Meta-analysis

Meta-analysis of intravenous lidocaine and postoperative recovery after abdominal surgery

E. Marret[1], M. Rolin[2], M. Beaussier[2] and F. Bonnet[1]

Departments of Anaesthesiology and Intensive Care, [1]Tenon University Hospital, Assistance Publique–Hôpitaux de Paris (AP-HP), Unité Institut National de la Santé et de la Recherche Médicale U707, and [2]St Antoine University Hospital, AP-HP, University Pierre et Marie Curie, Paris, France
Correspondence to: Dr E. Marret, Department of Anaesthesiology and Intensive Care, Hôpital Tenon, 4 Rue de la Chine, 75970 Paris Cedex 20, France (e-mail: emmanuel.marret@tnn.ap-hop-paris.fr)

Background: **Continuous intravenous administration of lidocaine may decrease the duration of ileus and pain after abdominal surgery.**

Methods: **Three databases (Medline, Embase and the Cochrane Controlled Trials Register) were searched to retrieve randomized controlled trials comparing continuous intravenous lidocaine infusion during and after abdominal surgery with placebo. Study design was scored using the Oxford Quality Score based on randomization, double-blinding and follow-up. Outcome measures were duration of ileus, length of hospital stay, postoperative pain, and incidence of nausea and vomiting.**

Results: **Eight trials were selected. A total of 161 patients received intravenous lidocaine, with 159 controls. Intravenous lidocaine administration decreased the duration of ileus (weighted mean difference (WMD) −8·36 h; $P < 0·001$), length of hospital stay (WMD −0·84 days; $P = 0·002$), postoperative pain intensity at 24 h after operation on a 0–100-mm visual analogue scale (WMD −5·93 mm; $P = 0·002$), and the incidence of nausea and vomiting (odds ratio 0·39; $P = 0·006$).**

Conclusion: **Continuous intravenous administration of lidocaine during and after abdominal surgery improves patient rehabilitation and shortens hospital stay.**

Presented in part to the Annual Meeting of the American Society of Anesthesiologists, San Francisco, California, USA, October 2007, and to the Annual Meeting of the Société Francaise d'Anesthésie Réanimation, Paris, France, September 2007

Paper accepted 10 July 2008

Published online in Wiley InterScience (www.bjs.co.uk). **DOI:** 10.1002/bjs.6375

Introduction

Postoperative ileus is a common reason for an extended hospital stay after major abdominal surgery, even when the surgical procedure is uncomplicated. Its pathophysiology is multifactorial. Anaesthetic agents such as opioids are thought to be among the causal factors. To reduce the stress response, the use of epidural anaesthesia with local anaesthetics has been advocated[1]. This provides better postoperative pain control than parenteral opioid analgesia and decreases surgical stress. Furthermore, it shortens the duration of postoperative ileus and, according to some studies, reduces the incidence of complications[1–3]. However, whether dependent on opioid or not, it increases the risk of urinary retention and arterial hypotension, induces partial muscle blockade thereby impairing mobilization and, in extreme but rare circumstances, causes serious complications such as epidural haematoma or abscess[3,4]. A meta-analysis has failed to demonstrate that epidural analgesia decreases length of hospital stay after colorectal surgery[3].

Intravenous lidocaine has analgesic, anti-inflammatory and antihyperalgesic properties[5]. As far back as in 1954, an intravenous infusion of lidocaine during general anaesthesia was shown to provide postoperative analgesia for more than 10 h, with a low incidence of postoperative nausea and vomiting[6]. Recent randomized controlled trials (RCTs) have suggested that continuous intravenous lidocaine administration may have beneficial effects on outcomes after colorectal surgery and may shorten hospital stay[7,8].

What follows is a systematic review of the literature aiming to assess the effect of intravenous lidocaine administration on recovery after abdominal surgery.

Special emphasis has been given to the following endpoints: length of hospital stay, pain intensity, duration of ileus, and incidence of complications and side-effects.

Methods

This review was conducted according to the recommendations published in the Quality of Reporting of Meta-analyses (QUORUM) statement[9].

Literature review and identification of studies

Three electronic databases were searched for studies published up to December 2007: Pubmed (Medline/Index Medicus), the Cochrane Controlled Trials Register and Embase. The medical subject heading (MeSH) terms used for the search were 'lidocaine' and 'ileus'. Additional articles were retrieved through hyperlinks and by manually searching reference lists in original published articles, review articles and correspondence. There was no language restriction. Authors were contacted for additional information on methods and results when required.

Study selection criteria

Study selection criteria were abdominal surgery, a randomized double-blind design, and an Oxford Quality Score of at least 3 (see below). Exclusion criteria were inclusion of children, an Oxford Quality Score of below 3, no control group, comparisons of intravenous lidocaine infusion with epidural analgesia only, lidocaine administered by bolus with no continuous infusion (for example lidocaine co-administered with morphine by a patient-controlled analgesia device), and no perioperative lidocaine administration.

