Trial protocol

Perioperative intravenous lidocaine administration in thoracoscopic surgery for improved postoperative pain control

A randomised, placebo-controlled, superiority study

Short title: Perioperative Lidocaine

Study Type:	Clinical trial with Investigational Medicinal Product (IMP)
Study Categorisation:	Risk category B (according to LHR)
Study Registration:	SNCTP000002500 Clinicaltrials.gov NCT03677817
Study Identifier:	N. A.
Sponsor, Sponsor-Investigator	Prof. Didier Lardinois, Division of Thoracic Surgery University Hospital Basel Spitalstrasse 21, 4031 Basel email: didier.lardinois@usb.ch; tel: +41 61 3287799
Co-Investigator:	Dr. Aljaz Hojski
Investigational Product:	Lidocain, Rapidocain® 2%
Protocol Version and Date:	Version 3.2, , 14.01.2021

Signature Page(s)

Study number	SNCTP000002500
Study Title	Perioperative intravenous lidocaine administration in thoracoscopic surgery for improved postoperative pain control A randomised, placebo-controlled, superiority study

The Sponsor-Investigator and trial statistician have approved the protocol version, 3.2 dated 14.01.2021 and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm if applicable and the local legally applicable requirements.

Sponsor-Investigator:
Didier Lardinois

Basel 2.2.21

Place/Date Signature

Statistician:
Gilles Dutilh

Basel 2.2.2020

Place/Date Signature

Signature Page(s)

Study number	SNCTP000002500
Study Title	Perioperative intravenous lidocaine administration in thoracoscopic surgery for improved postoperative pain control A randomised, placebo-controlled, superiority study

The Sponsor-Investigator and trial statistician have approved the protocol version, 3.2 dated 14.01.2021 and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm if applicable and the local legally applicable requirements.

Sponsor-Investigator:
Didier Lardinois

Place/Date Signature

Statistician:
Gilles Dutilh

Basel 2/2/2021

Place/Date Signature

Co- Investigator at study site*:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines and the local legally applicable requirements.

Site	Universitätsspital Basel
Co-Investigator	Dr. Aljaz Hojski

Basel, 4.2.2021

Place/Date Signature

Note: In multicentre studies, this page must be individually signed by all participating Local Principal Investigators.

Table of Contents

STUDY SYNOPSIS

Sponsor / Sponsor-Investigator	Prof. Didier Lardinois
Study Title:	Perioperative intravenous lidocaine administration in thoracoscopic surgery for improved postoperative pain control: A randomised, placebo-controlled, superiority study
Short Title / Study ID:	Perioperative Lidocaine
Protocol Version and Date:	Version 3.2 14.01.2021
Trial registration:	Clinicaltrials.gov NCT03677817
Study category and Rationale	Risk category B - Clinical trial – use outside the indication
Clinical Phase:	Phase III Study
Background and Rationale:	Perioperative administration of lidocaine during laparoscopic interventions has repeatedly been shown to be associated with decreased postoperative pain, faster recovery (of bowel function) and shortened hospital stay in some fields of surgery. A recent study in Canada showed no difference between placebo- and Lidocaine- treated patients but the morphine consumption was already quite low for the control group and the population size was extremely small with 19 experimental and 17 control patients. We would therefore like to test the hypothesis in our clinic with more patients and using a score with a higher statistical power.
Objective(s):	Primary Objective: Lidocaine administration provides superior postoperative analgesia compared to placebo administration. Secondary Objectives: • Length of hospital stay • Time to first defecation • Postoperative nausea and vomiting • 30-day mortality • Chronic pain assessment
Outcome(s):	Primary outcomes: • Total Morphine consumption in mg and pain intensity (VAS) within the first 24 hours, measured at 1 hour, 2 hours, 4 hours, 8 hours, 16 hours, and 24 hours after skin closure. Secondary outcomes: • Pain intensity (VAS) and total morphine consumption in mg at 1, 2, 4, 8, 16, 24 and 48 hours after skin closure • Length of hospital stay • Time to first defecation after surgery • Presence or absence of postoperative nausea and vomiting • 30-day mortality • Pain assessed at follow up 2 (+2 weeks) weeks, 3 months and 6 months (± 7 days) after surgery
Study design:	This is a randomised, placebo-controlled, double-blind, superiority study.

Inclusion / Exclusion criteria:	**Inclusion criteria:** • Patients undergoing video-assisted thoracoscopic procedures under general anaesthesia. • American Society of Anesthesiologists (ASA) physical status classes I to III • age ≥ 18 years • Patient informed consent **Exclusion criteria:** • Contraindications to the class of drugs under study, e.g. known hypersensitivity or allergy to class of drugs or the investigational product, • Contraindications to self-administration of opioids, • Women who are pregnant or breast feeding, • Steroid therapy, • Chronic pain therapy, • Atrioventricular block grade II to III, • Congestive heart failure, • Liver insufficiency, • Known or suspected non-compliance, drug or alcohol abuse, • Inability to follow the procedures of the study, e.g. due to language problems, psychological disorders, dementia, etc. of the participant, • Participation in another study with investigational drug within the 30 days preceding and during the present study, • Enrolment of the investigator, his/her family members, employees and other dependent persons,

Measurements and procedures:	Patients undergoing video-assisted thoracoscopic surgery under general anaesthesia with planned operation time inside 90 minutes, will be computer-randomised to obtain either IMP or placebo perioperatively. The randomisation will be performed by CTU Basel. There will be no change in the postoperative treatment of the patients. Intraoperative analgesia will be given as deemed necessary by the anaesthesiologist, using fentanyl boli (1-2 µg/kg) as well as continuous infusion of remifentanil. The following rules need to be applied concerning opioid administration: Before surgical incision administration of at least 4 µg/kg of fentanyl IV, no more than 1 µg/kg of fentanyl per hour IV thereafter; additional analgesia is covered by adjusting remifentanil infusion; the last dose of fentanyl is administered at least 60 min before the end of the surgical procedure. This should minimize the variability of intraoperative opioid administration during the study. No infiltration of local anaesthetics is allowed. At the end of surgery, after haemostasis and if not contraindicated, metamizol 1 g will be given IV. Patient-controlled analgesia treatment (morphine) occurs according to in-house standards. Patients will be treated additionally with metamizol, if necessary. Deviations from the standard procedures will be documented. As per routine treatment in the Department of Thoracic Surgery, the patients will have a follow up 2 weeks, 3 months and 6 months, in the outpatient clinic or per telephone inquiry. The routine data of pain intensity and painkiller usage will be collected. The following data will be collected from the medical records: date of birth, weight, height, perioperative data such as duration of surgery, number of trocars, etc, patient-controlled analgesia (PCA) data, pain, nausea, time to first defecation etc. Drop outs (patients who need conversion to open surgery for any reason, patients who withdraw and do not allow the use of their data, patients that die during surgery) will not be replaced as the sample size covers a drop-out rate of 25 %. In addition a sensitivity analysis will be performed on all patients (including the ones who die or withdraw before the last follow-up visit). Assuming that the absence of outcomes is at random, multiple imputations are used for this analysis to assign outcomes to every patient. In case of doubt about this assumption, further sensitivity analyses are described in the analysis plan.
Study Product / Intervention:	**Lidocaine arm**: Intravenous [IV bolus] injection of lidocaine 1,5 mg/kg before intubation and at least 30 minutes before incision, followed by a continuous IV infusion of lidocaine 3,0 mg/kg/h, until 2 hours after skin closure. The patient can be transferred to the ward after the PACU discharge criteria are met. PACU discharge criteria are standardized for the University Hospital Basel.
Control Intervention (if applicable):	**Placebo arm**: Likewise procedure as in the lidocaine arm, but with placebo solution (NaCl 0,9%).
Number of Participants with Rationale:	113 For this study, 113 patients should be recruited to ensure 42 evaluable patients, assuming a drop-out rate of 25 %. This sample size allows with a power of 0.8 to show a group difference in the SIA score assuming a daily reduction in morphine consumption due to lidocaine of 2 mg and a reduction in the pain score of 1.5 points. We have to expand the 59 to 113 patients since we intend to include in our final statistical analysis only patients who are treated with lidocaine stored as described in the product information. The storage temperature is correctly monitored since November 2020.
Study Duration:	The study should take about 4 years to be completed.

