

PAIN

Systemic lidocaine fails to improve postoperative morphine consumption, postoperative recovery and quality of life in patients undergoing posterior spinal arthrodesis. A double-blind, randomized, placebo-controlled trial

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Abstract

Background. It is inconclusive whether the perioperative administration of systemic lidocaine provides effective postoperative analgesia and enhances recovery in major orthopaedic surgery. We hypothesised that in adolescent and adult patients undergoing posterior spinal arthrodesis, a perioperative lidocaine infusion would reduce opioid requirements during the first 24 postoperative h.

Methods. 70 patients undergoing posterior arthrodesis were enrolled in this prospective, randomised, double-blind, placebo-controlled clinical trial. Patients received total i.v. anaesthesia with propofol and remifentanyl and were randomized to an adjuvant therapy with either lidocaine [i.v.-bolus injection of 1.5 mg kg⁻¹ at induction of anaesthesia, followed by an infusion of 1.5 mg kg⁻¹ h⁻¹ which was continued until six h after arrival at the post-anaesthesia care unit] or placebo (equal volumes of saline). Postoperative pain was treated with patient-controlled i.v. morphine. Primary endpoints of this study were morphine requirements in the first postoperative 24 h.

Results. Systemic lidocaine did not decrease morphine requirements in the first 24 postoperative h [lidocaine-group: 48 (23) mg (mean(sd)) vs placebo-group: 51(19) mg, $P = 0.22$]. Likewise, groups were not different with respect to the severity of postoperative pain, morphine consumption after 48 and 72 h, incidence of postoperative nausea and vomiting, perioperative inflammation, time to recovery of intestinal function, hospital length of stay, and quality of life (assessed preoperatively and one month postoperatively using the SF-12 physical and mental composite scores).

Conclusions. In our study, systemic lidocaine had no analgesic benefits in posterior arthrodesis when added to an opioid-based anaesthetic regimen.

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Key words: lidocaine; pain; postoperative; spinal fusion

Editor's key points

- I.V. lidocaine has analgesic benefit in abdominal surgery; effects in spinal surgery are unclear.
- This study evaluated i.v. lidocaine effects on analgesia and adverse effects in spinal surgery.
- There was no reduction in opioid consumption or postoperative pain with systemic lidocaine.
- The type of surgery should be considered in tailoring multimodal analgesia.

Postoperative pain management after extensive spine surgery remains a challenging problem. The underlying mechanisms of postoperative pain in spine surgery are likely multifactorial and are the result of direct surgical trauma to osseous tissue at multiple levels, laminar decortication, and the corrective forces that are exerted on the spine after instrumentation.¹ Adequate postoperative pain relief is imperative to improve functional outcome, accelerate early ambulation and discharge from the hospital and to prevent the development of chronic pain.^{2,3}

Opioids are still considered the corner stone for postoperative analgesia, but their use can cause clinically relevant adverse effects including respiratory depression, sedation, constipation, itching, ileus, urinary retention and postoperative nausea and vomiting.⁴ These side-effects can increase perioperative morbidity and can delay hospital discharge. Therefore, modern analgesic strategies aim at reducing postoperative opioid consumption using a multimodal approach.^{1,5,6}

Lidocaine is an amide local anaesthetic that has analgesic,⁴ anti-hyperalgesic⁷ and anti-inflammatory properties.⁸ While in major abdominal surgery, the perioperative administration of i.v. lidocaine for postoperative pain relief has repeatedly been reported to provide effective postoperative analgesia, decrease opioid consumption, lessen the incidence of ileus and facilitate rehabilitation, the data on the efficacy of lidocaine in major orthopaedic surgery remain inconclusive.^{5,9,10}

We hypothesised that in adolescent and adult patients undergoing posterior spinal arthrodesis, a perioperative lidocaine infusion would reduce opioid requirements during the first 24 postoperative h.

Methods

Study design and population

Seventy patients undergoing posterior spinal arthrodesis were enrolled in this prospective, double-blind, randomized, placebo-controlled clinical trial.

The study protocol was approved by the Ethics Committee of the University Hospitals of the KU Leuven, Belgium (EC OG032, May 6th, 2013, Chairperson Prof W. Van den Bogaert) and by the Belgian government. The study has been registered in the publicly accessible study register of the European Medicines Agency (EUDRACT 2012-005264-98). Patients were enrolled between

September 2013 and July 2015. In our initial study protocol, inclusion criteria were an ASA physical status I-III and an age between 12 and 18 yr. Eight months after the beginning of the study, our Ethics Committee approved a modification of the inclusion criteria (EC OG032, December 23th, 2013) so that patients up to 75 yr could be included. This modification became necessary to increase the number of eligible patients. The exclusion criteria included hypersensitivity to lidocaine, liver disease (defined as total serum bilirubin ≥ 2 mg dl⁻¹), renal impairment (defined as Glomerular Filtration Rate ≤ 60 ml min⁻¹ 1.73 m⁻²), cardiac arrhythmias, epilepsy, intellectual disability and preoperative chronic medication with strong opioids (e.g. morphine or transdermal fentanyl).

After obtainment of written informed consent (either by the patients themselves or - in patients younger than 18 yr - by the parents), patients were randomized to either the lidocaine group (L-group) or the placebo group (P-group) using a computer-generated random table (Graphpad Software Inc., La Jolla, CA, USA) and an allocation ratio of 1:1.