Quality assessment of studies

Study design quality was assessed by two investigators (M.R., E.M.) who were not blinded to the study authors or results. Disagreements were resolved by discussion with co-authors. Each article was scored using a five-point scale for randomization, blinding and patient follow-up[10]. A study was allocated one point if the design was randomized and an additional point if the randomization method was described and appropriate (such as a computer-generated table of random numbers). However, a point was subtracted if the randomization method was described but inappropriate (for example alternate allocation or allocation by date of birth). A study was also allocated one point if it was double-blind and two points if the double-blinding method was described and appropriate (for example identical placebo, active placebo, double-dummy). However, studies in which the double-blinding method was described but inappropriate received no points. Finally, one point was allocated to studies specifying numbers of, and reasons for, withdrawals and dropouts. The highest possible score was thus 5.

Endpoints

The primary endpoint was time to recover bowel function, that is the duration of postoperative ileus (time to first flatus, faeces or bowel movement). Secondary endpoints were length of hospital stay, 24- and 48-h postoperative pain scores measured on a visual analogue scale (VAS), opioid consumption, incidence of opioid side-effects, such as nausea and vomiting and sedation, and systemic lidocaine toxicity. The incidence of complications was recorded for each study as reported. To analyse continuous data, numerical data were extracted from the text of the article. If data were missing, the authors were contacted. In the absence of a reply, the data were extrapolated from figures. When nausea and vomiting were reported as separate outcomes, the authors were contacted to discover how many patients had nausea and vomiting. If they did not reply, the greater of the two numbers (number for either nausea or vomiting) was recorded.

Statistical analysis

If not reported in the article, an intention-to-treat analysis of the original data was carried out. All analyses were performed using Review Manager software (version 4.2, Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). For dichotomous data, the odds ratio and 95 per cent confidence interval (c.i.) were calculated using a fixed-effect model. When the test for heterogeneity (Cochran Q test) was significant ($P < 0{\cdot}100$), a random-effects model analysis was carried out. For continuous data (length of hospital stay, VAS scores), weighted mean differences (WMDs) were calculated, taking into account study size and s.d. as reported in the individual trials. When mean(s.d.) values were not given, they were estimated from the median, range and size of the samples or from the interquartile range. Forest plots were used to show the information from the individual studies that was used in the meta-analysis. Sensitivity analysis was performed to explore the effect of lidocaine in different situations, namely cholecystectomy *versus* colonic resection and laparoscopic *versus* open surgery. The number needed to treat (NNT) was calculated as the reciprocal of the risk

difference of postoperative nausea and vomiting between the lidocaine and control groups. The c.i. of the NNT were constructed by inverting and exchanging the limits of the 95 per cent c.i. for the risk difference. All tests were two sided, and $P < 0{\cdot}050$ was considered statistically significant.

Results

Studies selected

Of 65 articles retrieved by electronic and hand searching, 57 were excluded for the following reasons: 25 were letters or literature reviews, 12 were animal studies (ten concerned lidocaine use for ileus, colic or colonic surgery in horses), 11 were not relevant, six were studies on epidural lidocaine, two were orthopaedic studies and one was a critical care study (*Fig. 1*). The eight selected double-blind RCTs included patients scheduled for abdominal surgery only. Overall, 161 received intravenous lidocaine and 159 received placebo.

Study details

All eight RCTs were published between 1985 and 2007 and conducted in single centres (*Table 1*). All patients were American Association of Anesthesiologists (ASA) grade I–III. The procedure was open surgery in six trials and laparoscopy in two trials. The median Oxford Quality Score was 4 (range 3–5).

