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Intravenous lidocaine has no impact on rocuronium-induced neuromuscular block. Randomised study

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Background: Intravenous lidocaine is increasingly used in surgical patients. As it has neuromuscular blocking effects, we tested the impact of an intravenous lidocaine infusion on the time course of a rocuronium-induced neuromuscular block.

Methods: Fifty-two adults undergoing surgery were randomly allocated to intravenous lidocaine 1.5 mg/kg followed by a continuous infusion of 2 mg/kg/h or physiological saline (control) throughout surgery. Anaesthesia was induced and maintained with a target-controlled propofol infusion and sufentanil. After loss of consciousness, rocuronium 0.6 mg/kg was given. Neuromuscular transmission was measured using train-offour (TOF)-watch SX (Organon, Swords Co., Dublin, Ireland) acceleromyography.

Results: Onset time (to 95% depression of first twitch) was on average 113.9 s (standard deviation 35.3) with lidocaine and 119.5 s (44.9) with saline (P = 0.618). Total recovery time (TOF ratio 0.9) was on average 58.1 min (15.1) with lidocaine and

54.3 min (16.9) with saline (P = 0.394). Clinical duration (until first twitch has recovered to 25%) was on average 33.3 min (7.2) with lidocaine and 30.6 min (8.1) with saline (P = 0.21). Recovery index (time between 25% and 75% recovery of the first twitch) was on average 11.5 min (5.0) with lidocaine and 10.6 min (4.1) with saline (P = 0.458). Recovery time (between 25% recovery of the first twitch and TOF ratio 0.9) was on average 24.8 min (9.3) with lidocaine and 23.2 min (9.2) with saline (P = 0.541).

Conclusion: A continuous intravenous infusion of lidocaine has no impact on the time course of the neuromuscular blockade induced by a standard intubation dose of rocuronium.

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LIDOCAINE is a local anaesthetic that is acting through a fast sodium-channel blocking mechanism. It has anti-arrhythmic,¹ analgesic,²⁻⁴ antihyperalgesic,⁵⁻⁷ and anti-inflammatory properties,⁸ and it reduces intraoperative requirements for various volatile anaesthetics.^{9,10} Systematic review of randomised trials suggested that an intraoperative lidocaine infusion may have a beneficial effect on bowel function, analgesia, and length of hospital stay after major abdominal surgery.¹¹

It has been known for a long time that local anaesthetics interact with non-depolarising neuromuscular blocking agents at the neuromuscular junction.¹² The usage of an intravenous lidocaine infusion as an

Presentation: Parts of this article have been presented in abstract form at the annual scientific meeting of the European Society of Anaesthesiology, Amsterdam, the Netherlands, 12 June 2011. Trial registration. clinicaltrials.gov identifier: NCT00828373. adjuvant to general anaesthesia begs the question as to whether lidocaine may have a clinically relevant impact on the time course of the neuromuscular block induced by a concomitantly administered non-depolarising neuromuscular blocking agent.

Three published clinical trials have studied interactions between intravenous lidocaine and nondepolarising neuromuscular blocking agents.^{13–15} In one study, pre-treatment with an intravenous bolus of lidocaine 1.5 mg/kg was shown to accelerate the onset time of vecuronium-induced neuromuscular block, but recovery times were not reported.¹³ In another study, an intravenous bolus of lidocaine 1.5 mg/kg had no impact on the onset time of rocuronium-induced neuromuscular block, but partially prolonged recovery times.¹⁴ Finally, in the third study, an intravenous bolus of lidocaine 1.5 mg/kg followed by a continuous infusion of 2 mg/kg/h did not prolong recovery times of





cisatracurium-induced neuromuscular block; unfortunately, onset times were not reported.¹⁵

Today, we still do not know whether an intravenous bolus, followed by a continuous infusion, of lidocaine has an impact on both onset and recovery times of rocuronium-induced neuromuscular block. We set out to address that question in a randomised placebo-controlled electrophysiological study.

Methods

This study was approved by the Institutional Ethics Committee (protocol N° NAC 08-063) and the Swiss agency for therapeutic products (Swissmedic). Written informed consent was obtained from all patients. Reporting follows the Consolidated Standards of Reporting Trials (CONSORT) 2010 recommendations.