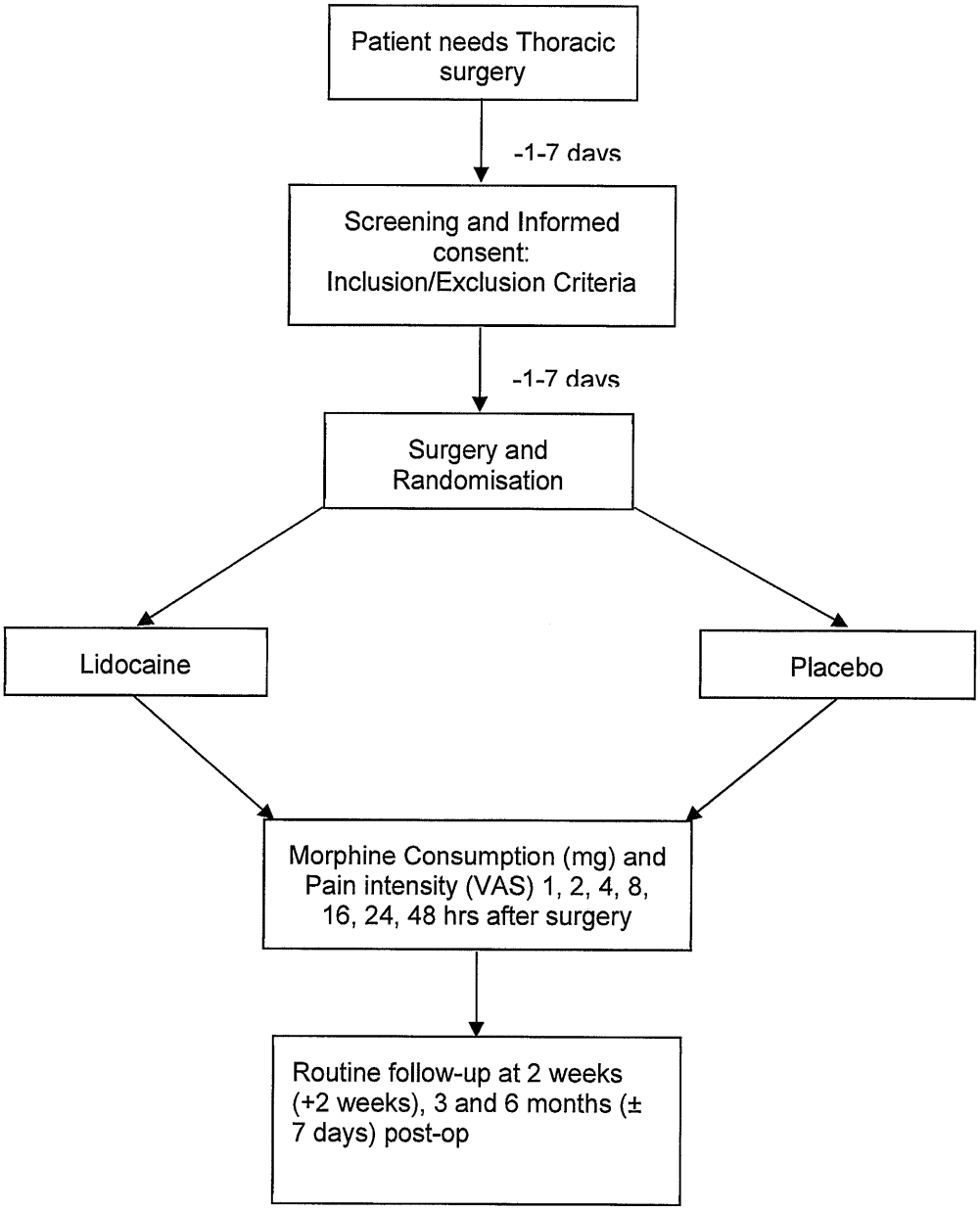
Study Schedule:	First-Participant-In: April 2019 Last-Participant-Out: anticipated December 2022
Investigator(s):	Prof. Dr. Lardinois Didier, Department of Thoracic Surgery, University Hospital Basel, Switzerland, email: didier.lardiois@usb.ch, tel: +41 61 328 7799 Dr Aljaz Hojski, Department of Thoracic Surgery, University Hospital Basel, Switzerland, email: aljaz.hojski@usb.ch, tel: +41 61 326 5282 Dackam Sandrine, MD, Department of Thoracic Surgery, University Hospital Basel, Switzerland, email: sandrine.Dackam@usb.ch, tel: +41 61 328 7170 Kaufmann Mark, MD, Department of Anesthesia, Surgical Intensive Care, Prehospital Emergency Medicine and Pain Therapy, University Hospital Basel, Switzerland, email: mark.Kaufmann@usb.ch, tel: +41 61 328 7268 Lampart Andreas, MD, Department of Anesthesia, Surgical Intensive Care, Prehospital Emergency Medicine and Pain Therapy, University Hospital Basel, Switzerland, email: andreas.Lampart@usb.ch, tel: +41 61 328 7273 Wiese Mark, MD, Department of Thoracic Surgery, University Hospital Basel, Switzerland, email: mark.wiese@usb.ch, tel: +41 61 328 7199 Prof. Dr. Bolliger Daniel, Department of Anesthesia, Surgical Intensive Care, Prehospital Emergency Medicine and Pain Therapy, University Hospital Basel, Switzerland, email: daniel.bolliger@usb.ch, tel: +41 61 32 86423 Seeberger Esther, SN, Department of Anesthesia, Surgical Intensive Care, Prehospital Emergency Medicine and Pain Therapy, University Hospital Basel, Switzerland, email: esther.seeberger@usb.ch, tel: +41 61 328 7242
Study Centre(s):	Single-centre
Statistical Considerations:	Detailed methodology for summaries and statistical analyses of the data collected in this study will be documented in a statistical analysis plan. The statistical analysis plan will be finalized before database closure and will be under version control at the Clinical Trial Unit, University Hospital Basel.
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP as well as all national legal and regulatory requirements.