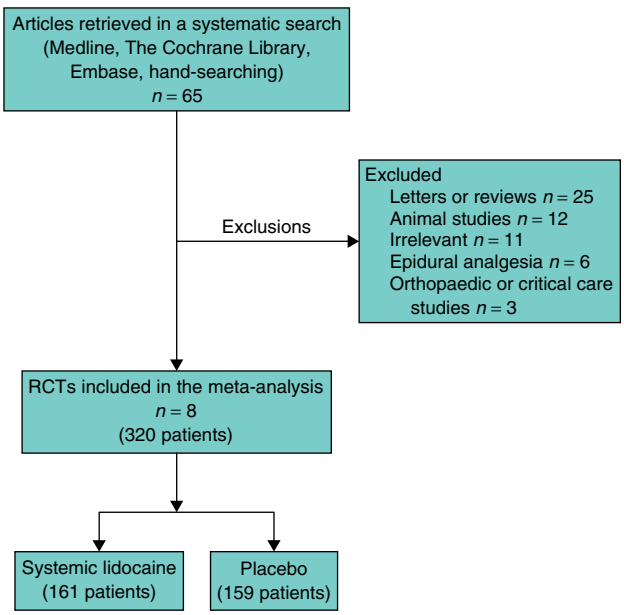

Fig. 1 Flow chart of systematic search

In seven of the eight RCTs, a lidocaine bolus (1·5–2 mg/kg) was given before surgical incision followed by a continuous infusion during and after operation. In the RCT with no lidocaine bolus, infusion was started 30 min before skin incision[16]. Three trials reported, in the patients receiving lidocaine, that the end-tidal concentration of halogenated anaesthetic was reduced on average by 25 per cent[7,14,16]. Lidocaine or placebo was administered for a period ranging from throughout surgery to 24 h after operation. Control patients received intravenous infusion of isotonic saline in all RCTs.

Exclusion criteria were chronic use of analgesics or steroids (six trials)[7,8,12–14,16], use of laxatives (one)[15], impaired liver function (three)[7,8,11], a psychiatric disorder (one)[7], ASA grade above II (two)[12,14], renal disease (one)[11], and cardiovascular disease, severe cardiac arrhythmia or treatment with antiarrhythmic drugs (three)[8,11,13]. Postoperative recovery programmes for fast-track surgery were implemented in four RCTs[7,8,14,16]. These programmes included multimodal analgesia with non-steroidal anti-inflammatory drugs (NSAIDs), normothermia during surgery, removal of the nasogastric tube at the end of the surgical procedure, active mobilization, active oral feeding and/or prophylaxis for nausea and vomiting[7,8,14,16]. The opioids used for postoperative pain relief were morphine, mepiridine or piritramide. All except one trial[8] showed a significant 30–50 per cent reduction in opioid consumption in the postoperative period with lidocaine infusion.

Outcomes

Recovery of bowel function was evaluated in all except one RCT[11]. Duration of postoperative ileus was significantly diminished by a continuous intravenous infusion of lidocaine (WMD −8·36 (95 per cent c.i. −13·24 to −3·47) h; $P < 0{\cdot}001$) (*Fig. 2*). A subgroup analysis was conducted to explore the effects of intravenous lidocaine on postoperative gut dysfunction in different situations. Lidocaine decreased the duration of ileus significantly in the cholecystectomy subgroup (WMD −1·23 (95 per cent c.i. −2·12 to −0·34) h; $P = 0{\cdot}007$)[15,16]. Similarly, lidocaine was associated with a decrease in duration of ileus after colonic resection (WMD −12·00 (95 per cent c.i. −14·86 to −9·13) h; $P < 0{\cdot}001$)[7,8,14]. Lidocaine also decreased postoperative ileus in patients in whom a laparoscopy was performed (WMD −1·06 (95 per cent c.i. −2·00 to −0·13); $P = 0{\cdot}030$)[7,16] or not (WMD −7·90 (95 per cent c.i. −9·88 to −5·91) h; $P < 0{\cdot}001$)[8,12–15]. Length of hospital stay was reported in five trials and was significantly shorter in patients receiving lidocaine than in controls (WMD −0·84 (95 per cent c.i. −1·38 to −0·31) days; $P = 0{\cdot}002$) (*Fig. 3*).

Table 1 Randomized controlled trials comparing continuous intravenous lidocaine and placebo after abdominal surgery