Allocation concealment was achieved by enclosing assignments in sealed, opaque, sequentially numbered envelopes, which were opened only after arrival of the patient in the operation theatre. Blinding of research personal was maintained throughout the entire observation period including all postoperative follow-ups.

Study intervention

Patients in the lidocaine-group were given an i.v. bolus injection of lidocaine 1.5 mg kg⁻¹ at induction of anaesthesia and then a continuous infusion of 1.5 mg kg⁻¹ h⁻¹ which was continued until six h after arrival at the PACU.^{9,11-15} Patients in the placebo-group received equivalent volumes of saline using the identical application scheme. The study medication was prepared by an anaesthetist not being member of the study team and participating neither in the treatment or follow-up of the study patients. The study drugs were prepared in a 20-ml (for the bolus injection) and a 50-ml syringe (for the continuous infusion). The 20-ml syringe contained 1% lidocaine solution according to the weight of the patient (0.15ml kg⁻¹) or an equal amount of 0.9% saline. The 50-ml syringe contained either 500 mg lidocaine (10 mg ml⁻¹) or 0.9% normal saline solution.

Anaesthesia and perioperative treatment

All patients received a standardised anaesthesia technique including premedication with alprazolam (0.25 mg for patients with a body weight < 50 kg, 0.5 mg for patients with a body weight > 50 kg) one h before surgery. Induction of anaesthesia was performed with a target controlled infusion (TCI) with propofol applying the Marsh model¹⁶ (Alaris® PK Syringe Pump, CareFusion, United Kingdom) with a targeted effective plasma concentration of 5 µg/ml, remifentanyl (0.5 µg kg⁻¹ min⁻¹) and cisatracurium (0.15 mg kg⁻¹). After tracheal intubation, anaesthesia was maintained with an i.v. infusion (TCI) of propofol and remifentanyl. The doses of both agents were titrated at the discretion of the anaesthetist. Patients were extubated in the

operation room after completion of the surgical procedure and admitted to the post anaesthesia care unit (PACU).

At the end of surgery, patients received acetaminophen (15 mg kg^{-1}) and morphine (0.2 mg kg^{-1}) for postoperative pain control. In the PACU and on the ward postoperative pain was treated with acetaminophen (15 mg kg^{-1}) using a fixed scheme. Patients between 12 and 18 yr received patient-controlled i.v. analgesia (PCIA) with morphine at a concentration of 1 mg ml^{-1} , a background infusion of $0.03 \text{ mg kg}^{-1} \text{ h}^{-1}$ and a demand dose of 0.01 mg kg^{-1} with a lockout-interval of 20 min. For patients > 18 yr, the PCIA was adjusted to a demand dose of 1.5 mg morphine with a lockout-interval of seven min, a maximum dose of $30 \text{ mg } 4 \text{ h}^{-1}$ and a morphine-concentration of 2 mg ml^{-1} . An additional bolus of 1 mg of morphine (i.v.) was given by the study nurse on the PACU if the NRS exceeded 3. If pain treatment was still inadequate, a clonidine bolus ($1 \mu\text{g kg}^{-1}$) was given, eventually continued with an infusion of clonidine ($0.3 \mu\text{g kg}^{-1} \text{ h}^{-1}$).

PONV-prophylaxis was performed with dexamethasone (0.1 mg kg^{-1} (max. 5 mg) at the start of anaesthesia) and ondansetron (0.1 mg kg^{-1} (max. 4 mg) at the end of surgery).

PONV was treated with alizapride 50 mg i.v. if the NRS for nausea exceeded 3.

Neurophysiological monitoring including somatosensory and motor evoked potentials was used intraoperatively in the majority of patients.

Study outcomes

Primary endpoint were the morphine requirements during the first 24 h postoperatively.

Secondary outcomes included: i) severity of postoperative pain as evaluated with the numeric rating scale (NRS; 0 = no pain, 10 = worst imaginable pain) at rest and coughing, assessed each 15 min the first two h postoperatively at the PACU, every h during the following 22 h, and once daily on day 2 and 3; ii) the incidence of PONV assessed on the basis of a NRS for nausea (0 = lack of nausea, 10 = worst imaginable form of nausea) and documenting the presence/absence of vomiting during the first 72 postoperative h simultaneously with the pain assessment; iii) inflammatory response, as measured by the serum concentrations of interleukin 6 (IL-6) and interleukin 1 receptor antagonist (IL-1Ra), measured at three distinct time points: T1, before induction of anaesthesia (baseline); T2, at the end of the operation and T3, the next morning at the PACU); iv) time to recovery of bowel function (defined as the time to first defecation and the time to the first postoperative intake of solid food¹⁷); v) length of hospital stay; vi) quality of life as assessed with the Acute Short-form (SF-12) health survey before and one month after surgery (administered by phone).¹⁸

A subgroup analysis (planned at the time the recruitment age had been extended) was conducted for patients with an age between 12 and 18 yr undergoing scoliosis correction.