ABBREVIATIONS

Provide a list of abbreviations used on the protocol - to be completed

AE	Adverse Event
CA	Competent Authority (e.g. Swissmedic)
CEC	Competent Ethics Committee
CRF	Case Report Form
CTCAE	Common terminology criteria for adverse events
DSUR	Development safety update report
FAS	Full analysis data set
GCP	Good Clinical Practice
IB	Investigator's Brochure
HFG	Humanforschungsgesetz (Law on human research)
HMG	Heilmittelgesetz
HRA	Federal Act on Research involving Human Beings
IMP	Investigational Medicinal Product
IIT	Investigator-initiated Trial
ISO	International Organisation for Standardisation
ITT	Intention to treat
KlinV	Verordnung über klinische Versuche in der Humanforschung *(in English: ClinO, in French OClin)*
LHR	Legal Health Regulation
OR	Operation Room
PACU	Post Anaesthesia Care Unit
PCA	Patient Controlled Analgesia
PI	Principal Investigator
SDV	Source Data Verification
SIA	Silverman integrating approach
SOP	Standard Operating Procedure
SPC	Summary of product characteristics
SN	Study nurse
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File

CLOCKINGSTUDY SCHEDULE



	Screening	OR	Ward							Follow up		
Day	-1 to -7	0	1						2	14(+14)	90 (±7)	180(±7)
Time (hr)		0	1	2	4	8	16	24	48			
Informed consent	X											
Demographics	X											
Medical history	X											
Pregnancy test	X											
In/Exclusion Criteria	X											
Randomisation		X										
Study medication administered		X										
Perioperative data		X										
PCA data			X	X	X	X	X	X	X			
Pain data			X	X	X	X	X	X	X	X	X	X
Nausea and vomiting			X	X	X	X	X	X	X			

1. STUDY ADMINISTRATIVE STRUCTURE

1.1 Sponsor, Sponsor-Investigator

Prof. Didier Lardinois
Department of Thoracic Surgery
University Hospital Basel
Spitalstrasse 21
4031, Basel

1.2 Co-Investigator(s)

Aljaz Hojski
Department of Thoracic Surgery
University Hospital Basel
Spitalstrasse 21
4031, Basel
Email: Aljaz.hojski@usb.ch
Phone: +41 61 65 282

1.3 Statistician ("Biostatistician")

Gilles Dutilh
CTU
University Hospital Basel
Spitalstrasse 12
4031 Basel
Phone:
Email : gilles.dutilh@usb.ch

1.4 Laboratory

n/a

1.5 Monitoring institution

Clinical Trial Unit Basel

1.6 Data Safety Monitoring Committee

n/a

1.7 Any other relevant Committee, Person, Organisation, Institution

Allgemeines Sekretariat
Department of Thoracic Surgery
University Hospital Basel
Spitalstrasse 12
4031, Basel
Phone : + 41 61 265 71 69

2. ETHICAL AND REGULATORY ASPECTS

Before this study will be conducted, the investigation plan, the proposed participant information and consent form as well as other study-specific documents will be submitted to a properly constituted Competent Ethics Committee (CEC) and Competent Authority (Swissmedic) in agreement with local legal requirements, for formal approval. Any amendment to the investigation plan must as well be approved.
The decision of the CEC and Swissmedic concerning the conduct of the study will be made in writing to the Sponsor-Investigator before commencement of this study. The clinical study can only begin once approval from all required authorities has been received. Any additional requirements imposed by the authorities shall be implemented.

2.1 Study registration

The study will be registered at ClinicalTrials.gov and in the Swiss Federal Complementary Database.

2.2 Categorisation of study

The study is Category B as the tested medication is authorised in Switzerland but is not used in the authorised indication in this study. A placebo will be used as control but no changes will be made to packaging.

2.3 Competent Ethics Committee (CEC)

Approval from the appropriate constituted Competent Ethics Committee is sought for each study site in the clinical trial. The reporting duties and allowed time frame are respected. No substantial changes are made to the investigation plan without prior Sponsor, CEC, CA approval, except where necessary to eliminate apparent immediate hazards to study participants.

Premature study end or interruption of the study will be reported within 15 days. The regular end of the study will be reported to the CEC within 90 days, the final study report shall be submitted within one year after study end. Amendments are according to chapter 2.10

2.4 Competent Authorities (CA)

The Sponsor will obtain approval from Swissmedic before the start of the clinical trial. Premature study end or interruption of the study will be reported within 15 days. The regular end of the study will be reported to the CA within 90 days, the final study report shall be submitted within one year after study end. Amendments are according to chapter 2.10.

2.5 Ethical Conduct of the Study

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, , the Swiss Law and Swiss regulatory authority's requirements. The CEC and regulatory authorities will receive annual safety and interim reports and be informed about study stop/end in agreement with local requirements.

2.6 Declaration of interest

The involved researchers in this study declare no conflict of interest.

2.7 Patient Information and Informed Consent

The investigator will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant must be informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment.

The participant must be informed that his/her medical records may be examined by authorized individuals other than their treating physician.

All participants for this study will be provided a participant information sheet and a consent form describing this study and providing sufficient information for participants to make an informed decision

about their participation in this study.

The formal consent of a participant, using the approved consent form, must be obtained before that participant is submitted to any study procedure.

The participant should read and consider the statement before signing and dating the informed consent form, and should be given a copy of the signed document. The consent form must also be signed and dated by the investigator (or his designee) and it will be retained as part of the study records.

2.8 Participant privacy and confidentiality

The investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilising subject identification code numbers to correspond to treatment data in the computer files.

For data verification purposes, authorised representatives of the Sponsor (-Investigator), a competent authority (e.g. Swissmedic), or an ethics committee may require direct access to parts of the medical records relevant to the study, including participants' medical history.

2.9 Early termination of the study

The Sponsor-Investigator may terminate the study prematurely according to certain circumstances, for example:

- ethical concerns,
- insufficient participant recruitment,
- when the safety of the participants is doubtful or at risk, respectively,
- alterations in accepted clinical practice that make the continuation of a clinical trial unwise,
- early evidence of benefit or harm of the experimental intervention

2.10 Protocol amendments

The PI, under the supervision of the Sponsor Investigator is allowed to make amendments to the protocol. All amendments will be communicated to the study team via email and a follow up telephone call.

Substantial amendments are only implemented after approval of the CEC and CA respectively.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the CEC/CA. Such deviations shall be documented and reported to the sponsor and the CEC/CA as soon as possible.

All Non-substantial amendments are communicated to the CA as soon as possible if applicable and to the CEC within the Annual Safety Report (ASR).

3. BACKGROUND AND RATIONALE

3.1 Background and Rationale

Pain after thoracic surgery is associated with alterations in lung function, potentially leading to pulmonary complications (e.g., atelectasis, pneumonia) and thus increased perioperative morbidity[1]. Furthermore, thrombosis, endocrine and cardiac complications are the consequences of insufficient treated postoperative pain (2-4). Optimized perioperative pain management, therefore, is paramount [2] especially in times of fast-track surgery, as patients are scheduled for discharge at the earliest possible time after abdominal surgery [3]. The administration of lidocaine perioperatively in open abdominal or laparoscopic abdominal surgeries where general anaesthesia is required, has been associated with decreased postoperative pain, faster recovery of bowel function, fewer opioid side effects and a shortened hospital stay [4,5]. However, although the perioperative administration of lidocaine seems advantageous in (some cases of) laparoscopic interventions, a recent study examining the effects of lidocaine in laparoscopic renal surgery found no such benefits [6]. Further, studies in orthopedic surgery, cardiac surgery or otorhinology showed no benefit either [7-9]. Because beneficial findings stem from laparoscopic interventions in the peritoneal cavity, a similar effect for interventions in the thoracic cavity may be postulated. Recently, Slovack et al. showed no effect of lidocaine in thoracic surgery but their population size was small and the morphine consumption in the control group was lower than has been shown in other groups[10].

