Anaesthesia 2016, 71, 405–410 doi:10.1111/anae.13368

Original Article

A randomised controlled trial of peri-operative lidocaine infusions for open radical prostatectomy*

L. Weinberg,[1] C. Rachbuch,[2] S. Ting,[3] W. Howard,[4,5] M. Yeomans,[6] I. Gordon,[7] L. McNicol,[8,9] K. James,[5] D. Story[10] and C. Christophi[11]

1 Associate Professor, 10, Professor and Chair, Anaesthesia, Peri-operative and Pain Medicine, 7 Professor, School of Mathematics and Statistics, 8 Associate Professor, 11 Professor, Department of Surgery, University of Melbourne, Melbourne, Victoria, Australia
2 Director, Department of Anaesthesia, Eastern Health, Box Hill, Victoria, Australia
3 Resident, Department of Anaesthesia, Monash Health, Clayton, Victoria, Australia
4 Head, 6 Clinical Nurse Specialist, Acute Pain Service, 5 Consultant, 9 Director, Department of Anaesthesia, Austin Hospital, Heidelberg, Victoria, Australia

Summary

We allocated 76 men scheduled for radical retropubic prostatectomy to peri-operative lidocaine 2% or saline 0.9%: a pre-operative 0.075 $ml.kg^{-1}$ intravenous bolus; an intra-operative intravenous infusion at 0.075 $ml.kg^{-1}.h^{-1}$; and 24 hours' postoperative subcutaneous infusion at 0.075 $ml.kg^{-1}.h^{-1}$. Lidocaine reduced the postoperative hospital stay by a mean (95% CI) of 1.3 (0.3–2.4) days, p = 0.017, from a mean (SD) of 4.6 (3.2) days with saline. Lidocaine reduced pain at rest during the first 24 postoperative hours by a mean (95% CI) of 1.8 (0.7–2.9) $mm.h^{-1}$, p = 0.001. Lidocaine reduced 24-h morphine consumption by a mean (95% CI) of 13.9 (2.2–25.7) mg, p = 0.021, from a mean (SD) of 52.3 (26.9) mg with saline. There were no differences in other outcomes.

Correspondence to: L. Weinberg
Email: laurence.weinberg@austin.org.au
Accepted: 30 November 2015
**Presented in part at the combined Australian and New Zealand College of Anaesthesia Annual Scientific Meeting, Hong Kong, May 2011.*

Introduction

Intravenous lidocaine reduces pain and shortens the duration of ileus and hospital stay after surgery [1–4]. A subcutaneous infusion of lidocaine may be similarly effective and is potentially safer than intravenous infusion by reducing the variability in plasma concentration. We conducted this randomised controlled trial to test whether intra-operative intravenous lidocaine combined with a postoperative 24-h subcutaneous lidocaine infusion, would decrease pain and hospital stay after radical retropubic prostatectomy.

Methods

The Research Ethics Units at Austin and Box Hill hospitals approved this registered study. Two investigators (LW, CR) recruited men scheduled for open retropubic radical prostatectomy, who were older than 18 years and ASA physical status < 4. All participants gave written informed consent.

We did not study patients with any of the following: intolerance to opioids local anaesthetics or non-steroidal anti-inflammatory drugs; second or third degree heart block, sino-atrial block without pacemaker; prescribed Class 1 anti-arrhythmic drugs or amiodarone; epilepsy, seizures, cognitive impairment, or craniotomy within the last five years; myasthenia gravis; pre-operative morphine consumption > 3 $mg.h^{-1}$ orally or > 1 $mg.h^{-1}$ intravenously, for more than one month. We also excluded patients with: [creatinine] > 200 $\mu mol.l^{-1}$; [bilirubin] > 30 $\mu mol.l^{-1}$ or [alkaline phosphatase] > 300 $iu.l^{-1}$; or [alanine transaminase] > 50 $iu.l^{-1}$ or [albumin] < 25 $g.dl^{-1}$; platelets < 150 $\times 10^9.l^{-1}$ or prothrombin time > 14 s; or APTT > 35 s or [fibrinogen] < 2 $g.l^{-1}$.