Safety

The study medication was administered to patients with default haemodynamic monitoring in the setting of a completely equipped operation theatre. This enabled immediate detection and management of potential adverse events. Administration of study drugs was to be immediately stopped in case that the study subject showed signs of systemic toxicity (metallic taste, tinnitus, headache, seizure activity and ECG irregularities). Also after leaving the operation room, all patients were closely monitored for the occurrence of eventual (severe) adverse events.¹⁹

Blood sample acquisition and laboratory analysis

In patients of both groups, arterial blood samples were obtained in a BD vacutainer® SST™ Advance (BD, Erembodegem, Belgium) before skin incision, at the end of surgery and the morning after surgery. Blood samples were immediately centrifuged at 3500 rpm for 15 min and were aliquoted in 1.8 ml Thermo Scientific™ Nunc™ cryotubes. All samples were stored at -80°C until the time of analysis. Cytokines were analysed using commercial enzyme-linked immunosorbent assay kits (Quantikine Elisa Kits) according to the manufacturer's instructions (R&D Systems Belgium 19 Barton Lane Abingdon Science Park Abingdon, Oxon OX14 3NB, United Kingdom).

Statistical analysis

Sample size calculation

The sample size estimation was based on data from our clinical routine. In 10 arbitrarily chosen patients undergoing posterior spinal arthrodesis before the start of the study, opioid consumption during the first 24 postoperative h was documented, with a mean value of 47 mg , a median level of 43 mg and a standard deviation (SD) of 12 mg . Hence, the coefficient of variation ($\text{CV} = \text{SD} / \text{mean}$) was 0.258 and based on a lognormal distribution, with a geometric mean of 45.7 mg . As the estimate of the coefficient of variation was based on sparse data, we assumed a more conservative estimate for the CV (i.e. a CV equal to 0.40). Based on a two-sided, two-sample pooled Student's t-test of a mean ratio with lognormal data and an alpha set at 5%, 30 subjects in each group were needed to achieve 80% power in order to detect the clinically meaningful reduction of 25% in (geometric) means. To counteract potential drop-outs, we included 70 patients in total (35 in each group).

Data analysis

The statistical analysis was primarily conducted on an intention-to-treat basis using SAS software (version 9.2 of SAS System for Windows) and GraphPad Prism version 6 (GraphPad Software, Inc., La Jolla, CA). Additionally, we performed a per-protocol analysis after exclusion of patients with partial loss-to-follow-up.

A Mann-Whitney U-test was used to compare the cumulative morphine usage (primary outcome) and other continuous or ordinal measurements between both groups. Fisher's exact test was used to compare proportions.

For the comparison of longitudinal measurements (daily number of PCIA-boli, NRS for pain), a multivariate linear model for repeated measures was used adopting a direct likelihood approach.²⁰ A constant 1 was added before transformation if zero values could occur. Least-squares means (and their 95% confidence interval) were given after back transformation to the original scale.

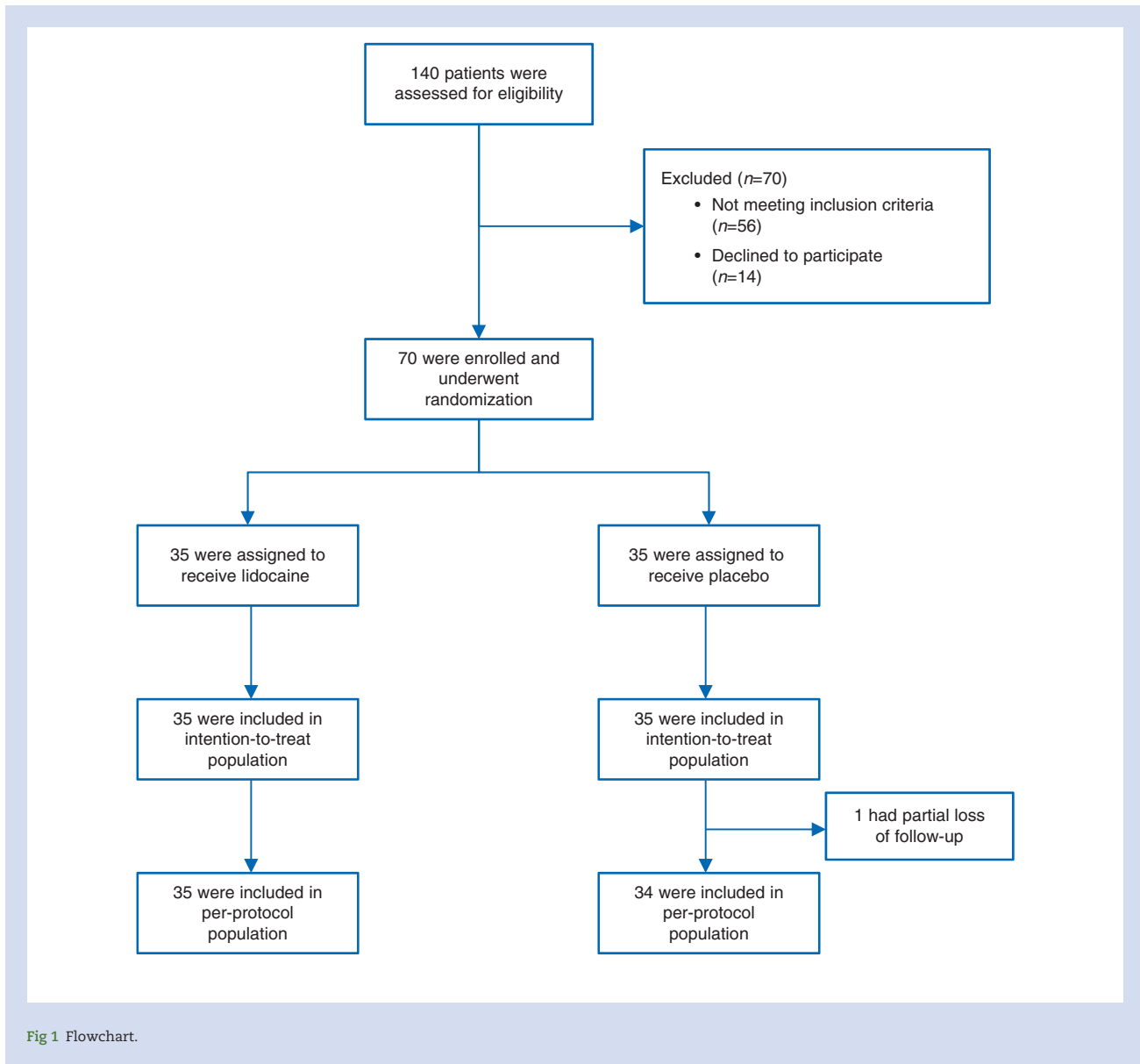
Kaplan-Meier estimates are given for hospital stay and time until first defecation. The latter were compared between the two groups using the log-rank (Mantel-Cox) test.