At the University Hospital Basel, the current standard of care for thoracoscopic interventions does not include the perioperative administration of lidocaine. Thus examining the benefits of intravenous treatment with lidocaine is of great interest to patients and surgeons and may lead to better postoperative pain management and less postoperative complications.

Therefore we hypothesize that the perioperative administration of lidocaine will lead to a decreased postoperative pain, shorter hospital stays, decreased development of chronic pain and decreased 30-day mortality.

The primary objective of this study is therefore, to determine the effect of lidocaine on postoperative pain management compared to conventional treatment (placebo). The secondary objectives will look at the effect of lidocaine on time to first defecation, nausea, length of stay in the hospital and chronic pain. In order to address these objectives, we will conduct a prospective, randomized, double blind, superiority clinical trial, evaluating the effect of perioperative lidocaine on postoperative opioid consumption, pain ratings, duration of hospital stay, time to first defecation, 30-day mortality and development of chronic pain in patients undergoing video-assisted thoracoscopic procedures.

3.2 Investigational Product (treatment) and Indication

The dosing regimen of lidocaine will be as follows: 1,5 mg/kg IV induction bolus dose followed by continuous infusion 3,0 mg/kg until 2 hours after skin closure. Signs of toxicity for the central nervous system (such as somnolence, tinnitus, slurred speech, cramps, visual disturbances, seizures) and for the heart (such as negative inotropic state, bradycardia, and vasodilation) may start to appear at plasma levels of 5 µg/ml. However, it usually takes up to 10 µg/ml of lidocaine plasma levels for these signs to appear. Using the regimen of lidocaine administration of 1,5 mg/kg, IV bolus, followed by continuous infusion at 3,0 mg/kg/h, the following plasma concentrations of lidocaine were observed: 1,9 ± 0,7 µg/ml[11] and 2,1 ± 0,4 µg/ml[7], respectively, far below the toxicity-inducing levels.

3.3 Preclinical Evidence

Lidocaine is widely used for infiltration anaesthesia and has a large safety record.
The efficacy profile of lidocaine as a local anaesthetic is characterized by a rapid onset of action and intermediate duration of efficacy because it is eliminated only by the liver. Its half-life is between 1.5 to 3.5 hours. Lidocaine is suitable for infiltration, block, and surface anaesthesia. It is also the most important class-1b-antiarrhythmic drug[12]

3.4 Clinical Evidence to Date

Kranke et al. did a Cochrane-based review of all clinical evidence up until May 2014 and found that intravenous lidocaine has an effect on postoperative pain at early time points after surgery (abdominal surgery mainly)[13]. They also found that lidocaine has an effect on gastrointestinal recovery, on length of hospital stay, postoperative nausea and intra- and post-operative opioid requirement. Their main concern was the small size of the studies[13].

3.5 Dose Rationale: Rationale for the intended purpose in study (pre-market MD)

Using the regimen of lidocaine administration of 1,5 mg/kg IV bolus, followed by continuous infusion at 3,0 mg/kg/h, the following plasma concentrations of lidocaine were observed: 1,9 ± 0,7 µg/ml[11] and 2,1 ± 0,4 µg/ml[7], respectively. Toxic effects of systemic lidocaine only start to appear at a plasma level of 5 µg/ml.

Most of the research done to date, use a bolus of 1,5 mg/kg, but there is a huge variation in the dosage (1,5 - 5 mg/kg/h) and the duration of the continuous infusion (1 hour to 48 hours post-surgical closure).

3.6 Explanation for choice of comparator (or placebo)

This is a superiority study, so we are comparing Lidocaine to the existing treatment. To have an unbiased outcome, we will use NaCl as a placebo. The existing treatment is as follows: Intraoperative analgesia will be given as deemed necessary by the anaesthesiologist, using fentanyl boli (1 µg/kg/h) as well as continuous infusion of remifentanil. The following rules need to be applied concerning opioid administration: Before surgical incision administration of at least 4 µg/kg of fentanyl IV, no more than 1 µg/kg of fentanyl per hour IV thereafter; additional analgesia is covered by adjusting remifentanil infusion; the last dose of fentanyl is administered at least 60 min before the end of the surgical procedure. This should minimize the variability of intraoperative opioid administration during the study. No infiltration of local anaesthetics is allowed. At the end of surgery, after haemostasis and if not contraindicated, metamizol 1 g will be given IV.

3.7 Risks / Benefits

Known risks related to Lidocaine usage are: hypotension, bradycardia, arrhythmia, headaches, tinnitus, agitation and seizures. These side effects are dose-dependant and not expected for the dosage used in this study, therefore the risks are minimal. The possible benefits of reduced pain, reduced post-operative side effects such as nausea and vomiting, reduced time to first bowel movement and decreased length of hospital stay, outweigh the risks.

3.8 Justification of choice of study population

We include all patients undergoing video-assisted thoracoscopic procedures, with planned operation time less than 90 minutes e.g. wedge resection, pneumothorax, small nodules in the lung parenchyma, under general anaesthesia, who have an American Society of Anaesthesiologists [ASA] physical status class I to III. Vulnerable patients (children, patients with cognitive impairment and patients with documented dementia) will be excluded from the study. We are interested in the effect of Lidocaine on post-operative pain in thoracic surgery patients because pain could lead to other morbidities.

4. STUDY OBJECTIVES

4.1 Overall Objective

The purpose of this study is to evaluate whether perioperative administration of lidocaine lowers morphine consumption and pain after skin closure until six months post-operative, compared to administration of placebo in participants who have undergone video-assisted thoracoscopic surgery.

4.2 Primary Objective

The primary objective of this study is to determine, whether perioperative administration of lidocaine provides superior analgesia in the early postoperative period (first 24 hours) compared to placebo treatment. This will be measured through total Morphine consumption in mg and pain intensity (VAS) within the first 24 hours, measured at 1 hour, 2 hours, 4 hours, 8 hours, 16 hours and 24 hours after skin closure.

4.3 Secondary Objectives

Secondary Objectives are to determine the effect of Lidocaine on the following, compared to placebo:

- Pain intensity (VAS) and total morphine consumption in mg 1, 2, 4, 8, 16, 24 and 48 hours (± 30 minutes) after skin closure
- Length of hospital stay
- Time to first defecation
- Postoperative nausea and vomiting
- 30-day mortality
- Chronic pain

4.4 Safety Objectives

n/a

5. STUDY OUTCOMES

5.1 Primary Outcome

The primary endpoint is a decrease in total morphine consumption (TMC) via PCA of on average 2 mg and a decrease in pain intensity of at least 1.5 units on the VAS, within the first 24 hours measured at 1, 2, 4, 8, 16, and 24 hours after skin closure.

5.2 Secondary Outcomes

- Pain intensity (VAS) and total morphine consumption at 1, 2, 4, 8, 16, 24 and 48 hours after skin closure. Length of hospital stay – Defined as the time (in days) from the date of surgery until the date of discharge.
- Time to first defecation – Defined as the time from skin closure to the time of first defecation.
- Occurrence of nausea and/or vomiting
- Chronic pain – pain intensity (VAS) will be assessed (with and without coughing) 2 weeks (+2 weeks), 3 and 6 months (± 7 days) after surgery

5.3 Other Outcomes of Interest

30-day mortality – because pain can lead to serious morbidities and thus mortality, lidocaine may reduce the number of mortalities after surgery.