Trial design

The study was designed as a randomised (1:1), stratified according to gender, placebo-controlled trial. Our study protocol was inspired by the protocol of a previously published rocuronium–magnesium interaction study¹⁶ and adhered to published guide-lines on pharmacodynamic studies of neuromuscular blocking agents.¹⁷

The protocol was registered before starting patient enrolment at http://clinicaltrials.gov (identifier, NCT00828373). There has been no important change made to the protocol after study commencement.

Participants

We recruited American Society of Anesthesiologists physical status I or II patients, aged 18 to 60 years, scheduled for elective surgery lasting at least 120 min at the University Hospital of Geneva.

Non-inclusion criteria included pregnant or breastfeeding women, patients with a history of an allergy to rocuronium or lidocaine, neuromuscular or epileptic disease, or atrioventricular heart block II or III. Patients with laboratory-confirmed abnormalities of electrolytes, total bilirubin (> $1.5 \times 25 \,\mu$ mol/l, i.e. $1.5 \times$ the upper limit normal according to the institutional laboratory), alanine aminotransferase $(> 2.5 \times 42 \text{ U/l})$, aspartate aminotransferase $(> 2.5 \times 42 \text{ U/l})$ 42 U/l), creatinine (> $1.5 \times 88 \mu mol/l$), or creatinine clearance (< 60 ml/min/1.73 m², estimated by the formula by Cockroft and Gault) were not considered. We also excluded patients receiving medications known to influence neuromuscular function (for instance, aminoglycosides or phenytoine), with a body mass index < 19 or > 28 kg/m², with expected difficult mask ventilation,¹⁸ or with expected difficult intubation (Mallampati classes III and IV, thyreomental distance < 6.5 cm, mouth opening < 3.5 cm).

Interventions

All patients were fasted for at least 6 h before anaesthesia and were pre-medicated with oral midazolam 7.5 mg. Standard monitoring included a three-lead electrocardiogram, non-invasive blood pressure, end-tidal partial pressure of carbon dioxide, and peripheral pulse oximetry.

Patients were randomly allocated to one of two groups (lidocaine or placebo). In the lidocaine group, patients received lidocaine 1.5 mg/kg intravenously as a bolus immediately before induction of anaesthesia, followed by an intravenous infusion of 2 mg/kg/h. This regimen was similar to the regimens that were used in clinical trials that studied the impact of intravenous lidocaine infusions on outcome after abdominal surgery.¹¹ Controls received the same regimen of 0.9% physiological saline. Study drugs were given using a perfusion pump (Base Primea, Fresenius-Vial, Brezins, France) throughout surgery until the end of the recording of the neuromuscular function (see neuromuscular monitoring).

Anaesthesia was induced with sufentanil 0.2 μ g/kg and propofol using a target-controlled infusion system (Base Primea) using the pharmacokinetic model of Schnider et al.¹⁹ The targeted effect-site concentration of propofol for induction was 4 ± 1 μ g/ml. As soon as the patient lost consciousness, the lungs were normo-ventilated through a face mask (end-tidal partial pressure of carbon dioxide, 4.6 to 6.0 kPa) with a 50% oxygen–air mixture. Maintenance of anaesthesia was with propofol effect-site concentrations of 4 ± 2 μ g/ml and intermittent doses of sufentanil 0.2 μ g/kg as required.

Neuromuscular monitoring was calibrated on the anaesthetised patient. Once a stable baseline measurement was obtained, a bolus dose of rocuronium 0.6 mg/kg was administered intravenously over 5 s, and neuromuscular measurements were started. Intubation was performed as soon as a 95% depression of the first twitch (T1) of the train-of-four (TOF) was reached. Plastic endotracheal tubes (Mallinck-rodt, Covidien, Tullamore, Ireland) with an internal diameter of 8.0 cm (male patients) and 7.0 cm (female patients) were used throughout. Laryngo-scopies were performed using disposable Macintosh size 3 blades (Comepa, Bagnolet, France). Intubation was performed by the same investigator (C. C.) who was unaware of treatment allocation.

