = dextromethorphan; **E** = epidural lidocaine; **F** = flow of pts; **IM CPM** = intramuscular chlorphenamine maleate; **intraop** = intraoperative; **IV** = intravenous; **NR** = not reported; **PACU** = postanaesthesia care unit; **PCA** = patient-controlled analgesia; **PCEA** = patient-controlled epidural analgesia; **postop** = postoperative; **R** = randomization; **VAS** = visual analogue scale.

with the placebo group when the lidocaine infusion was maintained for 24 hours postoperatively.[13,14] In radical prostatectomy patients, lidocaine infusion was maintained for 1 hour postoperatively and resulted in a 50% reduction in morphine requirements in the postanaesthesia care unit (PACU) but not on the ward.[15] One study involving colorectal surgery in which the lidocaine infusion was maintained for 4 hours after surgery reported no difference in overall piritramide consumption at any time interval.[18] In a more recent study in abdominal hysterectomy patients, the lidocaine infusion was maintained intraoperatively only and no difference in patient-controlled epidural analgesia use postoperatively was found.[20] Lidocaine infusion begun postoperatively and administered for 24 hours after small bowel and colorectal surgery also resulted in no difference in postoperative morphine consumption (table I).[19]

Six of the eight studies reported data on return of bowel function after open abdominal surgery.[14-19] Five studies showed that lidocaine significantly accelerated return of bowel function.[14,15,17-19] First passage of flatus occurred 8–24 hours earlier[15,17,18] and the first bowel movement occurred 12–28 hours earlier[15,18,19] in lidocaine-treated patients compared with placebo recipients. In the study by Rimback et al.,[14] evidence of significantly earlier return of propulsive motility in the colon was shown in the lidocaine-treated group. Radiopaque markers in the lidocaine group were propelled significantly earlier from the cecum/ascending colon to the transverse colon and appeared significantly earlier in the descending colon and rectosigmoid colon than in the saline-treated patients. Although the mean time to postoperative defecation occurred 17 hours earlier in the lidocaine-treated group, this was not found to be statistically significant, as was time to first passage of flatus. In another study, time until tolerating solid foods also occurred significantly earlier in lidocaine-treated patients.[18] In this same study, Herroeder and colleagues[18] reported gastrointestinal atonia, defined as postoperative ileus for >5 days, in eight patients in the control group compared with two patients in the lidocaine group. In the study

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by Koppert et al.,[16] bowel movement occurred 6 hours earlier with lidocaine, but the difference was not statistically significant compared with the control group (table II).

Five studies reported on length of hospital stay.[15-19] In three studies, patients in the lidocaine group were discharged home significantly earlier than their control counterparts. Time to hospital discharge was an average of 1.1 days shorter in the lidocaine-treated groups amongst the three studies.[15,18,19] Although duration of hospital stay was 1.4 days shorter in the lidocaine-treated group in the study by Koppert et al.,[16] this was not found to be statistically significant when compared with the control group (table II).

One study reported data on volatile agent use and supplemental intraoperative opioid use. End-tidal desflurane concentrations were reduced by 18% in the intravenous lidocaine group when compared with controls. Fentanyl supplementation was needed in 85% of patients in the control group as compared with only 5% in the intravenous lidocaine group. Total intraoperative fentanyl use was reduced by 39% in the intravenous lidocaine group when compared with placebo.[17]

2.1.2 Laparoscopic Surgery

Lidocaine regimens in patients undergoing laparoscopic surgeries ranged from an infusion of 3 mg/kg/hour starting before surgery without a bolus,[21] to an intravenous bolus of 1.5 mg/kg followed by an infusion of 2 mg/kg/hour[22-24] until the end of surgery[21,23,24] or for 24 hours postoperatively (table I).[22]

Two of four trials involving laparoscopic surgery reported a significant reduction in pain scores.[21,22] In the study by Kaba et al.[22] in patients undergoing laparoscopic colectomy, a lidocaine infusion maintained for 24 hours postoperatively was more effective in reducing pain during mobilization and when coughing than at rest for 0–24 hours. Abdominal discomfort was also significantly reduced by lidocaine compared with the placebo group.[22] In laparoscopic prostatectomy patients who received a lidocaine infusion intraoperatively and for 24 hours postoperatively, there was no difference in VAS pain scores from 0 to 72 hours.[23] Of the two trials in laparoscopic cholecystectomy patients, one reported better pain control with lidocaine during cough up to 24 hours after surgery, and at rest for up to 12 hours.[21] However, the other study showed no significant difference in pain intensity between the groups from 0 to 24 hours postoperatively,[24] although lidocaine infusion was discontinued at the end of surgery in both studies (table I).