5.4 Safety Outcomes

n/a

6. STUDY DESIGN

6.1 General study design and justification of design

In this study we will conduct a prospective, randomized, double blind, single centre clinical trial, to evaluate the effect of perioperative lidocaine on postoperative total morphine consumption and postoperative pain in patients undergoing thoracoscopic procedures with operation time inside 90 minutes. Intraoperative analgesia will be given as deemed necessary by the anaesthetist, using fentanyl boli (1-2 µg/kg) as well as continuous infusion of remifentanil. The following rules need to be applied concerning opioid administration: Before surgical incision administration of at least 4 µg/kg of fentanyl IV, no more than 1 µg/kg of fentanyl per hour IV thereafter; additional analgesia is covered by adjusting remifentanil infusion; the last dose of fentanyl is administered at least 60 min before the end of the surgical procedure. This should minimize the variability of intraoperative opioid administration during the study. No infiltration of local anesthetics is allowed. At the end of surgery, after haemostasis and if not contraindicated, metamizol 1g will be given IV.

The study addresses the analgesic potential of perioperative lidocaine infusion in addition to the normal analgesia by comparing:

- Lidocaine 2% (LA):
  Immediately at anaesthesia induction, bolus injection of lidocaine 1,5 mg/kg approximately 30 minutes before incision, followed by a continuous IV infusion of lidocaine at 3,0 mg/kg/h, until 2 hours after skin closure.
- Placebo (PA) (normal analgesia) :
  Same procedure as in the lidocaine arm, but with placebo solution (NaCl 0,9%)

6.2 Methods of minimising bias

6.2.1 Randomisation

Each eligible participant will be allocated to Lidocaine or Placebo treatment using an unstratified block randomisation procedure as implemented in the electronic data capture (EDC) software secuTrial. An allocation ratio of 1:1 and a block size of 8, ensure a balance in sample size across both groups over time.

6.2.2 Blinding procedures

The treatment assignment is done by the randomization algorithm and recorded in the EDC software secuTrial. The access to secuTrial is password protected and restricted to the trained staff only. The randomizing anaesthesiologist, dedicated study nurse of the department or thoracic surgeon will not be involved in patient care or patient assessment.
The Lidocaine/placebo will be prepared after patient inclusion and randomization in syringes marked with patients study number by the anaesthesiologist or dedicated study nurse of the department that is not participating in surgery (according to the delegation log) just before surgery and storage in a designated cooler until administered. The IMPs data will be recorded in the dispensing log accessible for a potential emergency unblinding.

6.2.3 Other methods of minimising bias

As both groups are treated exactly the same way we prohibit performance bias The analgesic potential of Lidocaine is quantified using a VAS (1-10). The post-operative pain will be assessed using the short-form McGill Pain Questionnaire[16] and the quality of recovery questionnaire (QoR-40)[17].

6.3 Unblinding Procedures (Code break)

The anaesthesiologist or thoracic surgeon can unblind each participant at any time by extracting the treatment assignment from the records in the EDC software. The anaesthesiologist or thoracic surgeon will report to the sponsor/principal investigator and document the unblinding process. Unblinding will occur if there are any indications of an allergic reaction, and/or the patients general and/or neurological condition worsens, and/or there are signs of adverse reaction to the medication.

7. STUDY POPULATION

7.1 Eligibility criteria

Participants fulfilling all of the following inclusion criteria are eligible for the study, for example:

- Informed Consent as documented by signature
- Need for thoracoscopic procedures under general anaesthesia,
- American Society of Anaesthesiologists [ASA] physical status class I to III.
- Age≥18 years

The presence of any one of the following exclusion criteria will lead to exclusion of the participant, for example:

- Contraindications to the class of drugs under study, e.g. known hypersensitivity or allergy to class of drugs or the investigational product,
- Contraindications to self-administration of opioids,
- Women who are pregnant or breast feeding; a pregnany test will be performed
- Steroid therapy,
- Chronic pain therapy,
- Atrioventricular block grade II to III,
- Congestive heart failure,
- Liver insufficiency,
- Known or suspected non-compliance, drug or alcohol abuse,
- Inability to follow the procedures of the study, e.g. due to language problems, psychological disorders, dementia, etc. of the participant,
- Participation in another study with investigational drug within the 30 days preceding and during the present study,
- Enrolment of the investigator, his/her family members, employees and other dependent persons,

7.2 Recruitment and screening

The patients will be recruited by the thoracic surgeons in the Department of Thoracic Surgery, University Hospital Basel. All thoracic surgeons will be informed about the study. Typically, patients are first seen in the ambulatory clinic or in the tumour board. Patients who need to undergo a thoracoscopic procedure will be approached and informed about the study. An informed consent will be obtained and the patients will be screened for eligibility.

The study should take about four years to be completed. Based on our previous experience we expected the presentation of 200 patients per year with the need for elective thoracoscopic procedures. From our experience, we initially expected about 70% of these patients to be eligible and consent to study participation. We therefore calculated a 2 year recruitment period, i. e. a study-duration of one year as additional 6 months for the last follow up. In the meantime we identified an eligibility and consent to study participation of 30 % of our patients. For this reason and due to a not correct monitoring of the storage temperature of the IMP we have to include further patients and extend the recruitment period (study duration) to 3,5 years and additional 6 months for the last follow-up. The deviation from the storage temperature specified in the product information (RT, 15 – 25°C) of IMP (average 26.2°C; 19.2 – 27.9°C) lasted 6 months (20.05.2020 – 09.11.2020). Before May 2020 storage temperature of the IMP was not monitored. We consulted the Manufacturer (Sintetica SA) concerning this issue and got the information that in-house studies (Sintetica SA), which are not available for clients, show, that the IMP will be stable for 6 months at 40°C without influencing IMP quality. Since the initiation of the trial neither events due to safety reasons occurred nor supplementary medical intervention were necessary due to application of IMP stored under elevated temperature. No SAE occurred due to application of IMP. For this reason a threat for study patients can be excluded. Since 13.11.2020 the IMP is stored as in product information described temperature.

7.3 Assignment to study groups

The assignment of each participant to LA or PA group is done by the anaesthesiologist, dedicated study nurse of the department or thoracic surgeon during the treatment preparation. The randomization procedure is described in section 6.2.1.

7.4 Criteria for withdrawal / discontinuation of participants

Patients have the right to withdraw from the trial at any time for any reason and without indicating a reason. The patient can be withdrawn from the study by the PI or its delegates for the following reasons:

- Withdrawal of informed consent
- Non-compliance
- The thoracoscopic procedure is converted to a thoracotomic procedure

8. STUDY INTERVENTION

8.1 Identity of Investigational Products (treatment)

8.1.1 Experimental Intervention (treatment)

Lidocaine is a sterile non pyrogenic solution that contains a local anaesthetic agent and is administered parenterally by continuous infusion.

In addition, it is also an antiarrhythmic drug. It was the first amino amide-type local anaesthetic in 1943.