Reference	Oxford Quality Score	No. of patients		Type of surgery	Lidocaine administration	Additional measures	Endpoints
		Lidocaine	Control				
Cassuto *et al*.[11]	3	10	10	Open cholecystectomy	Bolus (100 mg), then 2 mg/min for 24 h postop.		Postop. pain (VAS) Postop. opioid PONV
Groudine *et al*.[12]	5	20	20	Radical retropubic prostatectomy	Bolus (1·5 mg/kg) before induction, then 3 mg/min (BW > 70 kg) or 2 mg/min (BW < 70 kg) for 1 h after skin closure	NSAIDs	Pain scores Postop. opioid Time to first flatulence or bowel movement Length of hospital stay
Herroeder *et al*.[8]	5	31	29	Open colorectal surgery	Bolus (1·5 mg/kg) before induction, then 2 mg/min until 4 h after skin closure	Fast-track protocol: normothermia, PONV prophylaxis, paracetamol, NSAIDs, AOF	Pain scores Gastrointestinal motility Inflammatory mediators Length of hospital stay
Kaba *et al*.[7]	5	20	20	Laparoscopic colectomy	Bolus (1·5 mg/kg) at induction, then 2 mg/kg/h intraop. and 1·33 mg/kg/h for 24 h postop.	Normothermia, paracetamol, NSAIDs, no postop. nasogastric tube, AOF, active mobilization	Pain scores Postop. opioid Fatigue scores Length of hospital stay Time to first flatus and defaecation Endocrine and metabolic responses Hospital discharge
Koppert *et al*.[13]	5	20	20	Major abdominal surgery	Bolus (1·5 mg/kg in 10 min), then 1·5 mg/kg/h (started 30 min before skin incision) and continued for 1 h after skin closure		Length of hospital stay Pain scores Postop. ileus Postop. opioid PONV
Kuo *et al*.[14]	4	20	20	Open colectomy for cancer	Bolus (2 mg/kg), then 3 mg/kg/h started 30 min before surgery throughout surgery	Normothermia, epidural analgesia	Length of hospital stay Pain relief Postop. epidural consumption PONV Time to flatus Cytokine surge
Rimback *et al*.[15]	3	15	15	Open cholecystectomy	Bolus (100 mg) before anaesthesia, then 3 mg/min for 24 h postop.		Return to motility (radio-opaque markers, abnormal radiographs) Duration of ileus
Wu *et al*.[16]	5	25	25	Laparoscopic cholecystectomy	Lidocaine 3 mg/kg/h started 30 min before and continued throughout surgery	Normothermia	Pain scores (VAS) Postop. opioid Time to first flatus

VAS, visual analogue scale; PONV, postoperative nausea and vomiting; BW, bodyweight; NSAID, non-steroidal anti-inflammatory drug; AOF, active oral feeding.

Postoperative pain intensity was measured with a 0–100-mm VAS in six RCTs including 250 patients. Pain scores at 24 h were significantly lower in patients receiving lidocaine than in controls (WMD −5·93 (95 per cent c.i. −9·63 to −2·23); $P = 0·002$) (*Fig. 4*).

Nausea and vomiting as a single entity was reported in five trials (170 patients). Its incidence was 32 per cent in the lidocaine group and 52 per cent in the control group (odds ratio 0·39 (95 per cent c.i. 0·20 to 0·76); $P = 0·006$) (*Fig. 5*). The NNT to avoid one instance

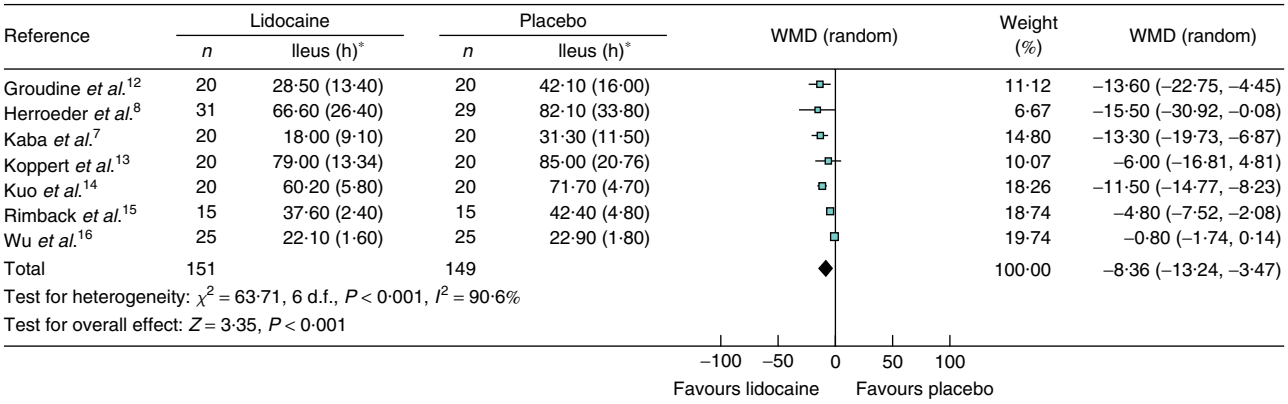

Fig. 2 Effect of intravenous lidocaine *versus* placebo on duration of postoperative ileus. *Values are mean(s.d.). Weighted mean differences (WMDs) are shown with 95 per cent confidence intervals