An independent statistician generated a computerised sequence of 76 allocation codes, 38 for each group (www.randomization.com). Pharmacy staff sealed the allocation codes into sequentially numbered opaque envelopes. The sequence was decoded after we had analysed the data. The study participants, surgeons, anaesthetists, nurses, and all peri-operative staff were blinded to treatment assignments. On the day of surgery, an independent clinical pharmacist prepared 50-ml and 200-ml infusions for intra-operative and postoperative use, respectively, labelled "2% lignocaine or saline", which contained lidocaine 2% or saline 0.9%. Before induction of anaesthesia, we injected 0.075 $ml.kg^{-1}$ of the infusate intravenously over three minutes, which we then infused at 0.075 $ml.kg^{-1}.h^{-1}$ until the end of surgery.

We induced anaesthesia intravenously with fentanyl 3 $\mu g.kg^{-1}$ and propofol 1–3 $mg.kg^{-1}$. We used a non-depolarising muscle relaxant to facilitate tracheal intubation. We maintained anaesthesia with sevoflurane titrated to bispectral indices of 40–60. We monitored ECG, pulse oximetry, capnography, invasive arterial blood pressure and core body temperature. We infused fentanyl 2.5 $\mu g.kg^{-1}.h^{-1}$, supplemented at the discretion of the anaesthetist with 1–2 $\mu g.kg^{-1}$ boluses. We maintained infusions of Hartmann's or Plasmalyte solutions at 5 $ml.kg^{-1}.h^{-1}$. We replaced blood loss with a colloid: we transfused blood for [haemoglobin] < 80 $g.l^{-1}$ or < 90 $g.l^{-1}$ when we anticipated further bleeding. We maintained the core temperature above 36 °C with warm fluids and forced-air warming (3M Bair Hugger® Total Temperature Management System, Critical Assist, Australia). We injected dexamethasone 8 mg and ondansetron 8 mg intravenously for antiemetic prophylaxis. We gave paracetamol 1 g intravenously and ketorolac 30 mg intramuscularly about 30 min before the end of surgery and stopped the fentanyl infusion. We stopped the intravenous lidocaine infusion after tracheal extubation. We did not use any local or regional anaesthesia.

In recovery, we inserted a subcutaneous cannula in the upper arm or abdomen (BD Saf-T-Intima™; BD Medical, Sandy, UT, USA), and started the allocated 0.075 $ml.kg^{-1}.h^{-1}$ subcutaneous infusion. We prescribed regular oral paracetamol 1 g and regular intramuscular ketorolac 30 mg for the first 24 postoperative hours [5]. Participants used morphine patient-controlled analgesia with a 1 mg bolus and a 5-min lockout. Staff could treat pain scores > 6 mm with a 0.05–0.10 $mg.kg^{-1}$ intravenous bolus of morphine, supplemented by a 20 min infusion of tramadol 100 mg and followed as necessary with intravenous ketamine, loaded at 0.1 $mg.kg^{-1}$ and maintained at 0.05–0.20 $mg.kg^{-1}.h^{-1}$. Intravenous metoclopramide 20 mg or droperidol 2.5 mg were used to treat nausea or vomiting. Participants could drink water in recovery and could eat on the ward. Participants sat out of bed six hours after surgery and walked with the assistance of physiotherapists the next day. The subcutaneous infusion was discontinued at 24 postoperative hours, after which participants could take oral oxycodone 10–20 mg every four hours as required for discharge. The urinary catheter remained in situ for two postoperative weeks.

The primary outcome was postoperative hospital stay, from the end of surgery to hospital discharge. The criteria for discharge were unassisted walking, eating and drinking without nausea or vomiting, defaecation, satisfactory oral analgesia and no evidence of medical or surgical complications, particularly infection. The secondary outcomes were postoperative pain, analgesia, side effects, and participant satisfaction. We measured pain at the incision site with a 0–10 mm visual analogue scale, at rest and on coughing, hourly for four consecutive postoperative hours and then every 4 h for 20 h and then every 6–12 h for the next 24 h. We recorded morphine consumption hourly for 24 postoperative hours, nausea, vomiting and rescue

antiemetic administration, unless given for a different indication, for instance metoclopramide for prokinesis. We categorised postoperative sedation as: awake; occasionally drowsy and easy to rouse; often drowsy but easy to rouse; somnolent and difficult to rouse; sleeping. We categorised participant satisfaction as: very dissatisfied; dissatisfied; ambivalent; satisfied; very satisfied. We asked participants if they had experienced any of the following symptoms in the first 24 postoperative hours: numbness around their mouth; dizziness or headache; muscle twitching; visual or auditory hallucinations or confusion. We measured plasma lidocaine concentrations at the end of surgery and 24 h later with a calibrated reversed-phase high-pressure liquid chromatography assay.