In two sensitivity analyses, postoperative morphine consumption was compared between both groups after correction for the difference in preoperative use of analgesics and for postoperative use of clonidine using an approach presented by Schacht and colleagues²¹

P-values smaller than 0.05 are considered significant.

Results

The study flow chart is shown in Figure 1.²² 140 patients planned for elective spine surgery were screened. 70 patients were



randomized to the interventional treatment with lidocaine ($n = 35$) or placebo ($n = 35$). All patients received the allocated treatment and were included in the intention-to-treat population.

The per-protocol-population (see supplemental data) included 69 patients, as one patient of the placebo group was admitted to the intensive care unit because of intraoperative massive haemorrhage with consecutive haemodynamic instability, rendering the assessment of the primary outcome impossible.

Preoperative assessment and intraoperative data

Patients in both groups did not differ with respect to patient characteristics, biometric and procedure-related data (Table 1).

Primary outcome

Morphine consumption during the first 24 postoperative h was not significantly different between the lidocaine-group and the

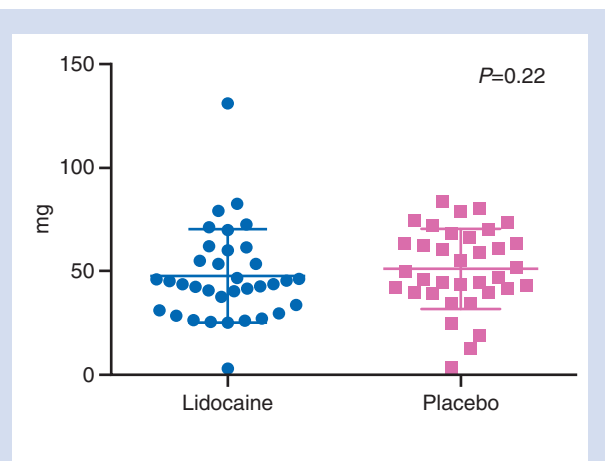
placebo-group [48 mg (23) mg (mean (sd)) vs 51 mg (19) mg], [43.9 (31.2; 60) (median (IQR)) vs 50 (39.6; 66.4)], $P = 0.22$ (Fig. 2). The Hodges-Lehman estimate for the difference in morphine consumption equals 5.8 mg (95% CI: -3.5 to 15.1). The lack of a difference held also true when morphine consumption was corrected for body weight: lidocaine-group 0.73 mg kg^{-1} (0.34) mg kg^{-1} (mean (sd)) vs control 0.84 mg kg^{-1} (0.36) mg, [0.78 mg kg^{-1} (0.51; 0.96) (median (IQR)) vs 0.83 (0.63; 1.0)], $P = 0.22$.

Sensitivity analyses

More subjects in the placebo- than in the lidocaine-group had chronic preoperative treatment with analgesics (25.7% vs 14.3%, $P = 0.23$). However, this did not explain the lack of a difference in postoperative morphine consumption. After correction for preoperative use of analgesics, the difference between both groups in postoperative morphine consumption remained of the same magnitude, being not significant ($P = 0.28$) (Supplementary file).