Lidocaine is rapidly metabolized by the liver, and less than 10% of a dose is excreted unchanged in the urine. Oxidative N dealkylation, a major pathway of metabolism, results in the metabolites monoethylglycinexylidide and glycinexylidide. The pharmacological/toxicological activities of these metabolites are similar to, but less potent than, lidocaine. The primary metabolite in urine is a conjugate of 4-hydroxy-2,6,-dimethylaniline. The elimination half-life of lidocaine following an intravenous bolus injection is typically 1.5 to 2 hours. There are data that indicate that the half-life may be 3 hours or longer following infusion of greater than 24 -hours[12].

The perioperative IV administration regimen of lidocaine will be as follows: 1,5 mg/kg IV induction bolus dose followed by continuous infusion of 3,0 mg/kg/h, until 2 hours after skin closure. Signs of toxicity (for central nervous system like somnolence, tinnitus, slurred speech, cramps, visual disturbances, seizures and for the heart like negative inotropia, bradycardia, vasodilation) may start to appear at plasma levels of 5 µg/ml. However, it usually takes up to 10 µg/ml of lidocaine plasma levels for these signs to appear. Using the regimen of lidocaine administration of 1,5 mg/kg, bolus dose, followed by continuous infusion at 3,0 mg/kg/h, the following plasma concentrations of lidocaine were observed: 1,9 ± 0,7 µg/ml[11] and 2,1 ± 0,4 µg/ml[7], respectively.

8.1.2 Control Intervention (standard/routine/comparator treatment)

Our control intervention is the placebo, NaCl.

A NaCl intravenous solution is a solution of sodium chloride in water for injection. It serves as a substitute for water, sodium and chloride, and can be used as fluid replacement in hyponatremia, hypochloremia and as a carrier solution for active pharmaceutical ingredients.

Sodium chloride (NaCl, Mr: 58,44 g/mol) is a white crystalline powder, colorless crystals or white pearls. It has a salty taste and is readily soluble in water. The solution is administered intravenously as an infusion. NaCl infusion solutions are well tolerated in general. Possible adverse effects include, as with other infusions, venous irritation and thrombophlebitis.

8.1.3 Packaging, Labelling and Supply (re-supply)

After randomisation process, the anaesthesiologist or dedicated study nurse of the department that is not participating in surgery (according to the delegation log) will label the IMPs with Patient ID and Chargen/Batchnumber on the day before surgery and will store the IMP max 24 hours at 6°C in a designated cooler until administration. Medication is available in the University Hospital Basel as it is used in several other indications.

8.1.4 Storage Conditions

Storage of IMP is according to standard hospital procedures in a key closed cupboard at room temperature and is monitored correctly since November 2020.

8.2 Administration of experimental and control interventions

8.2.1 Experimental Intervention

IV bolus injection of lidocaine 1,5 mg/kg and approximately 30 minutes before incision, followed by a continuous IV infusion of lidocaine of 3,0 mg/kg/h until 2 hours after skin closure. Signs of toxicity (for central nervous system like somnolence, tinnitus, slurred speech, cramps, visual disturbances, seizures and for the heart like negative inotropia, bradycardia, vasodilation) may start to appear at plasma levels of 5 µg/ml. However, it usually takes up to 10 µg/ml of lidocaine plasma levels for these signs to appear. Using the regimen of lidocaine administration of 1,5 mg/kg, IV bolus dose, followed by continuous infusion at 3,0 mg/kg/h, the following plasma concentrations of lidocaine were observed: 1,9 ± 0,7 µg/ml[11] and 2,1 ± 0,4 µg/ml[7], respectively

8.2.2 Control Intervention

Same procedure as in the lidocaine arm, but with blinded placebo solution (NaCl 0,9%)

8.3 Dose / Device modifications

The drug dose is based on the body weight, which was evaluated preoperatively. No dose modifications are provided in the intervention.

8.4 Compliance with study intervention

n/a

8.5 Data Collection and Follow-up for withdrawn participants

Data from patients who are withdrawn from the study due to surgical conversion will not be used in the study. Data from patients who withdraw after the surgery, will anonymized still be used, and the patient will not be replaced.
Lidocaine is a well-known and well-used medication that has been on the market since 1943. It has a short half-life of 2-3 hours. Withdrawn patients or patients who have withdrawn from the study, will still obtain their routine check-ups. There are no follow up visits specifically for the study.

8.6 Trial specific preventive measures

There are no trial specific preventive measures.

8.7 Concomitant Interventions (treatments)

Intraoperative analgesia will be given as deemed necessary by the anaesthesiologist, using fentanyl as well as continuous infusion of remifentanil. The following rules need to be applied concerning opioid administration: Before surgical incision administration of at least 4 µg/kg of fentanyl IV as bolus, no more than 1 µg/kg of fentanyl per hour IV thereafter; additional analgesia is covered by adjusting remifentanil infusion; the last dose of fentanyl is administered at least 60min before the end of the surgical procedure. This should minimize the variability of intraoperative opioid administration during the study. No infiltration of local anaesthetics is allowed. At the end of surgery, after haemostasis and if not contraindicated, metamizol 1 g will be given IV.

8.8 Study Drug Accountability

Lidocaine and NaCl are standard medical products at our hospital. They are available in the OR and are in general use and accordingly stored following their SOPs. Batch numbers but no info regarding the medication used, will be archived in the dispensing log.
The Lidocaine/placebo will be prepared after patient inclusion and randomization in syringes marked with patients study number (Patient ID) by the anaesthesiologist or dedicated study nurse of the department that is not participating in surgery (according to the delegation log) just before surgery and storage in a designated cooler until administered. The IMPs data will be recorded in the Drug Accountability Sheet accessible for a potential emergency unblinding. The dedicated investigator or