We calculated that 38 participants in each group would have an 80% power to detect an 18 h reduction in hospital stay from the mean (SD) duration in 2009 of 98.4 (28.8) hours at a significance level of 0.05 [6]. We used t-tests and Mann–Whitney U-tests as appropriate for continuous data and chi-squared tests for categorical data with the Newcombe–Wilson method to calculate the 95% confidence interval [7]. We considered p values < 0.05 significant. We used standard methods to report this trial [8].

Results

We recruited 76 men (Fig. 1 and Table 1), 56 in Austin hospital and 20 in Box Hill hospital. We excluded one man in the lidocaine group whose operation was cancelled after anaphylaxis to cephalosporin antibiotic, given on induction of anaesthesia. We analysed the outcomes for another man in the lidocaine group who was not given intra-operative and postoperative infusions after lidocaine 1 g was inadvertently injected before anaesthetic induction; a brief period of hypotension was treated with a single dose of metaraminol.

Lidocaine reduced the postoperative stay by a mean (95% CI) of 1.3 (0.3–2.4) days, p = 0.017, from a mean (SD) of 4.6 (3.2) days with saline (Fig. 2). There were no differences between Austin and Box Hill hospitals in mean (SD) postoperative stays:

Table 1 Characteristics of men before radical retropubic prostatectomy. Values are mean (SD) or number.

	Lidocaine (n = 37)	Saline (n = 38)
Age; years	61.1 (6.3)	60.0 (7.6)
Weight; kg	85.2 (14.1)	82.9 (11.9)
Body mass index; $kg.m^{-2}$	28.5 (5.0)	27.7 (3.5)
ASA 1/2	24/13	26/12
Gleason Scores	6.6 (0.9)	6.7 (0.6)
PSA; $ng.ml^{-1}$	8.7 (5.0)	7.8 (4.9)
Hypertension	10	9
Diabetes mellitus	1	3
Peripheral arterial disease	1	0
COPD	1	0

ASA, ASA physical status; COPD, chronic obstructive pulmonary disease; PSA, prostate-specific antigen.

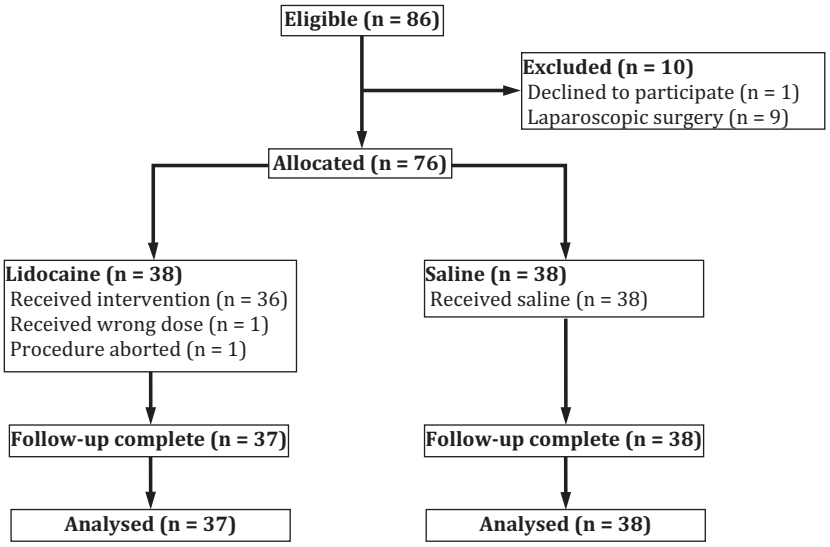

Figure 1 CONSORT diagram of patients receiving lidocaine or saline during radical retropubic prostatectomy.