Table 1 Patient characteristics. Data are given as absolute numbers (n), percentage (%) of the whole population (N) and median [interquartile range], as appropriate

| | | Lidocaine (n = 35) | Placebo (n = 34) |
|---|-------------------|--------------------|------------------|
| Age | yr | 49 [15; 56] | 46 [16; 57] |
| Gender | n (%) | | |
| Male | | 14 (40) | 8 (24) |
| Female | | 21 (60) | 26 (76) |
| Weight | kg | 59 [50; 84] | 62 [52; 72] |
| Height | cm | 168 [160; 178] | 166 [161; 175] |
| BMI | kg/m ² | 23 [19; 27] | 22 [20; 26] |
| ASA | n (%) | | |
| I | | 11 (32) | 11 (33) |
| II | | 22 (65) | 22 (67) |
| III | | 1 (3) | 0 (0) |
| Adolescents 12–18 yr | n (%) | 15 (43) | 13 (38) |
| PONV history | n (%) | | |
| No | | 21 (62) | 23 (68) |
| Yes | | 13 (38) | 11 (32) |
| SF-12 | | | |
| Physical component summary | | 36 (28; 50) | 40 (31; 49) |
| Mental component summary | | 51 (46; 59) | 47 (39; 55) |
| Preoperative medication with gabapentinoids | n (%) | 2 (6) | 1 (3) |
| Preoperative medication with tramadol hydrochloride | n (%) | 5 (14) | 7 (20) |

**Fig 2** Cumulative morphine requirements (milligrams) in the first 24 postoperative h for the lidocaine and the placebo group. Data are shown as individual values and as mean (SD). There was no significant difference between the lidocaine group (closed circles, n = 35) and the placebo group (closed squares, n = 35) ($P = 0.22$).

Both groups did not differ with respect to the postoperative administration of i.v. clonidine (12.5% in the placebo-group vs 8.9% in the lidocaine-group, $P = 0.70$). Consequently, the difference between both groups in postoperative morphine consumption remained not significant after correction for the postoperative use of clonidine ($P = 0.38$).

Secondary outcomes

The mean morphine consumption on the second and third day did not differ between groups (Table 2). Groups did not differ

regarding mean NRS for pain at rest at any time-point between groups (Fig. 3). Both groups also did not differ with respect to the total number of PCA-boli demanded by the patients and PCA-boli delivered by the pump, in the first three postoperative days (Table 2). PONV incidence, time to return of intestinal function (defined as the time to the first defecation (Fig. 4) and time to the first postoperative intake of solid food (Table 2)) and length of hospital stay were not significantly different between the groups (Table 2, Fig. 4). Likewise, the SF-12 generic health survey did not differ between the groups, both in terms of physical and mental health concerns (Table 2).

Laboratory findings

The serum concentrations of IL-6 and IL-1Ra did not differ significantly between the groups at any time point (Table 2).

Intra- and postoperative safety data

Incidence of adverse events did not differ significantly between groups (Table 2).

No patient receiving lidocaine reported subjective symptoms of local anaesthetic systemic toxicity.

Subgroup analysis

A subgroup analysis comprising only patients between 12 and 18 yr undergoing scoliosis correction ($n = 28$) showed no significant difference for the primary outcome parameter, the mean opioid consumption during the first postoperative 24 h, between the lidocaine-group and the placebo-group [46 mg (12) mg (mean(SD)) vs 56 mg (14) mg], $P = 0.08$.

Per-protocol analysis

Also in the per-protocol analysis, lidocaine failed to affect the primary outcome.

Table 2 Intraoperative data and secondary outcomes. Data are given as absolute numbers (n), percentage (%) of the whole population (N) and median [interquartile range] as appropriate. Postoperative day 1(POD1)

| | | | Lidocaine (n = 35) | Placebo (n = 34) | P-value |
|----------------------------|----------------------------------|----------------|--------------------|-------------------|---------|
| Intraoperative data | Duration of surgery | min | 265 [201; 315] | 242 [180; 321] | 0.59 |
| | Cumulative propofol dose | mg | 2620 [2120; 3740] | 2625 [1900; 3345] | 0.47 |
| | Cumulative remifentanyl dose | µg | 6950 [4650; 8568] | 5850 [4500; 7400] | 0.37 |
| | Superior vertebral region | n (%) | | | 0.80 |
| | Thoracic | | 22 (63) | 23 (68) | |
| | Lumbosacral | | 13 (37) | 11 (32) | |
| | Number of operated levels | n | 8 [2; 12] | 7 [1; 12] | 0.41 |
| | Use of instrumentation | n (%) | 35 (100) | 33 (97) | 0.49 |
| | Blood loss | ml | 800 [500; 1600] | 800 [425; 1275] | 0.36 |
| | Postoperative clonidine | n (%) | 4 (11) | 5 (15) | 0.73 |
| Secondary outcomes | Morphine consumption | mg | | | |
| | Day 2 | | 45 [28; 58] | 37 [17; 50] | 0.09 |
| | Day 3 | | 32 [12; 55] | 37 [5; 48] | 0.31 |
| | Total number of morphine boli | n | | | |
| | Demanded | | 117 [61; 209] | 116 [67; 159] | 0.59 |
| | Delivered | | 71 [46; 131] | 72 [40; 101] | 0.51 |
| | PONV | n (%) | | | |
| | Nausea | | 23 (66) | 21 (62) | 0.80 |
| | Vomiting | | 6 (17) | 4 (12) | 0.52 |
| | SF-12 | | | | |
| | Physical component summary - 1mo | | 41[33; 47] | 40[31; 49] | 0.77 |
| | Mental component summary - 1mo | | 53[44; 59] | 52[40; 58] | 0.50 |
| | First solid food | days | 2 [1; 3] | 2 [1; 2] | 0.79 |
| | Length of hospital stay | days | 8 [8; 9] | 8 [7;10] | 0.52 |
| | Adverse events | n (%) | 1 (3) | 5 (16) | 0.10 |
| | Pancreatitis | | 0 | 1 | |
| | Pneumonia | | 0 | 1 | |
| | Dura leak | | 0 | 2 | |
| | Delirium | | 1 | 0 | |
| | Cytokines | pg/ml | | | |
| | IL-6 | | | | |
| | Baseline | | 0.9 [0.5–1.9] | 1.7 [0.4–2.8] | 0.42 |
| | End of surgery | | 16 [10–31] | 15 [6.4–26] | 0.34 |
| POD1 | | 51 [33–77] | 38 [26–65] | 0.25 | |
| IL-1Ra | | | | | |
| Baseline | | 46 [30–68] | 49 [39–90] | 0.26 | |
| End of surgery | | 72 [48–135] | 87 [52–189] | 0.51 | |
| POD1 | | 92 [55–198] | 86 [68–158] | 0.93 | |