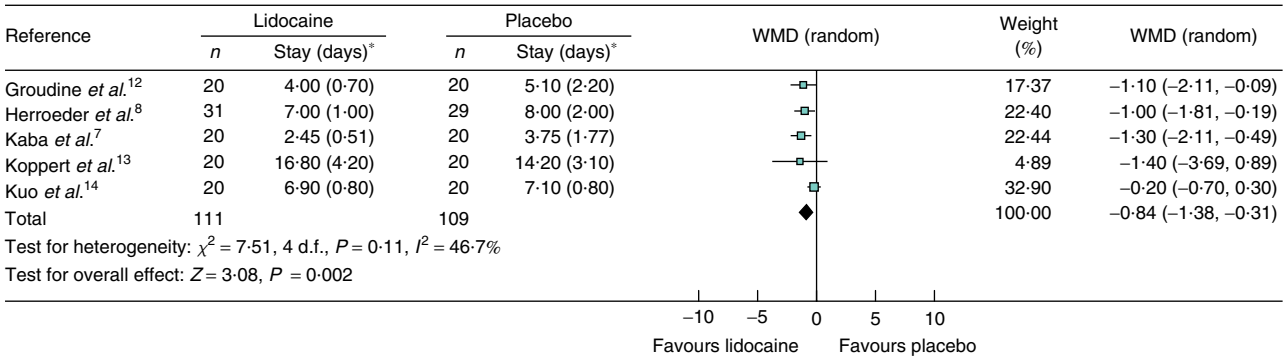

Fig. 3 Effect of intravenous lidocaine *versus* placebo on length of hospital stay. *Values are mean(s.d.). Weighted mean differences (WMDs) are shown with 95 per cent confidence intervals

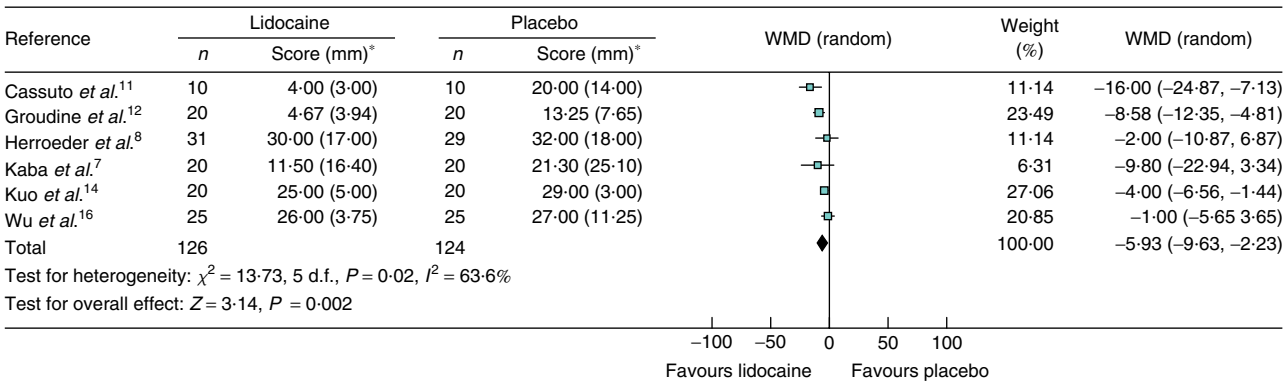

Fig. 4 Effect of intravenous lidocaine *versus* placebo on postoperative pain at 24 h after surgery. *Values are mean(s.d.). Weighted mean differences (WMDs) are shown with 95 per cent confidence intervals

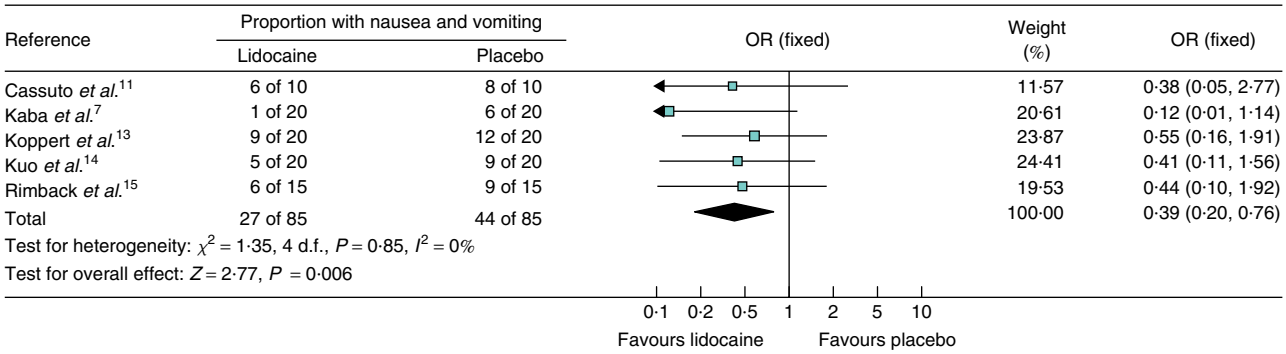

Fig. 5 Effect of intravenous lidocaine *versus* placebo on postoperative nausea and vomiting. Odds ratios (ORs) are shown with 95 per cent confidence intervals

of nausea and vomiting was 5 (95 per cent c.i. 3 to 17).