Three of four studies in patients undergoing laparoscopic surgery reported a significant reduction in postoperative analgesic requirements.[21,22,24] In laparoscopic colectomy patients, lidocaine infusion was maintained for 24 hours after surgery and resulted in >50% reduction in piritramide consumption from 0 to 24 hours.[22] In the two studies in patients undergoing laparoscopic cholecystectomy, the lidocaine infusion was terminated at the end of surgery. In the first study, fentanyl requirements in the lidocaine group were reduced by 36% compared with the placebo group from 0 to 3 hours postoperatively but there was no difference at 24 hours.[24] The other study by Wu et al.[21] reported a 42% reduction in pethidine (meperidine) requirements from 0 to 48 hours postoperatively. In the most recent study by Lauwick et al.[23] in patients undergoing laparoscopic prostatectomy, lidocaine infusion started after surgery and maintained for 24 hours resulted in no difference in morphine consumption on postoperative day 1, with a trend toward less morphine consumption in the lidocaine group on postoperative day 2 (table I).

Three of four studies reported data on return of bowel function after laparoscopic abdominal surgery.[21-23] In patients undergoing laparoscopic colectomy, return of first flatus was 12 hours earlier and return of defecation was 24 hours earlier in patients treated with lidocaine. Lidocaine-treated patients were able to tolerate a normal diet the day after surgery, whereas three patients in the control group required prolongation of postoperative fasting.[22] In the study by Wu et al.[21] in patients undergoing laparoscopic cholecystectomy, there was no difference in time to first passage of flatus between the lidocaine-only

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Table II. Return of bowel function, duration of postanaesthesia care unit (PACU) and hospital stays, and adverse effects

Study (year)	Effect on bowel function	PACU stay	Duration of hospital stay	Adverse effects
McKay et al.[28] (2009)	NR	No difference in length of PACU stay between groups	NR	None
Yardeni et al.[20] (2009)	NR	NR	NR	None
Harvey et al.[19] (2009)	No difference in time to return of flatus after surgery. Return of bowel movement in the lidocaine group occurred at a mean of 28 h earlier than in the placebo group ($p = 0.0286$)	NR	Time to hospital discharge was a mean of 1.17 d shorter in the lidocaine group (3.76 ± 0.24) than in the placebo group (4.93 ± 0.42) [$p = 0.0277$]	None
Lauwick et al.[23] (2009)	No difference in time to return of flatus, time to first bowel movement or time to first full diet between groups	NR	No difference in length of stay between groups	No difference in PONV between groups
Lauwick et al.[24] (2008)	NR	No difference in length of PACU stay between groups	NR	No difference in PONV between groups
Martin et al.[25] (2008)	NR	NR	No difference in length of stay between groups	None
Herroeder et al.[18] (2007)	Return of bowel sounds and first flatus was 8 h earlier in the lidocaine group ($p < 0.05$). Time to first bowel movement was 16 h earlier in the lidocaine group ($p < 0.05$). Time until tolerating solid food was 24 h earlier for the lidocaine group ($p < 0.05$)	No difference in length of PACU stay between groups	Median time to hospital discharge was 1 d earlier in the lidocaine group than in the control group: 7 d vs 8 d ($p = 0.004$)	None
Kaba et al.[22] (2007)	Return of first flatus was ~12 h earlier and return of defecation was ~24 h earlier in the lidocaine group ($p = 0.001$)	NR	Time to hospital discharge was ~1 d earlier in the lidocaine group ($p = 0.001$)	No difference in PONV between groups
Kuo et al.[17] (2006)	Times of first flatus were 50.2 (4.9), 60.2 (5.8) and 71.7 (4.7) h in the epidural lidocaine, IV lidocaine, and control groups, respectively ($p < 0.01$)	NR	No difference in length of stay between groups	3 pts had occasional bradycardia in the IV lidocaine group, with other vital signs stable. No adverse events related to IV lidocaine infusion
Wu et al.[21] (2005)	No difference in time to first passage of flatus between the lidocaine and control groups. Passage of first flatus was 9 h earlier in the DM+L group when compared with control ($p < 0.001$) or either single-treatment group ($p < 0.05$)	NR	NR	No difference in PONV between groups. One pt in the DM+L and lidocaine groups had an occasional arrhythmia with stable vital signs