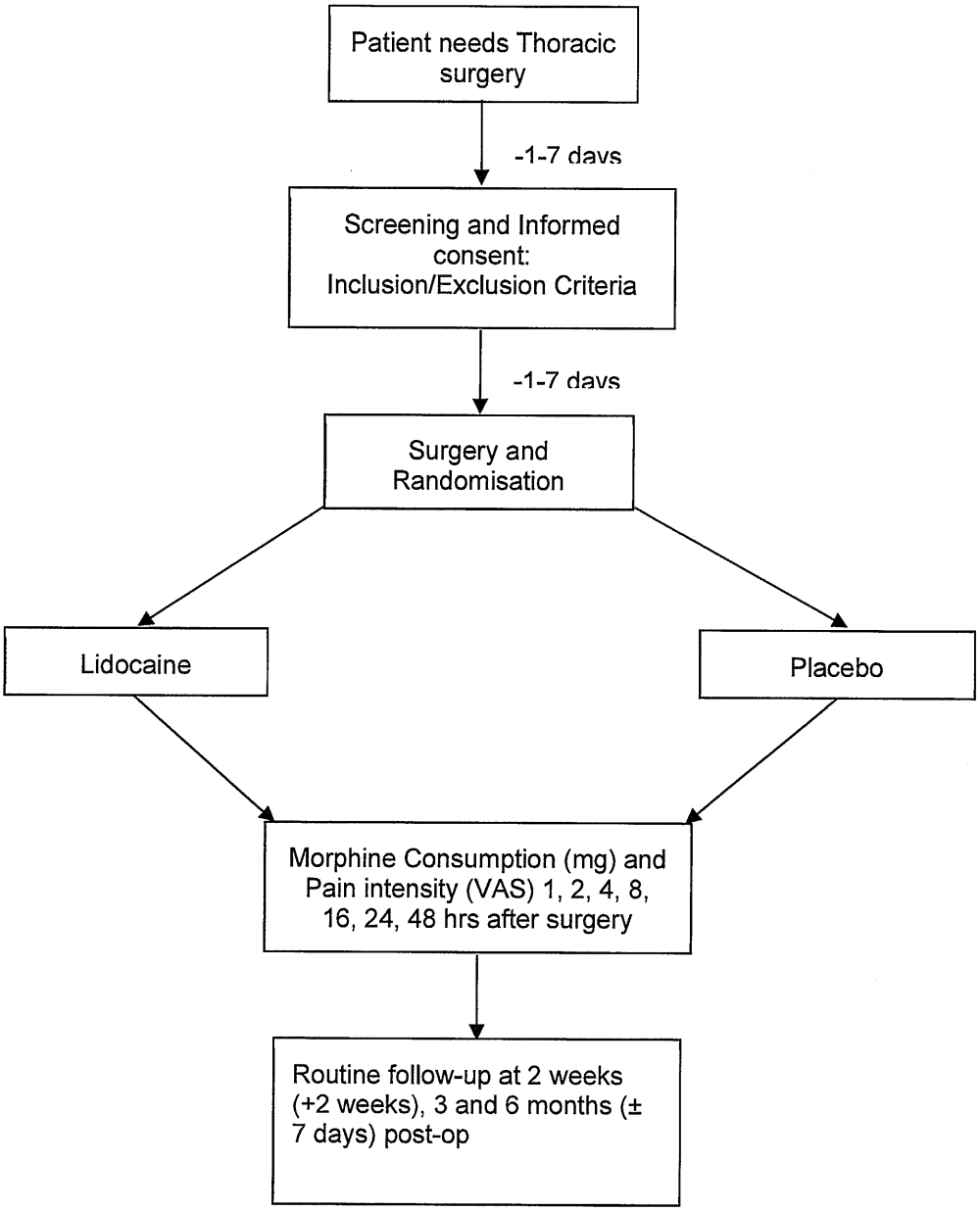
delegate will keep an accurate Drug Accountability Log including the physical location dates (despense to Participant), batch number expiry date,and quantities (prepared, returned,).

8.9 Return or Destruction of Study Drug

Used IMP should be disposed in accordance with local practice following reconciliation and the completion of the relevant log (see 8.8.)

9. STUDY ASSESSMENTS

9.1 Study flow chart(s) / table of study procedures and assessments



9.2 Assessments of outcomes

9.2.1 Assessment of primary outcome

Pain Service Team will instruct the patient in the use of PCA according to hospital standards. PCA will be started (PCA setting: demand dose of 2 mg morphine and a lockout of 12 min; if required, it can be adjusted to patient's need).

Total PCA requests and positive PCA requests, are recorded by the equipment.
Pain intensity using the VAS and total morphine consumption in mg will be recorded at timepoints 1 hr, 2 hrs, 4 hrs, 8 hrs, 16 hrs, and 24 hrs after skin closure. The pain score will be documented when the patient is immobile and when the patient is coughing.

9.2.2 Assessment of secondary outcomes

Pain and morphine consumption

Pain intensity using the VAS and total morphine consumption will be recorded 1, 2, 4, 8, 16, 24 and 48 hours after skin closure.

Nausea and vomiting
On arrival in the PACU the patient will be asked if they are nauseous.
The patients will be instructed to inform the staff of any nausea or vomiting that they may experience.

First defecation
Once on ward, the patients will be questioned at timepoints 1 hr, 2 hrs, 4 hrs, 8 hrs, 16 hrs, 24 hrs and 48 hrs after skin closure regarding their bowel movements and the patients will be instructed to inform the staff of their first defecation.

The approximate time of the first defecation will be recorded in the CRF.

Length of hospital stay
Defined as time from surgery until patients are discharged from the hospital

Chronic pain assessment

During follow up at 2 weeks (+2 weeks), 3 and 6 months (±7days), patients will be assessed for pain intensity (VAS 1 to 10) while being immobile and while coughing, pain experience (no pain, mild, discomforting, distressing, horrible, excruciating) and for the sensory and affective dimension of pain with the short-form McGill Pain Questionnaire

9.2.3 Assessment of other outcomes of interest

30-day mortality
To be assessed from the patient records. Defined as death within the first 30 days after surgery.

9.2.4 Assessment of safety outcomes

9.2.4.1 *Adverse events*
n/a

9.2.4.2 *Laboratory parameters*
n/a

9.2.4.3 *Vital signs*
Nothing specific to the study. Only routine measurements

9.2.5 Assessments in participants who prematurely stop the study

Patients who have withdrawn from the study or who have been withdrawn will still have their routine surgical follow up at 2 weeks, 3 months and 6 months after the surgery.

9.3 Procedures at each visit

	Screening	OR	Ward							Follow up		
Day	-1 to -7	0	1						2	14(+14)	90 (±7)	180(±7)
Time (hr)		0	1	2	4	8	16	24	48			
Informed consent	X											
Demographics	X											
Medical history	X											
Pregnancy test	X											
In/Exclusion Criteria	X											
Randomisation		X										
Study medication administered		X										
Perioperative data		X										
PCA data			X	X	X	X	X	X	X			
Pain data			X	X	X	X	X	X	X	X	X	X
Nausea and vomiting			X	X	X	X	X	X	X			

9.3.1 Screening visit (Day -1 to -7)

Study explained to patient
Informed consent obtained
Patients are screened for eligibility
Pregnancy of females in reproductive age:
Before study inclusion a serum beta HCG test is required if a pregnancy can not be definite excluded otherwise (e.g. hysterectomy, ≥ 45 years of age and has not had menses for greater than 1 year). Serum beta HCG test is valid within 7 days before study inclusion.

9.3.2 Pre-operative day (may be the same day as the screening visit)

The routine procedure is that the patients will be instructed how to use a patient controlled analgesia (PCA) pump, how to rate pain intensity on a visual analog scale (VAS: 0 as "no pain" and 10 as "worst

imaginable pain") and answer the short-form McGill Pain Questionnaire (pre operation). The following baseline data will be collected:

- Date of Informed Consent signed (day/month/year)
- Gender
- Weight and height
- Inclusion/Exclusion criteria
- Date of admission to the hospital (day/month/year)
- Diagnosis and type of planned surgery
- Operative risk as evaluated according to the American Society of Anaesthesiologists (ASA)

9.3.3 Perioperative (day -1 to day 0)

Randomization by anesthesiologist, delegated study nurse of the department or thoracic surgeon not involved in the patient care or assessment.
Notation of treatment of sequentially numbered patient on drug accountability sheet which is only available for doctor not involved in the care and/or assessment of the patients in the study and on Drug accountability Log for Lidocaine and NaCl
Collection of perioperative data by surgical nurse and study coordinator:

- Surgeon
- Type of surgery
- Date of surgery (day/month/year)
- Duration of Surgery (skin-incision-skin closure) (min)
- Duration of anaesthesia (min)
- Number of trocars
- Intraoperative fentanyl (µg) and Remifentanyl (µg)
- Duration of study medication infusion (min)
- Intraoperative study medication infused (mg) (will be later calculated to avoid unblinding)
- Additional analgesic medication (metamizol,)
- Intraoperative complications