Discussion

In our trial, we could not demonstrate any beneficial effect of i.v. lidocaine on postoperative opioid consumption in patients undergoing elective major spine surgery. Moreover, lidocaine failed to accelerate postoperative recovery, to shorten length of stay and to improve quality of life.

Our observations are in contrast with the findings of two studies published only after the start of our trial and also investigating the efficacy of systemic lidocaine in spine surgery.^{5, 10} Both trials reported a significant effect of i.v. lidocaine on the visual analogue scores for pain^{5, 10} and a reduction in opioid consumption, but this reduction was only significant in one trial.¹⁰

Moreover, the results of our study contradict several meta-analyses that demonstrated significant analgesic effects for the perioperative administration of systemic lidocaine, an improved gastro-intestinal recovery and a significant reduction in hospital length of stay.^{23–25} Of note, these meta-analyses included primarily patients undergoing major abdominal surgery. For other surgical procedures, data on the analgesic efficacy of lidocaine are much less convincing. Several studies in non-abdominal surgery (including breast surgery,¹³ total hip arthroplasty,⁹ coronary artery bypass surgery²⁶) and in abdominal surgery not involving the intestines (including renal surgery,²⁷ laparoscopic tubal ligation,¹⁵ and laparoscopic prostatectomy²⁸) failed to demonstrate a significant analgesic effect of lidocaine.²⁹ Even

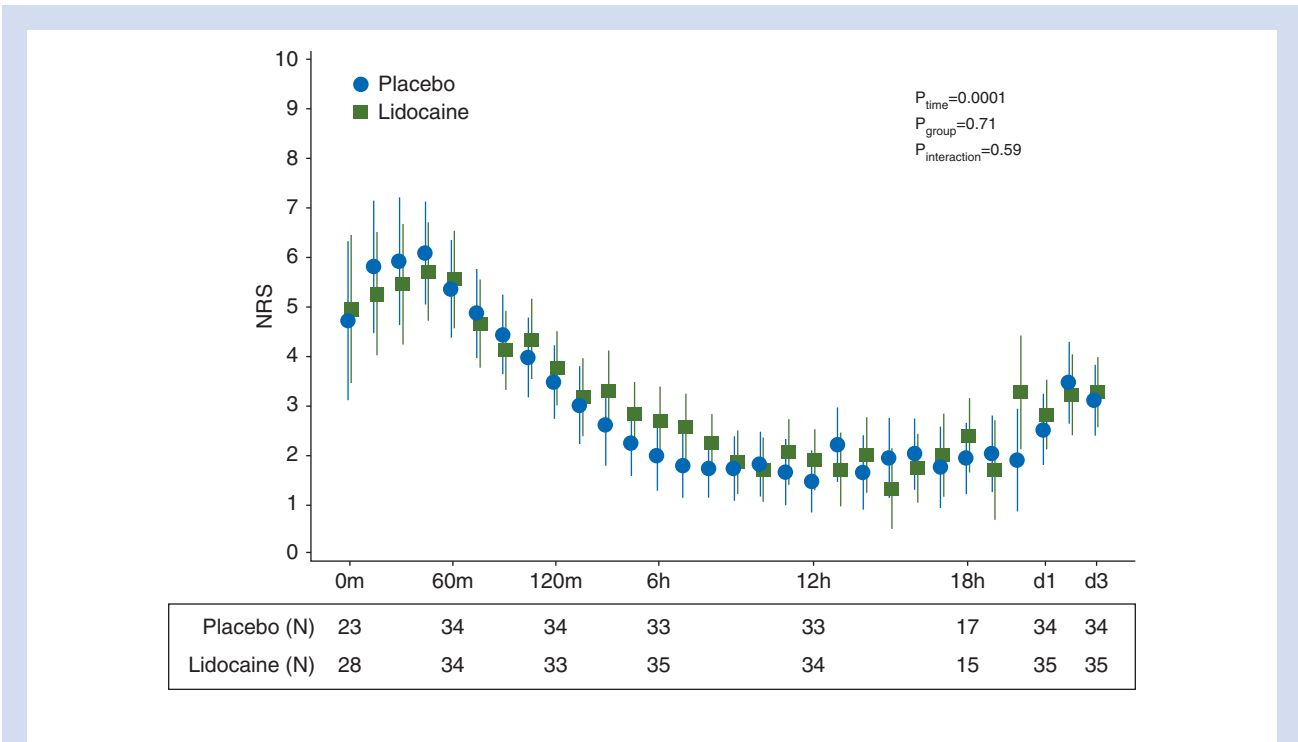


Fig 3 Pain scores (as assessed with the numeric rating scale (NRS) for pain) in both groups during the first three postoperative days. No significant difference was found for the mean NRS between the two groups (main effect time: $P < 0.0001$; main effect group: $P = 0.71$; interaction effect: $P = 0.59$). m = min, h = h after arrival at the postanesthesia care unit, d = day.