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Table II. Contd

Study (year)	Effect on bowel function	PACU stay	Duration of hospital stay	Adverse effects
Koppert et al.[16] (2004)	No difference in time to first bowel movement between groups	NR	No difference in length of stay between groups	None
Groudine et al.[15] (1998)	First flatus occurred 23 h earlier ($p<0.01$), and first bowel movement 12 h earlier ($p<0.02$) in the lidocaine group compared with the control group	NR	Time to hospital discharge was 1.1 d shorter in the lidocaine group ($p<0.05$)	None
Insler et al.[26] (1995)	NR	NR	No difference in length of stay between groups	None
Rimback et al.[14] (1990)	No difference in the time to first passage of flatus or faeces between groups. Propulsive motility in the colon occurred 15–20 h earlier in the lidocaine group ($p<0.05$), as measured by radiopaque markers and serial abdominal radiographs	NR	NR	None, except for sedation in 2 pts in the lidocaine group
Cassuto et al.[13] (1985)	NR	NR	NR	None

DM+L = dextromethorphan + lidocaine; **IV** = intravenous; **NR** = not reported; **PONV** = postoperative nausea and vomiting; **pt(s)** = patient(s).

group and the control group; however, passage of first flatus was 9 hours earlier in the lidocaine plus dextromethorphan group than in the control or either single-treatment groups. Most recently, Lauwick et al.[23] found no difference in return of bowel function in patients undergoing laparoscopic prostatectomy when treated with lidocaine (table II).

Two studies reported data on the length of hospital stay.[22,23] One study showed no difference in hospital stay between groups,[23] while the study by Kaba et al.[22] reported that hospital stay was 1 day shorter in the lidocaine-treated group.

All four studies reported data on volatile agent use intraoperatively,[21-24] while only one reported data on supplemental intraoperative opioid use.[22] Intraoperative infusion of lidocaine during laparoscopic cholecystectomy and laparoscopic prostatectomy resulted in volatile agent sparing in three studies.[22-24] Kaba et al.[22] found a 35% reduction in end-tidal sevoflurane concentration. Intraoperative sufentanil consumption was also reduced when compared with placebo: 16.3 ± 3.6 μg (saline) versus 13.0 ± 3.7 μg (lidocaine). In the first study by Lauwick et al.,[24] the end-tidal concentration of desflurane was reduced by 7% when compared with placebo. In the second study by the same author, end-tidal desflurane concentrations were reduced by 11% when compared with placebo.[23] Another study during laparoscopic cholecystectomy reported a 25% reduction in end-tidal desflurane concentration in the lidocaine-only and lidocaine plus dextromethorphan groups when compared with controls.[21]

2.1.3 Results of a Meta-Analysis of Studies in Abdominal Surgery

A meta-analysis of six RCTs that included 250 patients undergoing open or laparoscopic abdominal surgery reported that pain scores at 24 hours were significantly lower in patients receiving lidocaine than in controls (weighted mean difference [WMD] –5.93 [95% CI –9.63, –2.23]).[29]

A meta-analysis of seven RCTs that included 300 patients undergoing open or laparoscopic abdominal surgery showed that the duration of