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Neuromuscular monitoring

Neuromuscular monitoring and measurements were done as recommended by an international consensus conference.¹⁷ Neuromuscular function was assessed using acceleromyography of the adductor pollicis (TOF Watch SX®, Organon, Swords Co., Dublin, Ireland). Surface electrodes (Red Dot® 3M Health Care; Neuss, Germany) were placed on cleaned skin over the ulnar nerve on the volar side of the wrist. The position of the transducer was secured by placing the thumb in a hand adapter (Hand Adapter[®]; Organon, Swords Co., Dublin, Ireland). The arm was fixed with a special board (arm-board TOF-Guard[®]; Organon, Swords Co., Dublin, Ireland) and kept in the same position during the entire study procedure. A temperature sensor was fixed at the distal end of the forearm. The temperature of the arm was maintained at > 32°C and rectal temperature at > 36°C using warming blankets covering body and arm (Bair Hugger®; Arizant Healthcare, Eden Prairie, MN, USA). After induction of anaesthesia and loss of consciousness, the acceleromyograph was calibrated using the implemented TOF-Watch SX[®] calibration mode 2. TOF stimulation was used (supramaximal square wave impulse of 200 µs duration, four stimuli at 2 Hz, 15 s interval). All data were stored on a laptop computer using a specific software (TOF-Watch SX[®], version 2.2.).

Intubation conditions

Because there was evidence from previous studies that intubation conditions may be improved in patients receiving intravenous lidocaine,^{20–22} we evaluated intubation conditions using a published score that takes into account the ease of laryngoscopy (easy, fair, difficult), vocal cords position (abducted, intermediate/moving, closed), and presence of diaphragmatic movement or coughing while inserting the tube (none, slight, vigorous/sustained).¹⁷ The final score summarised intubation conditions as excellent (all qualities are excellent), good (all qualities are either excellent or good), or poor (presence of a single quality listed under 'poor').

Outcomes

Our primary outcome was total recovery time, i.e. total duration of the neuromuscular block defined as the time from start of injection of rocuronium until TOF ratio 0.9 (DurTOF0.9).

Secondary end points included onset time, measured as the time in seconds from start of injection of rocuronium until 95% depression of the T1 of the TOF and partial recovery times. Partial recovery times were the time from start of injection of rocuronium until T1 of the TOF has recovered to 25% of the final T1 value (Dur25%, clinical duration), the time between 25% and 75% recovery of the final T1 value (recovery index), and the time between 25% recovery of the final T1 value and a TOF ratio of 0.9 (recovery time). For all measurements, the first of three consecutive responses with the same or increasing value of T1 was recorded.¹⁷ An additional outcome was the scoring of intubation conditions recorded as a categorical variable (excellent, good, or poor).

Sample size

We hypothesised that in the context of our study (i.e. intravenous bolus followed by a continuous infusion of lidocaine), the total duration of the neuromuscular block after a single intubation dose of rocuronium would be prolonged. We defined a prolongation of 20% (about 12 min) as being clinically relevant. According to a previously published study, we expected an average total recovery time of the neuromuscular block with a single intubation dose of rocuronium, without lidocaine, of 58 min [standard deviation (SD), 14 min].¹⁶ Nineteen patients would have been needed in both active and control groups to test this hypothesis (alpha = 0.05 and beta = 0.1). We eventually randomised two times 26 patients in each group to allow for dropouts.

Randomisation

The random allocation sequence was produced by the pharmacy of Geneva University Hospitals using random sampling of coloured balls (red = lidocaine, green = placebo). Due to a known influence of gender on the time course of neuromuscular block induced by rocuronium (females are more sensitive than males),²³ randomisation was stratified according to gender.

The pharmacy produced the study drugs as indistinguishable, numbered vials, which were administrated sequentially. Throughout the study, the random sequence was kept concealed by the pharmacy. Patients were screened for inclusion by a study nurse. The main investigator C.C. enrolled the patients and administrated the study drugs.

Blinding

Patients, care providers, and investigators were all blinded to the study drugs because these were produced as indistinguishable numbered vials by the pharmacy.