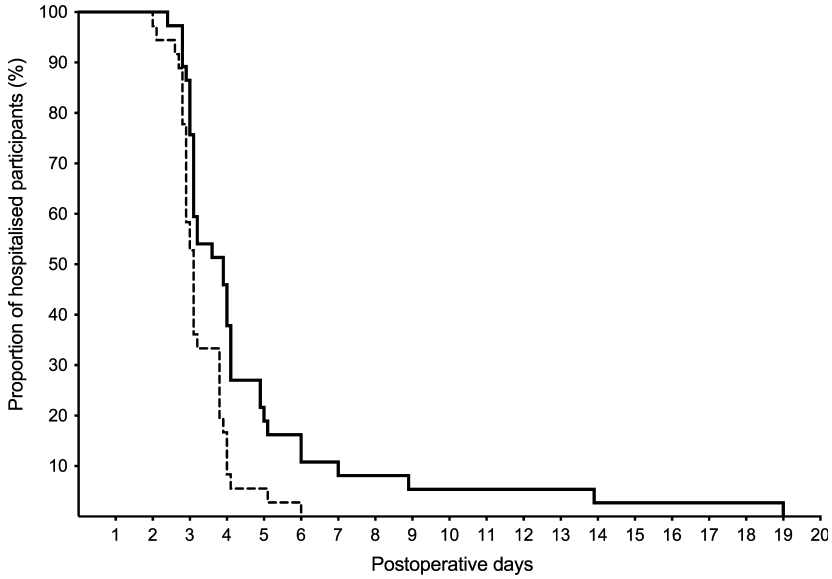

Figure 2 Cumulative postoperative stay after peri-operative infusions of lidocaine (---) or saline (—).

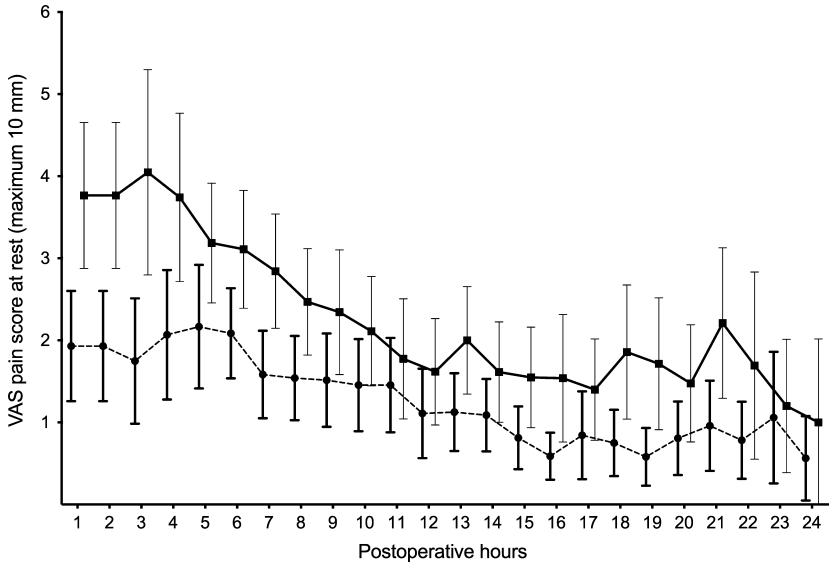

Figure 3 Postoperative pain scores at rest after peri-operative infusions of lidocaine (---) or saline (—) for radical retropubic prostatectomies in 75 men. Values are mean (SD).

after lidocaine, 3.3 (0.9) days vs 3.4 (0.7) days, p = 0.90; or after saline, 4.7 (2.3) days vs 4.5 (5.1) days, p = 0.89. Lidocaine reduced the time to mobilisation by a mean (95% CI) of 4.6 (2.5–6.7) h, p = 0.001, from a mean (SD) of 22.0 (4.4) h after saline. Water was tolerated a mean (95% CI) of 3.9 (1.5–6.3) postoperative hours sooner after lidocaine, p = 0.002, than the mean (SD) of 13.6 (5.0) h after saline. Similarly, food was tolerated a mean (95% CI) of 5.4 (2.1–8.6) h sooner after lidocaine, p = 0.002, than the mean (SD) of 20.9 (7.5) h after saline.