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postoperative ileus was significantly shorter with a continuous intravenous lidocaine infusion than with placebo (WMD –8.36 [95% CI –13.24, –3.47] hours). A subgroup analysis was conducted to explore the effects of intravenous lidocaine on postoperative gut dysfunction in different surgical populations. Lidocaine decreased the duration of ileus significantly in the cholecystectomy subgroup (WMD –1.23 [95% CI –2.12, –0.34] hours), which included both open and laparoscopic surgeries. Similarly, lidocaine was associated with a decrease in duration of ileus after colonic resection (WMD –12.00 [95% CI –14.86, –9.13] hours), which also included both open and laparoscopic surgeries. Lidocaine also decreased postoperative ileus in patients in whom laparoscopy was performed (WMD –1.06 [95% CI –2.00, –0.13] hours).[29]

A meta-analysis of five RCTs including 220 patients undergoing open or laparoscopic abdominal surgery showed a shorter length of hospital stay in patients receiving lidocaine than in controls (WMD –0.84 [95% CI –1.38, –0.31] days).[29]

2.2 Orthopaedic Surgery

In one study in patients undergoing total hip arthroplasty, lidocaine was given as an initial intravenous bolus dose of 1.5 mg/kg after induction of anaesthesia followed by an infusion at 1.5 mg/kg/hour up to 1 hour postoperatively (table I). There was no significant reduction in pain scores with lidocaine at rest or during movement at 24 hours, 48 hours and 3 months, nor did lidocaine infusion result in any reduction in postoperative analgesic requirements or duration of hospital stay (table I).[25]

2.3 Cardiac Surgery

For coronary artery bypass surgery, lidocaine was given as an initial intravenous bolus dose of 1.5 mg/kg after induction of anaesthesia followed by an infusion of 30 μg/kg/minute for up to 48 hours postoperatively (table I). Lidocaine infusion did not result in any significant reduction in VAS pain scores, postoperative fentanyl requirement, time to discharge from ICU or length of hospital stay.[26]

2.4 Tonsillectomy

In one study in patients undergoing tonsillectomy, lidocaine was given as an initial bolus dose of 1.5 mg/kg 30 minutes before the beginning of surgery followed by an infusion at 2 mg/kg/hour for 6 hours and then 0.5 mg/kg/hour for an additional 18 hours. Lidocaine infusion did not result in any significant reduction in VAS scores or postoperative analgesic requirements (table I).[27]

2.5 Ambulatory Surgery

The study by McKay et al.[28] involved a variety of ambulatory procedures, including laparoscopic general, open general, endocrine, breast, laparoscopic gynaecology, minor gynaecology, urology, plastics, minor orthopaedic, and minor ear, nose and throat surgeries. Lidocaine was given as an initial intravenous bolus dose of 1.5 mg/kg after induction of anaesthesia followed by an infusion of 2 mg/kg/hour until 1 hour after arrival in the PACU.[28] VAS pain scores were significantly lower at rest in the PACU in the lidocaine group, but no difference was found in VAS scores at 24 hours.[28] In patients receiving lidocaine a 50% reduction in morphine requirement was demonstrated in the PACU, but no difference in opioid consumption was found after discharge from the PACU.[28] In addition, there was no difference in PACU stay between patients who received lidocaine and those who received placebo (table I).[28]

2.6 Adverse Effects

PONV was evaluated in eight studies involving both open and laparoscopic abdominal surgery.[13,14,16,17,21-24] No statistically significant difference in the incidence of PONV was found between groups in seven of the eight studies.[13,14,16,21-24] A meta-analysis of five RCTs involving abdominal surgery including 170 patients reported an incidence of PONV of 32% in the

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lidocaine group and 52% in the control group (odds ratio 0.39 [95% CI 0.20, 0.76]).[29]

Two trials evaluated sedation during the postoperative period after open abdominal surgery, but found no statistically significant difference between groups.[14,16] In patients following coronary artery bypass grafting, although the overall sedation score did not differ significantly between the two groups, the lidocaine group did have a significantly higher score during the first 4 hours postoperatively. This effect did not continue into the later postoperative period even though the infusion was continued for up to 48 hours.[26]

In one study, one patient in the lidocaine group developed an occasional arrhythmia with stable vital signs during laparoscopic cholecystectomy.[21] Occasional intraoperative bradycardia with stable haemodynamics occurred in three of 20 patients in the intravenous lidocaine group in the study by Kuo et al.,[17] with no similar occurrences in the control or epidural lidocaine groups.