Three trials[11,13,15] evaluated sedation during the postoperative period. Six patients were sedated in the lidocaine groups *versus* seven in the control groups. Other side-effects of opioids were not always reported, precluding a pooled analysis. Cardiac arrhythmia with stable vital signs was reported in one patient who received lidocaine[16].

Discussion

This meta-analysis of eight RCTs favours continuous perioperative intravenous lidocaine administration in that it reduces the duration of postoperative ileus, pain, nausea and vomiting, and the length of hospital stay. These endpoints are addressed in turn below.

Gastrointestinal dysfunction after abdominal surgery has many causes, including autonomic nervous system dysfunction, inflammatory response, administration of anaesthetics and opioids, and gastrointestinal hormone disruption[17]. Intravenous lidocaine may shorten the duration of ileus by reducing opioid consumption (as noted in seven of eight trials), by preventing inflammatory processes and by decreasing sympathetic tone. In the two trials that addressed inflammatory response, systemic lidocaine significantly blunted any postoperative rise in plasma concentration of proinflammatory cytokines and complement, as well as any increase in integrin (CD11b) and selectin (CD62L and CD62P) expression at the surface of leucocyte and platelet–leucocyte aggregates[8,14]. However, the effects of intravenous lidocaine on sympathetic tone are less certain. At least two groups did not detect any difference in plasma or urinary catecholamine concentrations in patients who did, and who did not, receive intravenous lidocaine during and after surgery[7,18]. Nevertheless, direct blockade of a tonic inhibitory action in the mesenteric nervous plexus leading to greater responsiveness to contractile stimulation cannot be ruled out. In experimental studies, lidocaine produces action potentials and increases the amplitude of contractions in intestinal muscle, probably by suppressing intrinsic nervous inhibition[19,20]. In addition, it can stimulate responses in intact intestinal wall and ganglion-free muscle preparations[21]. These features suggest that postoperative ileus may be shorter as a result of a direct effect on smooth muscle cells.

Local anaesthetics to relieve pain after abdominal surgery are usually administered continuously through an epidural catheter. However, epidural analgesia is inadequate in almost 30 per cent of patients because the catheter is either removed prematurely or malpositioned[22,23]. In addition, epidural analgesia conveys a risk of side-effects, such as hypotension, urinary retention and motor blockade. Intravenous lidocaine is, on the other hand, devoid of side-effects. The meta-analysis has established that intravenous lidocaine significantly decreases the intensity of postoperative pain and reduces opioid consumption. Consequently, lidocaine appears to be an appropriate option for pain relief when epidural analgesia is not possible, or when it is inappropriately invasive for the surgical procedure in question (for example video laparoscopy). The mechanism of pain relief by lidocaine may be inhibition of the ectopic impulse discharge generated at sites of experimental nerve injury and in axotomized dorsal root ganglion[24]. In experimental studies, lidocaine treatment before trauma suppressed secondary hyperalgesia mainly by peripheral mechanisms[25,26]. The safety of continuous intravenous lidocaine has not been evaluated in a large cohort of surgical patients but no local toxicity other than a single episode of transient arrhythmia[16] was observed in any of the trials in this meta-analysis.

The meta-analysis has also shown that continuous intravenous lidocaine administration reduces the length of hospital stay. Treatment of postoperative ileus by gastrointestinal opioid receptor antagonists, or by multimodal analgesia with NSAIDs, may also shorten stay after abdominal surgery by accelerating recovery of bowel function[27,28]. However, epidural analgesia after colonic surgery, despite decreasing postoperative ileus, does not reduce hospital stay[3]. Possible reasons include side-effects or technical failures, or because reducing hospital stay was simply not an objective of these trials[3]. In addition, active rehabilitation implemented in the more recent trials of epidural analgesia might mask an effect of epidural analgesia on hospital stay[3]. A direct comparison between epidural analgesia and intravenous lidocaine administration in patients within an active rehabilitation protocol might well be worthwhile.

By lengthening hospital stay after elective surgery, ileus has an impact on hospital costs[29]. In a retrospective review of 83 patients, 25 per cent of hemicolectomies and 18 per cent of hysterectomies were associated with postoperative ileus and prolonged hospital stay; this increased costs per patient by US $12 416 (€8481) and $4512 (€3082) per patient respectively[30]. The benefit in terms of postoperative ileus is pronounced patients having colonic resection or an open procedure. Intravenous lidocaine may therefore be of greater interest in patients scheduled for major abdominal surgery where postoperative ileus has an impact on hospital stay. For colonic resection, lidocaine decreases ileus by around 12 h. Interestingly, some authors have found that decreasing time to first flatus by even half a day accelerates time to hospital discharge[28,31]. Nausea and vomiting may also increase costs after surgery. They are reduced in patients receiving intravenous lidocaine, probably because of lower opioid consumption[32]. Prophylactic antiemetic therapy has been shown to be cost-effective[33]. In summary, as the present meta-analysis has shown a significant reduction of nausea and vomiting, duration of ileus and hospital stay, intravenous lidocaine may be considered as a cost-effective strategy after abdominal surgery.