Lidocaine reduced pain at rest during the first 24 postoperative hours by a mean (95% CI) of 1.8 (0.7–2.9) $mm.h^{-1}$, p = 0.001 (Fig. 3). The change in pain scores during movement in the first 24 postoperative hours was similar between the groups with a mean

(95% CI) of 1.2 (0.6–2.9) $mm.h^{-1}$, p = 0.2. Lidocaine reduced 24-h morphine consumption by a mean (95% CI) of 13.9 (2.2–25.7) mg, p = 0.021, from a mean (SD) of 52.3 (26.9) mg with saline (Fig. 4). The median (IQR [range]) 24-h sedation score was 1.0 (1.0–1.5 [2.0–3.0]) with lidocaine and 1.0 (1.0–2.0 [1.0–3.0]) with saline, p = 0.14. There were no differences in other outcomes (Table 2).

Plasma lidocaine was not detectable after saline. Lidocaine infusions resulted in mean (SD) plasma concentrations of 1.36 (0.48) $\mu g.ml^{-1}$ in recovery (maximum 2.80 $\mu g.ml^{-1}$) and 3.20 (0.95) $\mu g.ml^{-1}$ at 24 h (maximum 4.96 $\mu g.ml^{-1}$). Plasma lidocaine levels did not correlate with cumulative morphine consumption, r = 0.09, p = 0.6.

Discussion

Peri-operative infusions of lidocaine up to 24 postoperative hours reduced pain, morphine consumption and hospital stay following radical prostatectomy.

Subcutaneous lidocaine can result in stable therapeutic plasma lidocaine concentrations [9, 10]. We modelled the subcutaneous lidocaine infusion regime on the doses described by studies of intravenous lidocaine [11, 12]. The lidocaine plasma levels that we measured were similar to those studies (2–5 $mg.ml^{-1}$). Postoperative intravenous lidocaine infusions can reduce pain and postoperative stay [13, 14]. The similarity of our results suggests that subcutaneous lidocaine may be equivalent to intravenous infusion,

Table 2 Secondary outcomes after peri-operative infusions of lidocaine or saline for radical retropubic prostatectomies in 75 men. Values are number (proportion).

	Lidocaine (n = 37)	Saline (n = 38)	p value
PONV	19 (51%)	17 (45%)	0.6
24-h rescue antiemetics	15 (41%)	18 (47%)	0.6
24-h rescue analgesia	0	2 (5%)	0.5
Ketamine infusion	0	1 (3%)	1.0
Tramadol	0	2 (5%)	0.5
Pruritus	6 (16%)	9 (24%)	0.6
Dizziness	14 (37%)	20 (53%)	0.2
Visual disturbances	4 (11%)	6 (16%)	0.7
Peri-oral numbness	2 (6%)	2 (5%)	1.0
Muscle weakness	1 (3%)	3 (8%)	0.6
Constipation	4 (11%)	10 (26%)	0.2
Very satisfied/ satisfied	20/17	16/22	0.4

PONV, postoperative nausea or vomiting.

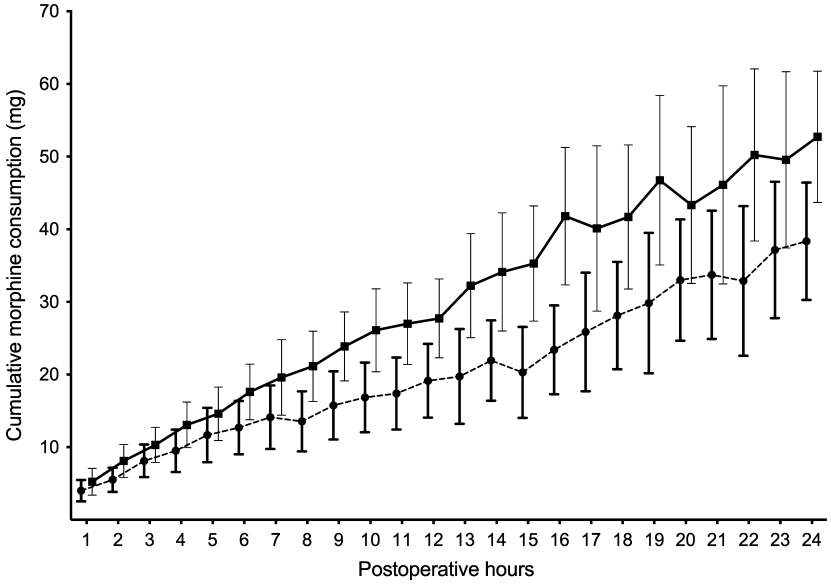

Figure 4 Cumulative postoperative morphine consumption after peri-operative infusions of lidocaine (---) or saline (—). Values are mean (SD).

although this should be tested within a randomised controlled trial. We do not know what plasma lidocaine concentrations might result from continuation of the subcutaneous infusion beyond 24 h.