2.7 Plasma Lidocaine Concentrations

Seven studies reported data on plasma lidocaine concentrations.[13,16,18,22,25-27] Plasma lidocaine concentrations were measured after bolus injection and at different time intervals during and after infusion. Toxic concentrations (>5 μg/mL) were not reached in any study following lidocaine infusion, with the exception of one asymptomatic patient presenting with a peak value of 5.8 μg/mL measured 5 minutes after lidocaine bolus in one study.[18] Mean plasma lidocaine concentrations ranged from 0.58 to 5 μg/mL.[3,16,18,22,25-27] The highest plasma lidocaine concentration at 24 hours was 4.6 μg/mL after infusion of 1.33 μg/kg/hour for 24 hours.[22] Plasma concentrations ranged between 2 and 5 μg/mL when infused for 48 hours at a rate of 30 μg/kg/minute.[26] In the study by Cassuto et al.,[13] where lidocaine was given as a 100 mg bolus followed by infusion of 2 mg/minute for 24 hours postoperatively, whole blood lidocaine concentrations averaged 1.52 μg/mL 8 hours after the start of infusion and 1.75 μg/mL at 20 hours.

2.8 Plasma Levels of Cytokines and Integrins

Three studies measured the plasma levels of cytokines.[17,18,20] Systemic lidocaine significantly attenuated plasma levels of complement and proinflammatory cytokines such as interleukin (IL)-6, IL-8 and IL-1 receptor antagonist (IL-1RA) at the end of surgery up to 72 hours postoperatively.[17,18] In one study, the levels of IL-6, IL-8 and IL-1RA returned to near baseline in all patients by 24 hours.[17] In another study, there were still significant differences in IL-6 and IL-8 levels between groups on postoperative day 3, but no significant difference in IL-1RA.[18] A more recent study found significant differences in IL-6 at 72 hours but no significant difference in IL-1RA after 24 hours.[20] Lidocaine also blunted increases in integrin (CD11b) and selectin (CD62L and CD62P) expression at the surface of leukocytes and platelet-leukocyte aggregates measured at the end of surgery and 2 hours and 3 days postoperatively.[18]

3. Discussion

This review shows that a perioperative intravenous infusion of lidocaine had a useful analgesic effect in patients undergoing abdominal surgery. Its administration facilitated early recovery and resulted in faster return of bowel function and a shorter duration of hospital stay. However, these benefits were not seen in patients undergoing orthopaedic surgery, cardiac surgery or tonsillectomy.

Lidocaine is an amide local anaesthetic that has many pharmacological properties. Its antiarrhythmic properties were first described in the 1950s. Since then, it has become a widely used agent for the treatment of cardiac arrhythmias.[30] Since the 1960s, intravenous lidocaine has been used to provide symptomatic relief from cancer pain,[31] diabetic neuropathies[32,33] and chronic pain,[34,35] without producing toxic side effects or significant cardiovascular changes. Two mechanisms have been investigated to explain the analgesic efficacy of lidocaine: a selective depression of pain transmission in the spinal cord[34,35] and a reduction in tonic neural

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discharge of active peripheral nerve fibres.[36,37] The peripheral nerve fibres mediating pain are A-δ and C-fibres, and these appear uniquely sensitive to the effects of lidocaine without threat of toxicity or disturbance in haemodynamics.[35]