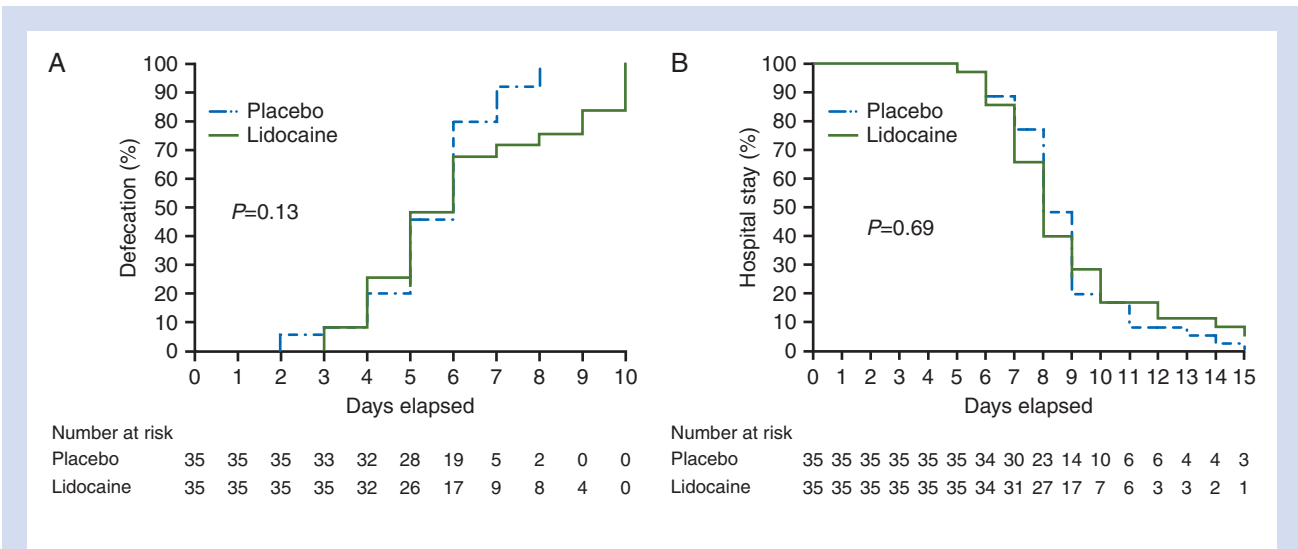


Fig 4 Kaplan-Meier survival plot showing the time until first defecation (A) and hospital stay (B). No significant difference was found for the time until first defecation and hospital stay between the lidocaine - and placebo group.

for colorectal surgery, several researchers were unable to observe a beneficial analgesic effect of lidocaine.^{30 31}

It is tempting to speculate why we - in contrast to the two above mentioned trials in spine surgery^{5 10} and the meta-analyses in abdominal surgery²³⁻²⁵ - found lidocaine to have no significant analgesic effects.

First, the patients included in the two spine trials differed considerably from our study subjects. All our patients underwent complex and extensive surgery, with instrumentation of in average more than twice the number of levels than in the other studies. Moreover, we included a subgroup consisting of adolescents known to show increased pain sensitivity.³²

Second, our type of anaesthesia differed from that of the other spine trials in which no opioids were used intraoperatively. In the present study, a remifentanyl-infusion was started at induction of anaesthesia and continued until the end of surgery. In addition, our patients received 0.2 mg kg^{-1} of morphine at the end of surgery. If present at all in orthopaedic surgery, analgesic effects of lidocaine may have been masked by the intraoperative use of opioids. Likewise, no analgesic effects were found for systemic lidocaine in total hip arthroplasty when sufentanil was given intraoperatively.⁹

Third, the dose with which systemic lidocaine was infused in our trial ($1.5 \text{ mg kg}^{-1} \text{ h}^{-1}$) was lower than in two other trials investigating the efficacy of lidocaine in spinal surgery ($2 \text{ mg kg}^{-1} \text{ h}^{-1}$).^{5 10} However, in one trial, no bolus of lidocaine was used and the lidocaine infusion was stopped after eight h.⁵ In the other trial, the lidocaine infusion was stopped at end of surgery with a maximum duration of 140 min.¹⁰ In our trial, a bolus was administered after induction of anaesthesia and the infusion of lidocaine was continued until six h after arrival on the PACU. This likely resulted in a higher cumulative lidocaine dose when compared with the other two trials. The failure of lidocaine to reduce morphine requirements should therefore not be attributed to possible underdosing.