Statistical methods

Continuous data were summarised as means (\pm SD) and median and interquartile ranges which were graphically displayed as box and whiskers. Variables with a Gaussian distribution were analysed using unpaired (onset and recovery times) Student's *t*-tests. Dichotomous data were analysed using Fisher's exact test. Significance was defined as *P* < 0.05. Analyses were performed using STATA (Version 10, STATA Corp, College Station, TX, USA).

Results

Participant flow

Fifty-two patients were randomised (26 patients per group; 13 men and 13 women in each group); all received the assigned study treatment. Onset time and intubation conditions could be recorded in all patients. Due to a technical failure, recovery times could only partially be recorded in two control patients.

Recruitment

Patients were enrolled from August 2009 to August 2010.

Baseline data

Patient characteristics were comparable between groups (Table 1).

Primary outcome – total recovery time

There was no significant difference in total recovery time (DurTOF0.9) between the two groups (Fig. 1, Table 2).

Secondary outcomes

Onset time and partial recovery times. There was no significant difference in the onset time (to 95%

Table	1
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Patient characteristics.				
	Placebo	Lidocaine		
	n = 26	<i>n</i> = 26		
Gender (m/f) Age (years) Weight (kg) Height (cm) BMI (kg/m ²)	13/13 34.8 (11.1) 65.1 (9.8) 171.0 (10.0) 22.3 (2.9)	13/13 32.8 (11.5) 64.5 (12.0) 170.5 (10.4) 22.1 (3.1)		

Values are numbers and means with (standard deviation). BMI, body mass index.

depression of T1) between the two groups (Fig. 2, Table 2). There were no significant differences either in any of the partial recovery times (Fig. 2, Table 2).

Intubation conditions. In lidocaine-treated patients, intubation conditions were scored significantly better compared with controls (Table 3). In the lidocaine group, 22 of 26 (85%) patients had excellent, and four (15%) had good intubation conditions; in the placebo group, 14 of 26 (54%) had excellent, and 12 (46%) had good intubation conditions (P = 0.034). The number-needed-to-treat for one patient to have excellent intubation conditions with intravenous lidocaine compared with placebo was 3.3 (95% confidence interval, 1.8 to 14). In no patient, intubation conditions were rated as poor.

In the lidocaine group, abduction of the vocal cords at laryngoscopy was complete in all patients; with placebo, this was the case in 85% only (P = 0.110). Also, with lidocaine, diaphragmatic movement or coughing during insertion of the tube or inflation of the cuff was completely absent in more patients (88%) compared with placebo (77%) (P = 0.465) (Table 3).

Adverse events

There were no adverse events reported.



Fig. 1. Recovery times. Total recovery time [DurTOF0.9, time from rocuronium injection to train-of-four (TOF) ratio 0.9]; clinical duration [Dur25%, time from rocuronium injection until 25% recovering of first twitch (T1)]; recovery index (Dur25–75%, time from 25% to 75% recovery of T1); recovery time (Dur25%TOF0.9, time from 25% recovery of T1 to TOF ratio 0.9). Grey: placebo, white: lidocaine. The box-and-whisker plots show 10th and 90th percentiles, lower and upper quartiles, median (horizontal bar), and mean (circle).

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Table 2

Onset and recovery times

	Placebo	Lidocaine	Mean difference (95% CI)	Р	
Onset					
Onset time (s)	n = 26 119.5 (44.9)	n = 26 113.9 (35.3)	-5.6 (-28.1 to 16.9)	0.618	
Recovery					
DurTOF0.9 (min)	n = 25 54.3 (16.9)	n = 26 58.2 (15.1)	3.9 (-5.11 to 12.9)	0.394	
Dur25% (min)	n = 25 30.6 (8.01)	n = 26 33.3 (7.2)	2.7 (-1.58 to 6.98)	0.210	
Dur25–75% (min)	n = 24 10.6 (4.12)	n = 26 11.6 (5.01)	1.0 (-1.62 to 3.62)	0.458	
Dur25%TOF0.9 (min)	n = 25 23.2 (9.2)	n = 26 24.8 (9.3)	1.6 (-3.61 to 6.81)	0.541	

Values are numbers and means with (standard deviation).