Intravenous lidocaine infusion had no beneficial effect on postoperative pain in total hip arthroplasty,[25] coronary artery bypass surgery[26] or tonsillectomy.[27] The investigators in the orthopaedic study relate the lack of effect to the low dose of lidocaine infused (1.5 mg/kg/hour) and, consequently, the low mean plasma concentration achieved of 2.1 μg/mL. This is in contrast to other studies where lidocaine was shown to be effective, which used similar doses and obtained mean plasma concentrations ranging from 1.75 to 2.7 μg/mL.[13,16,22] Tanelian and MacIver[35] have established that the clinically effective pain-relieving serum lidocaine concentration that is sufficient to reduce tonic injury discharge in both A-δ and C-fibres is 2–10 μg/mL. Although mean plasma lidocaine concentrations in the study by Martin et al.[25] were between adequate bounds, the analgesic properties of lidocaine seemed to depend on the dose infused. Animal studies have shown that small doses of lidocaine suppress ectopic impulse generation in chronically injured peripheral nerves, whereas moderate doses suppress central sensitization and central neuronal hyperexcitability. Large doses have general analgesic effect but induce systemic toxicity.[38] The study by Koppert et al.,[16] which utilized a similar dose and duration of lidocaine infusion as the study by Martin et al.,[25] reported a significant reduction in analgesic requirement and pain scores with movement for up to 72 hours postoperatively.

In seven of the 12 abdominal studies, as well as in the study on a range of ambulatory surgery patients, intravenous lidocaine had a favourable effect on postoperative pain.[13,15-17,20-22,28] This is consistent with the ability of lidocaine to alleviate visceral pain in animal models. It was shown that intravenous lidocaine had inhibitory effects on visceromotor and cardiovascular reflexes, as well as on the evoked and spontaneous activity of neurons excited by colorectal distension, suggesting that sodium channel antagonists may have a role in the treatment of visceral pain.[39]

Lidocaine regimens varied amongst the studies included in this review. The goal of intravenous lidocaine infusion is to achieve therapeutic steady-state concentrations while avoiding systemic toxicity. The half-life of lidocaine has been reported to be about 100 minutes following bolus injection or infusions lasting less than 12 hours, showing more linear pharmacokinetics.[40] The short half-life of infusions lasting less than 12 hours may explain the greater reduction in VAS pain scores in the earlier postoperative period in the studies by McKay et al.,[28] Yardeni et al.,[20] Kuo et al.[17] and Wu et al.,[21] in which lidocaine infusion was discontinued at the end of surgery or 1 hour postoperatively.

Following prolonged intravenous infusions, lidocaine exhibits time-dependent, or nonlinear, pharmacokinetics. In patients receiving prolonged lidocaine infusions after myocardial infarction, lidocaine concentrations continued to rise for about 48 hours and the half-life was prolonged up to 4 hours.[41] Although the results of some of the studies included in this review point towards a greater analgesic effect of increasing the duration of lidocaine infusion rather than the dose of lidocaine, the study by Koppert et al.[16] that utilized a lower dose of lidocaine infusion for up to just 1 hour postoperatively showed prolonged positive results lasting up to 72 hours.

With the exception of the study by Wu et al.,[21] the studies that reported lower pain scores and decreased postoperative analgesic requirement used bolus dosing prior to infusion of intravenous lidocaine.[13,15-17,20,22,24,28,38] Since this technique increases plasma concentrations to a therapeutic range more quickly, the majority of studies in this review chose to use a bolus dose of 100 mg or 1.5–2 mg/kg. No ideal regimen for lidocaine therapy has been determined, though Aps et al.[42] have suggested that a suitable regimen would be a single injection (over 2 minutes) of 50–100 mg followed by an infusion of 4 mg/minute for 30 minutes, 2 mg/minute for 2 hours and then 1 mg/minute. This regimen avoids the dip in concentrations to below the therapeutic range that occurs 1–3 hours after a single loading dose[42] but is more labour intensive. However, this regimen was developed in patients who had

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had a recent myocardial infarction and might not be applicable in the perioperative period.

Weight-based dosing of lidocaine takes into account its high hepatic extraction ratio. Plasma clearance of lidocaine is about 10 mL/kg/minute in patients with relatively normal hepatic blood flow and function. To achieve steady-state concentrations of 3 μg/mL, an infusion rate of 30 μg/kg/minute[43] or 1.8 mg/kg/hour would be required. The weight-based lidocaine regimens used in the studies reviewed, which ranged from 1.33 to 3 mg/kg/hour, should have achieved adequate plasma concentrations in the range of 2–5 μg/mL. However, adequate plasma concentrations did not always correlate with analgesic benefit. The relationship between the dose of lidocaine used, duration of infusion and postoperative analgesic effect is therefore not clear and warrants further investigation.