Fourth, the analgesic effects of lidocaine that have been reported in abdominal surgery are likely related to the improvement of bowel function, with a reduction of visceral pain caused by bowel distention.³³ In abdominal surgery, postoperative ileus is mainly caused by direct injury to the intestines and inflammation, both caused by bowel manipulation. Lidocaine seems to counteract both of these mechanisms, by attenuation of the inflammatory response³⁰ and by inhibition of the evoked and spontaneous activity of spinal neurons which are excited by colorectal distention.³³ In contrast, spine surgery triggers postoperative ileus by operative manipulation/distraction of the various plexuses of splanchnic nerves that are located on the anterior lumbar column.³⁴ Protective effects of lidocaine against this direct neurological injury are not described for lidocaine. Consequently, we did not observe a reduction in the time to return of intestinal function in our trial.

Fifth, cytokines are of crucial importance in several mechanisms underlying pain and hyperalgesia.²⁸ While pro-inflammatory cytokines have been demonstrated to modulate pain sensitivity, pain can also influence the synthesis and release of cytokines.^{12 35} Lidocaine was shown to have anti-inflammatory characteristics by attenuating plasma concentrations of the proinflammatory cytokines IL-6, IL-8 and IL-1 Ra.^{4 8 12 36 37} Extensive spine surgery is not only associated with significant postoperative pain, but provokes also a significant systemic inflammatory reaction.⁵ The inflammatory reaction affects outcome after surgery significantly, as an exorbitant stimulation of the inflammatory cascade can lead to a systemic inflammatory response syndrome, organ dysfunction and pain.¹² In our patients, lidocaine however failed to exert anti-inflammatory and consequently also analgesic effects.

Sixth, it has been demonstrated that the analgesic effects of lidocaine depend on the total dose of infused lidocaine. In small doses ($2 \mu\text{g ml}^{-1}$), lidocaine suppresses ectopic impulse generation in chronically injured peripheral nerves, while in moderate doses ($5 \mu\text{g ml}^{-1}$), lidocaine inhibits central sensitization and neuronal hyperexcitability. Large doses ($10 \mu\text{g ml}^{-1}$) have general analgesic effects but also cause systemic toxicity.³⁸ In our trial, the lidocaine infusion was started at induction and continued until six h after arrival at the PACU. The fact that we failed to observe an analgesic effect can therefore most probably not

be attributed to an insufficient duration of lidocaine treatment, as was suggested in the total hip arthroplasty trial.⁹ Of note, a recent meta-analysis found that continuing the administration of lidocaine beyond 60 min after surgery shows no additional analgesic benefit.³⁹

We did not find significant differences in PONV incidence. This result is in accordance with the results of the previous spine trials, in which no difference in PONV incidence could be observed between the groups.

In contrast to several studies in abdominal surgery^{30 31 40 41} and to one study in lumbar microdiscectomy,¹⁰ hospital length of stay was not reduced by the treatment with lidocaine, most probably because lidocaine failed to produce positive effects on postoperative pain and bowel function, both of which are determining factors for hospital discharge.

We would like to note that our study is subject to multiple limitations. First, it can be discussed if the NRS for pain is an adequate tool for measuring the effect of lidocaine on pain control. The NRS is significantly influenced by the amount of opioids that have been given. However, in our trial, postoperative pain medication was standardized and no difference was found in opioid requirements between both groups. Second, we did not analyse the lidocaine concentrations in our patients. However, both the dose and the duration of lidocaine treatment used in our study have been described to be effective in other clinical trials.^{9 11 42} Third, we included both adults and adolescents (between 12 and 18 yr) in our study, causing a considerable heterogeneity that may have influenced our results. Nevertheless, both treatment groups did not differ statistically regarding the age of the included patients. Fourth, our sample size estimation was based on the morphine consumption that had been observed in 10 preliminary adolescents, undergoing spine surgery in our institution before the start of our study. During the study, we opened the recruitment to adult patients, hereby also including degenerative pathology. Theoretically, this could have affected severity of pain and hence may have resulted in greater variations of opioid requirements. However, the sample size calculation was based on an assumed CV of 0.4, which is only slightly lower than the observed CV (equalling 0.43 based on a pooled SD). Of note, this small underestimation was largely compensated for by the fact that we included 69 patients in total (i.e. nine more patients than required by the initial sample size estimation). Hence, the negative result in the current study was likely not caused by a lack of power.

Fifth, the study was powered solely for the primary endpoint. It cannot be excluded that significant effects on secondary outcomes may be unveiled after inclusion of a larger patient number. Sixth, the use of remifentanyl for intraoperative analgesia can be criticized. Remifentanyl has been demonstrated to have N-methyl-D-aspartate agonistic properties,⁴³ eventually causing anti-analgesic effects in the postoperative period. The use of remifentanyl was however mandatory in this study to allow neurophysiological monitoring (somatosensory and motor evoked potentials) in the majority of patients. Last, we did not investigate whether lidocaine had beneficial effects on chronic post-surgical pain in our patient population.

In conclusion, in spinal surgery, systemic lidocaine has no analgesic efficacy when added to opioid based balanced anaesthesia. Our findings add further evidence that multimodal analgesia with lidocaine is of limited or no value in orthopaedic surgery. Further research should focus on the characterization of patient groups that unambiguously benefit from perioperatively administered lidocaine, and on the clear identification of the putative mechanism of analgesic action.

Authors' contributions

Study design/planning: G.D., P.M., M.V., S.R.
 Study conduct: G.D., S.R.
 Data analysis: S.F., G.D., S.R.
 Writing paper: G.D., S.R.
 Revising paper: all authors

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

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Declaration of interest

None declared.

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