Onset time, time from rocuronium injection until 95% depression of first twitch (T1) of the train-of-four (TOF); DurTOF0.9, time from rocuronium injection until TOF ratio of 0.9; Dur25%, time from rocuronium injection until T1 has recovered to 25% of the final T1 value; Dur25–75%, time between 25% and 75% recovery of final T1 value; Dur25%TOF0.9, time between 25% recovery of the final T1 value and TOF ratio of 0.9; CI, confidence interval.



Fig. 2. Onset time (time from start of rocuronium injection until 95% depression of the first twitch of the train-of-four in seconds). Grey: placebo, white: lidocaine. The box-and-whisker plots show 10th and 90th percentiles, lower and upper quartiles, median (horizontal bar), and mean (circle).

Discussion

Interactions between lidocaine and nondepolarising neuromuscular blocking agents, both of the amino–steroidal and benzylisoquinoline types, have been tested before. However, none of

Intubation conditions.					
	Placebo	Lidocaine	Р		
	(<i>n</i> = 26)	(<i>n</i> = 26)			
	n (%)	n (%)			
Laryngoscopy					
Excellent	23 (88.5)	25 (96.2)	0.610		
Good	3 (11.5)	1 (3.8)			
Poor	0 (0.0)	0 (0.0)			
Vocal cords position					
Excellent (abducted)	22 (84.6)	26 (100)	0.110		
Good (intermediate/moving)	4 (15.4)	0 (0.0)			
Poor (closed)	0 (0.0)	0 (0.0)			
Reaction*					
Excellent (none)	20 (76.9)	23 (88.5)	0.465		
Good (slight)	6 (23.1)	3 (11.5)			
Poor (vigorous/sustained)	0 (0.0)	0 (0.0)			
Intubation conditions					
Excellent	14 (53.9)	22 (84.6)	0.034		
Good	12 (46.1)	4 (15.4)			
Poor	0 (0.0)	0 (0.0)			

Intubation score according to Fuchs-Buder¹⁷ et al.

Excellent, all qualities are excellent; Good, all qualities are either excellent or good; Poor, the presence of a single quality listed under 'poor'.

*Diaphragmatic movement/coughing while insertion of the tracheal tube and cuff inflation. *P*-values are computed two-sided using Fisher's exact test.

these trials was similar to ours. Either they tested a single intravenous lidocaine bolus only,^{13,14} or they tested non-depolarising neuromuscular blocking agents other than rocuronium.^{13,15} Also, some reported on onset time only,¹³ others on recovery time only.¹⁵ Our study is the first in investigating the impact of an intravenous bolus of lidocaine,

followed by a continuous infusion, on the complete time course of the neuromuscular block after a single, standard intubation dose of rocuronium. Both onset and recovery times were similar in patients who received lidocaine or placebo.

Only one study has reported on a significant interaction between lidocaine and rocuronium.¹⁴ Cardoso et al. administered a single intravenous bolus of lidocaine 1.5 mg/kg before rocuronium 0.6 mg/kg and reported on an unchanged onset time but a significantly prolonged clinical duration (Dur25%).¹⁴ In controls, clinical duration was on average 32 min, and with lidocaine, it was 37 min. It may be argued that this small difference (16%) was of no clinical relevance. Recovery index and total duration were not prolonged.¹⁴

Two other trials studied interactions between lidocaine and vecuronium¹³ or cisatracurium.¹⁵ Nonaka et al. studied the effect of an intravenous bolus of lidocaine on onset time with vecuronium.¹³ They reported on a significantly reduced onset time by almost 33% with lidocaine (on average, 115 s) compared with control (on average, 174 s). The authors did not report on recovery times. It remains unclear why pre-treatment with a lidocaine bolus shortened onset time of vecuronium but not of rocuronium. It may be speculated that onset times with vecuronium are relatively slower compared with rocuronium (in our study, 120 s) and that, therefore, lidocaine has more scope to shorten onset time of vecuronium. Finally, in the study by Hans et al., recovery times of a cisatracurium-induced neuromuscular block were not prolonged when patients received an intravenous bolus and a subsequent continuous infusion of lidocaine.¹⁵ In summary, data from four relevant studies, including ours, suggest that pre-treatment with lidocaine may shorten onset time of the neuromuscular block induced by a longer-acting agent such as vecuronium and does not prolong total recovery time of rocuronium- or cisatracurium-induced neuromuscular block; data on onset time with cisatracurium and on recovery times with vecuronium are lacking.