The lack of a statistically significant analgesic effect in some of the included studies might have been due to the small sample size used.[19,23] The use of co-analgesics may also explain the non-significant differences in VAS pain score and analgesic requirement in several of the studies in this review.[18,23] The study by Herroeder et al.,[18] for instance, administered dipyrone (metamizole) or paracetamol (acetaminophen) every 6 hours postoperatively as a co-analgesic, while the patients in the study by Lauwick et al.[23] all received paracetamol every 6 hours and naproxen every 12 hours for the first 72 hours.

Intravenous lidocaine significantly accelerated the return of bowel function. Gastrointestinal dysfunction after abdominal surgery is multifactorial. The most commonly accepted pathophysiological features of postoperative ileus is surgically induced abdominal pain, which activates a spinal reflex arc, and sympathetic hyperactivity, which inhibits intestinal motility and propulsive activity. Paravertebral reflexes relayed through the prevertebral ganglia might also play a role in postoperative ileus.[44] Other important causes include the inflammatory response to abdominal surgery, administration of anaesthetics and opioids, and gastrointestinal hormone disruption.[45] The stimulatory actions of lidocaine on postoperative colonic motility could be due to blockade of the afferent and/or efferent link of the sympathetic inhibitory spinal and prevertebral reflexes.[46,47] The urinary output of catecholamines has been shown to be reduced during the second postoperative day with lidocaine infusion, suggesting a more rapid decline in the postoperative sympathoadrenal response with lidocaine.[48] Intravenous lidocaine may shorten the duration of ileus by reducing opioid consumption, as reported in seven of the 12 abdominal surgery trials.[13-15,17,21,22,24]

Lidocaine also has significant anti-inflammatory properties[4] and was shown to decrease cytokine release both *in vitro* and *in vivo* by inhibiting neutrophil activation.[49-51] The three studies included in this review that measured plasma cytokine levels showed that intravenous lidocaine attenuated the production of inflammatory cytokines such as IL-6, IL-8 and IL-1RA. The lowest cytokine response was associated with the best bowel function.[17,18] The inflammatory cytokine IL-6, the level of which is proportionate to the extent of tissue injury,[52] can induce peripheral and central nervous system sensitization leading to hyperalgesia.[53] The chemokine IL-8 potentially recruits neutrophils and monocytes into the inflammatory site, accelerating inflammation.[54] IL-8 is identified as the first endogenous mediator for evoking hyperalgesia involving the sympathetic nervous system.[55] The study by Kuo et al.[17] included in this review showed that epidural and intravenous lidocaine suppressed the perioperative increase in IL-8 and provided effective pain relief. IL-1RA is released with IL-1β, signalling the acute phase response, which correlates well with the grade of inflammation.[56]

Intravenous lidocaine did not have an impact on length of hospital stay in orthopaedic or coronary artery bypass surgery.[25,26] However, in the abdominal surgeries, intravenous lidocaine decreased the length of hospital stay in three studies by an average of 1.1 days.[15,18,22] This was mainly due to earlier return of bowel function. This has an important impact on hospital costs. In 2002, the annual cost of postoperative ileus was estimated at $US1.46 billion.[57] In one study,[58] reducing hospital stay from 8 to 5 days resulted in a 32% decrease in hospital costs per patient.

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4. Conclusions

Continuous infusion of perioperative lidocaine has a clear advantage in patients undergoing abdominal surgery as it provides significant pain relief, reduces postoperative opioid consumption, decreases opioid-induced nausea and vomiting, and promotes faster return of bowel function, allowing for a shorter hospital stay. However, these benefits were not demonstrated in patients undergoing total hip arthroplasty, cardiac surgery or tonsillectomy. Further studies are needed to assess the efficacy of intravenous lidocaine in other surgical populations. The optimum dose, timing and duration of infusion of lidocaine also need to be established.

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