The meta-analysis has several limitations. First, data were included only from patients undergoing abdominal surgery. Intravenous lidocaine inhibits visceromotor and cardiovascular reflexes evoked by colorectal distension suggesting a clear benefit on visceral pain[34]. The conclusions cannot, however, be extrapolated to other settings, such as orthopaedic surgery. Second, the duration of postoperative ileus was the primary endpoint in only three RCTs[7,12,15]. Third, all outcomes were not reported in all trials (*Table 1*). Finally, only RCTs with small patient numbers were retrieved, and the discrepancies between meta-analyses and large RCTs are well known[35]. On the other hand, a distinct advantage of the present meta-analysis is that all eight included trials were double-blind RCTs with a high Oxford Quality Score[36]. The risk of concluding that there is a benefit when there is none is, therefore, reduced.

In conclusion, continuous perioperative and postoperative intravenous lidocaine infusion after abdominal surgery decreases the duration of ileus, the incidence of nausea and vomiting, the severity of pain and the length of hospital stay. It offers a simple clinical solution that can be applied in conjunction with, or instead of, the many popular postoperative regimens currently in use.

References

1 Liu S, Carpenter RL, Neal JM. Epidural anesthesia and analgesia. Their role in postoperative outcome. *Anesthesiology* 1995; **82**: 1474–1506.

2 Wu CL, Cohen SR, Richman JM, Rowlingson AJ, Courpas GE, Cheung K *et al*. Efficacy of postoperative patient-controlled and continuous infusion epidural analgesia *versus* intravenous patient-controlled analgesia with opioids: a meta-analysis. *Anesthesiology* 2005; **103**: 1079–1088.

3 Marret E, Remy C, Bonnet F. Meta-analysis of epidural analgesia *versus* parenteral opioid analgesia after colorectal surgery. *Br J Surg* 2007; **94**: 665–673.

4 Giebler RM, Scherer RU, Peters J. Incidence of neurologic complications related to thoracic epidural catheterization. *Anesthesiology* 1997; **86**: 55–63.

5 Hollmann MW, Durieux ME. Local anesthetics and the inflammatory response: a new therapeutic indication? *Anesthesiology* 2000; **93**: 858–875.

6 de Clive-Lowe SG, Gray PWS, North J. Succinyldicholine and lignocaine by continuous intravenous drip: report of 1000 administrations. *Anaesthesia* 1954; **9**: 96–104.

7 Kaba A, Laurent SR, Detroz BJ, Sessler DI, Durieux ME, Lamy ML *et al*. Intravenous lidocaine infusion facilitates acute rehabilitation after laparoscopic colectomy. *Anesthesiology* 2007; **106**: 11–18.

8 Herroeder S, Pecher S, Schonherr ME, Kaulitz G, Hahnenkamp K, Friess H *et al*. Systemic lidocaine shortens length of hospital stay after colorectal surgery: a double-blinded, randomized, placebo-controlled trial. *Ann Surg* 2007; **246**: 192–200.

9 Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet* 1999; **354**: 1896–1900.

10 Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ *et al*. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; **17**: 1–12.

11 Cassuto J, Wallin G, Hogstrom S, Faxen A, Rimback G. Inhibition of postoperative pain by continuous low-dose intravenous infusion of lidocaine. *Anesth Analg* 1985; **64**: 971–974.

12 Groudine SB, Fisher HA, Kaufman RP Jr, Patel MK, Wilkins LJ, Mehta SA *et al*. Intravenous lidocaine speeds the return of bowel function, decreases postoperative pain, and shortens hospital stay in patients undergoing radical retropubic prostatectomy. *Anesth Analg* 1998; **86**: 235–239.

13 Koppert W, Weigand M, Neumann F, Sittl R, Schuettler J, Schmelz M *et al*. Perioperative intravenous lidocaine has preventive effects on postoperative pain and morphine consumption after major abdominal surgery. *Anesth Analg* 2004; **98**: 1050–1055.

14 Kuo CP, Jao SW, Chen KM, Wong CS, Yeh CC, Sheen MJ *et al*. Comparison of the effects of thoracic epidural analgesia and i.v. infusion with lidocaine on cytokine response, postoperative pain and bowel function in patients undergoing colonic surgery. *Br J Anaesth* 2006; **97**: 640–646.

15 Rimback G, Cassuto J, Tollesson PO. Treatment of postoperative paralytic ileus by intravenous lidocaine infusion. *Anesth Analg* 1990; **70**: 414–419.