We do not know whether our results are applicable to other scheduled (or emergency) major abdominal operations or to older, sicker or obese patients. We do not know how much the effects of peri-operative lidocaine were the result of pre-operative bolus, intra-operative intravenous infusion or postoperative subcutaneous infusion. We cannot extrapolate our lidocaine infusion results to different combinations of rate, duration or route. We cannot exclude important plasma lidocaine levels between the two sampling times. We did not measure concentrations of active but less potent lidocaine metabolites, including monoethylglycinexylidide and glycinexylidide.

In summary, a combination of peri-operative intravenous and subcutaneous lidocaine, up to 24 hours after radical prostatectomy, reduced pain, morphine consumption and hospital stay compared with saline.

Acknowledgements

We would like to thank Professor Julia Fleming, Director of the Professor Tess Cramond Multidisciplinary Pain Centre, The University of Queensland, for her expert advice and guidance in the preparation of this manuscript.

Funding was provided by a Pfizer Australian and New Zealand College of Anaesthetists Research Fellow grant, and an Australian and New Zealand College of Anaesthetists Academic Enhancement grant. No conflicts of interest declared.

References

1. McCarthy GC, Megalla SA, Habib AS. Impact of intravenous lidocaine infusion on postoperative analgesia and recovery from surgery: a systematic review of randomized controlled trials. *Drugs* 2010; **70**: 1149–63.
2. Marret E, Rolin M, Beaussier M, Bonnet F. Meta-analysis of intravenous lidocaine and postoperative recovery after abdominal surgery. *British Journal of Surgery* 2008; **95**: 1331–8.
3. Sun Y, Li T, Wang N, Yun Y, Gan TJ. Perioperative systemic lidocaine for postoperative analgesia and recovery after abdominal surgery: a meta-analysis of randomized controlled trials. *Diseases of the Colon and Rectum* 2012; **55**: 1183–94.
4. Vigneault L, Turgeon AF, Côté D, et al. Perioperative intravenous lidocaine infusion for postoperative pain control: a meta-analysis of randomized controlled trials. *Canadian Journal of Anesthesia* 2011; **58**: 22–37.
5. Acute pain management measurement toolkit. http://www.health.vic.gov.au/qualitycouncil/downloads/toolkit_introduction.pdf (accessed 19/11/2015).
6. Weinberg L, Chen S, Dissanayake I, Ko A, Story D, Peyton P. Perioperative anaesthetic outcomes after open radical retropubic prostatectomy: a 13-year experience in a tertiary care centre. *Anaesthsia and Intensive Care* 2010; **38**: A1116.
7. Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. *Statistics in Medicine* 1998; **17**: 873–90.
8. Schulz KF, Altman DG, Moher D, For the CONSORT group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *British Medical Journal* 2010; **340**: c332.
9. Scott DB, Jebson PJ, Braid DP, Ortengren B, Frisch P. Factors affecting plasma levels of lignocaine and prilocaine. *British Journal of Anaesthesia* 1972; **44**: 1040–9.
10. Brose W, Cousins M. Subcutaneous lidocaine for treatment of neuropathic cancer pain. *Pain* 1991; **45**: 145–8.
11. Hsu YW, Somma J, Newman MF, Mathew JP. Population pharmacokinetics of lidocaine administered during and after cardiac surgery. *Journal of Cardiothoracic and Vascular Anesthesia* 2011; **25**: 931–6.
12. Kaba A, Laurent SR, Detroz BJ, et al. Intravenous lidocaine infusion facilitates acute rehabilitation after laparoscopic colectomy. *Anesthesiology* 2007; **106**: 11–8.
13. Harvey KP, Adair JD, Isho M, Robinson R. Can intravenous lidocaine decrease postsurgical ileus and shorten hospital stay in elective bowel surgery? A pilot study and literature review. *American Journal of Surgery* 2009; **198**: 231–6.
14. Choi SJ, Kim MH, Jeong HY, Lee JJ. Effect of intraoperative lidocaine on anesthetic consumption, and bowel function, pain intensity, analgesic consumption and hospital stay after breast surgery. *Korean Journal of Anesthesiology* 2012; **62**: 429–34.