Several trials reported on the effect of epidurally administered local anaesthetics on the neuromuscular blocks induced by neuromuscular blocking agents.^{24–27} In one study in adults, epidurally administered bupivacaine was reported not to interact with onset time of atracurium but to prolong recovery time.²⁴ In children, epidurally administered bupivacaine did not prolong recovery time of vecuronium.²⁵ However, in the same study, doses

of vecuronium that were necessary to produce a 10%, 50%, or 95% block were about 20% lower in the bupivacaine group compared with the control group (P = 0.04). Also, there was a significant correlation between bupivacaine plasma concentrations and the potency of vecuronium.²⁵ Munakata et al. investigated the effect of epidural lidocaine on vecuronium-induced neuromuscular block in adults. There was no significant difference in onset time, but mean clinical duration was significantly prolonged, and the maintenance dose of vecuronium was significantly smaller in patients receiving epidural lidocaine.²⁶ Finally, Suzuki et al. investigated the effect of epidurally administered mepivacaine on onset and recovery times of a single intubation dose of vecuronium.27 There was no difference in onset times, but spontaneous and neostigmine-facilitated recovery to a TOF ratio of 0.9 was significantly longer in the epidural mepivacaine group. In all these four epidural studies, none of the differences that reached statistical significance were reported to be of any clinical relevance by the original authors.

Intubation conditions were improved in patients receiving lidocaine. Strictly speaking, we did not study intubation conditions during a classic induction procedure. Our patients were anaesthetised and were manually ventilated using a face mask until calibration was finished and a stable signal was obtained. Only then, rocuronium was injected and intubation conditions were scored as soon as 95% depression of the T1 of the TOF was reached. It is likely that our patients were more deeply anaesthetised at the time of intubation compared with a classic induction procedure, and this may explain why none of our patients (even controls) presented poor intubation conditions. The beneficial effect of intravenous lidocaine on intubation conditions was not unexpected as it has been described before both in adults receiving a neuromuscular blocking agent to facilitate intubation²⁰ and in children who were intubated without a neuromuscular blocking agent.²² Also, when inserting a laryngeal mask airway, intravenous lidocaine was reported to decrease the risk of coughing and laryngospasm.²⁸ We observed fewer diaphragmatic movements and/or coughing on tracheal tube insertion and cuff inflation in patients who were pre-treated with lidocaine. It has been described almost 50 years ago that intravenous lidocaine suppressed the cough reflex.²⁹ In a study designed to determine the most effective dose and time of intravenous lidocaine for suppression of coughing during tracheal intubation,

Yukioka et al. found that 2 mg/kg was the most effective dose and without adverse effects.²¹ According to these authors, the best timing for the administration of this dose was 1 min prior to intubation. Cough depression correlated well with a lidocaine plasma concentration in excess of $3 \mu \text{g/ml.}^{21}$

Our study has some limitations. We did not study the interaction between systemic lidocaine and a continuous infusion or repeated injection regimen of rocuronium. Thus, our results may not necessarily be applicable to every surgical setting, as for instance, patients undergoing major abdominal surgery necessitating a continuous and deep neuromuscular block throughout the procedure. Also, we tested one lidocaine regimen only. We cannot exclude that with a higher bolus and/or maintenance dose, a clinically relevant interaction with rocuronium may become evident.

In conclusion, our study suggests that when using a pre-operative intravenous bolus of lidocaine 1.5 mg/kg followed by an intraoperative continuous infusion of 2 mg/kg/h, there is no neuromuscular interaction with a single intubation dose of rocuronium. However, intubation conditions are likely to be improved.

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Conflict of interest: None.

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