16 Wu CT, Borel CO, Lee MS, Yu JC, Liou HS, Yi HD *et al*. The interaction effect of perioperative cotreatment with dextromethorphan and intravenous lidocaine on pain relief and recovery of bowel function after laparoscopic cholecystectomy. *Anesth Analg* 2005; **100**: 448–453.

17 Holte K, Kehlet H. Postoperative ileus: a preventable event. *Br J Surg* 2000; **87**: 1480–1493.

18 Wallin G, Cassuto J, Hogstrom S, Linden I, Faxen A, Rimback G *et al*. Effects of lidocaine infusion on the sympathetic response to abdominal surgery. *Anesth Analg* 1987; **66**: 1008–1013.

19 Biber B, Fara J. Intestinal motility increased by tetrodotoxin, lidocaine, and procaine. *Experientia* 1973; **29**: 551–552.

20 Wood JD. Excitation of intestinal muscle by atropine, tetrodotoxin, and xylocaine. *Am J Physiol* 1972; **222**: 118–125.

21 Bortoff A, Muller R. Stimulation of intestinal smooth muscle by atropine, procaine, and tetrodotoxin. *Am J Physiol* 1975; **229**: 1609–1613.

22 Ready LB. Acute pain: lessons learned from 25 000 patients. *Reg Anesth Pain Med* 1999; **24**: 499–505.

23 Rigg JR, Jamrozik K, Myles PS, Silbert BS, Peyton PJ, Parsons RW *et al*. Epidural anaesthesia and analgesia and outcome of major surgery: a randomised trial. *Lancet* 2002; **359**: 1276–1282.

24 Devor M, Wall PD, Catalan N. Systemic lidocaine silences ectopic neuroma and DRG discharge without blocking nerve conduction. *Pain* 1992; **48**: 261–268.

25 Kawamata M, Sugino S, Narimatsu E, Yamauchi M, Kiya T, Furuse S *et al*. Effects of systemic administration of lidocaine and QX-314 on hyperexcitability of spinal dorsal horn neurons after incision in the rat. *Pain* 2006; **122**: 68–80.

26 Kawamata M, Takahashi T, Kozuka Y, Nawa Y, Nishikawa K, Narimatsu E *et al*. Experimental incision-induced pain in human skin: effects of systemic lidocaine on flare formation and hyperalgesia. *Pain* 2002; **100**: 77–89.

27 Taguchi A, Sharma N, Saleem RM, Sessler DI, Carpenter RL, Seyedsadr M *et al*. Selective postoperative inhibition of gastrointestinal opioid receptors. *N Engl J Med* 2001; **345**: 935–940.

28 Sinatra RS, Boice JA, Loeys TL, Ko AT, Kashuba MM, Jahr JS *et al*. Evaluation of the effect of perioperative rofecoxib treatment on pain control and clinical outcomes in patients recovering from gynecologic abdominal surgery: a randomized, double-blind, placebo-controlled clinical study. *Reg Anesth Pain Med* 2006; **31**: 134–142.

29 Bosio RM, Delaney CP, Senagore AJ. Economic impact of POI and prolonged length of stay. *Semin Colon Rectal Surg* 2005; **16**: 235–238.

30 Salvador CG, Sikirica M, Evans A, Pizzi L, Goldfarb N. Clinical and economic outcomes of prolonged postoperative ileus in patients undergoing hysterectomy and hemicolectomy. *Pharmacy and Therapeutics* 2005; **30**: 590–595.

31 Senagore AJ, Bauer JJ, Du W, Techner L. Alvimopan accelerates gastrointestinal recovery after bowel resection regardless of age, gender, race, or concomitant medication use. *Surgery* 2007; **142**: 478–486.

32 Marret E, Kurdi O, Zufferey P, Bonnet F. Effects of nonsteroidal antiinflammatory drugs on patient-controlled analgesia morphine side effects: meta-analysis of randomized controlled trials. *Anesthesiology* 2005; **102**: 1249–1260.

33 Hill RP, Lubarsky DA, Phillips-Bute B, Fortney JT, Creed MR, Glass PS *et al*. Cost-effectiveness of prophylactic antiemetic therapy with ondansetron, droperidol, or placebo. *Anesthesiology* 2000; **92**: 958–967.

34 Ness TJ. Intravenous lidocaine inhibits visceral nociceptive reflexes and spinal neurons in the rat. *Anesthesiology* 2000; **92**: 1685–1691.

35 LeLorier J, Gregoire G, Benhaddad A, Lapierre J, Derderian F. Discrepancies between meta-analyses and subsequent large randomized, controlled trials. *N Engl J Med* 1997; **337**: 536–542.

36 Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M *et al*. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* 1998; **352**: 609–613.