9.3.4 Data of patient-controlled analgesia (PCA)

- Total morphine consumption (mg)
- Total PCA requests
- Positive PCA requests
- Negative PCA requests
- Pain intensity (VAS Score) – with coughing and when immobile
- Riker sedation agitation scale[18]PONV [nausea, present or not; vomiting, number of events]
- Adverse events of lidocaine infusion (light headedness, drowsiness, perioral numbness, visual disturbances, metal taste)
- Additional analgesic medication including dose and time of intake during the hospital stay

9.3.5 Hospital stay and follow up data (postoperative day 1 and 2, follow up 2-4 weeks, 3 and 6 months later

Daily ward rounds until discharge by the surgeon and his delegates to assess the patient for complications. Follow up is performed by the surgeon and the study coordinator during the visit at our outpatient clinic or per telephone inquiry

- Date of discharge from the hospital (day/month/year)
- Pain intensity [VAS Score] – with coughing and when immobile
- Additional analgesic medication including dose and time/date of intake during the hospital stay

10. SAFETY

10.1 Drug studies

During the entire duration of the study, all serious adverse events (SAEs) are collected, fully investigated and documented in source documents and case report forms (CRF). Study duration encompassed the time from when the participant signs the informed consent until the last protocol-specific procedure has

been completed, including a safety follow-up period.

10.1.1 Definition and assessment of (serious) adverse events and other safety related events

n/a

A **Serious Adverse Event (SAE)** is classified as any untoward medical occurrence other than those listed, that:

- results in death,
- is life-threatening,
- requires in-patient hospitalization or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

In addition, important medical events that may not be immediately life-threatening or result in death, or require hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above should also usually be considered serious. [ICH E2A]

SAEs should be followed until resolution or stabilisation. Participants with ongoing SAEs at study termination (including safety visit) will be further followed up until recovery or until stabilisation of the disease after termination.

Assessment of Causality

Both Investigator and Sponsor-investigator make a causality assessment of the event to the study drug, based on the criteria listed in the ICH E2A guidelines:

Relationship	Description
Definitely	Temporal relationship Improvement after dechallenge* Recurrence after rechallenge (or other proof of drug cause)
Probably	Temporal relationship Improvement after dechallenge No other cause evident
Possibly	Temporal relationship Other cause possible
Unlikely	Any assessable reaction that does not fulfil the above conditions
Not related	Causal relationship can be ruled out
*Improvement after dechallenge only taken into consideration, if applicable to reaction	

Unexpected Adverse Drug Reaction

An "unexpected" adverse drug reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for drugs that are not yet approved and Product Information for approved drugs, respectively). [ICH E2A]

Suspected Unexpected Serious Adverse Reactions (SUSARs)

The Sponsor-Investigator evaluates any SAE that has been reported regarding seriousness, causality and expectedness. If the event is related to the investigational product and is both serious and unexpected, it is classified as a SUSAR.

This is a double-blinded study. In case unblinding is needed in order to determine SUSAR, the treatment allocation should not be disclosed to the investigator, nor to the study staff, in order not to make the subject ineligible.

Assessment of Severity

The SAE terms will be reported according to the Common Terminology Criteria for Adverse Events

(CTCAE, Version 4.0).

10.1.2 Reporting of serious adverse events (SAE) and other safety related events

Reporting of SAEs

Underlying disease (e. g. metastatic lung cancer with expected 1 year survival of 27-37%) is an acute or chronic comorbidity or condition designated as one of the principal diagnosis not related to the procedure that alters short and/or long term survival of the patient.

All SAEs, except those related to the underlying disease of the patient, must be reported immediately and within a maximum of 24 hours to the Sponsor-Investigator of the study. The Sponsor-Investigator will re-evaluate the SAE form and return the form to the site.

SAEs resulting in death, except those related to the underlying disease of the patient, are reported to the Ethics Committee via BASEC within 7 days.

Reporting of SUSARs

A SUSAR needs to be reported to the Ethics Committee (local event via local Investigator) via BASEC and to Swissmedic (via Sponsor-Investigator) within 7 days, if the event is fatal, or within 15 days (all other events).

Reporting of Safety Signals

All suspected new risks and relevant new aspects of known adverse reactions that require safety-related measures, i.e. so-called safety signals, must be reported to the Sponsor-Investigator within 24 hours. The Sponsor-Investigator must report the safety signals within 7 days to the local Ethics Committee (local event via local Investigator) and to Swissmedic.

Periodic reporting of safety

An annual safety report is submitted once a year to the local Ethics Committee via local Investigator and to Swissmedic via Sponsor-Investigator.

10.1.3 Follow up of (Serious) Adverse Events

Participants terminating the study (either regularly or prematurely) with

- reported ongoing SAE

will return for a follow-up investigation. This visit will take place up to 30 days after terminating the treatment period. Follow-up information on the outcome will be recorded on the respective AE page in the CRF. All other information has to be documented in the source documents. Source data has to be available upon request.

In case of participants lost to follow-up, efforts should be made and documented to contact the participant to encourage him/her to continue study participation as scheduled. In case of minor AEs a telephone call to the participants may be acceptable.

All new SAE that the investigators will be notified of within 30 days after discontinuation of study medication have to be reported in appropriate report forms and in the CRF if required.

Follow-up investigations may also be necessary according to the investigator's medical judgment even if the participant has no AE at the end of the study. However, information related to these investigations does not have to be documented in the CRF but must be noted in the source documents.

11. STATISTICAL METHODS

Detailed methodology for summaries and statistical analyses of the data collected in this study will be documented in a statistical analysis plan. The statistical analysis plan will be finalized before database closure and will be under version control at the Clinical Trial Unit, University Hospital Basel.

11.1 Hypothesis

H_0: Patients treated with lidocaine suffer the same integrated pain expression (as quantified using the SIA score) as patients in the placebo arm.

H_1: Patients treated with lidocaine suffer less integrated pain expression (as quantified using the SIA score) as patients in the placebo arm.

The SIA score integrates total morphine consumption and pain quantified using a VAS. It will be calculated as described in Dai *et al.*(2013)[14] involving all three steps described in the paper.

11.2 Original Sample Size estimation

The original sample size was determined using simulations based on to sources of information:

- The results reported in a similar Study (Dai *et al.*[14] 2013) were used to make an informed assumption about the variability of pain intensity as well as the correlation between experienced pain and the amount of morphine taken.
- The variability in morphine consumption was estimated based on pilot data from patients treated in Basel.

The original estimate of 56 patients was based on the following assumptions:

- Standard deviation of pain: 1.91
- Standard deviation of morphine dose: 1.60 (not log transformed)
- Correlation between pain and morphine: 0.22

The sample size was calculated to achieve an 80% power to find a SIA difference associated with a pain reduction of 1.5 points on the visual analogue scale and a reduction of morphine consumption of 2 mg.

11.3 Interim analysis to update sample size estimation

As planned in the study protocol, we updated our sample size estimate based on the data when at least 10 evaluable patients per arm are recruited. Specifically, the sample size re-estimation was performed when a total of 34 were recruited with 15 patients in the smallest treatment arm. Note that this sample size re-estimation was performed on the data that is not used for the final analysis, for reasons discussed above concerning the layering temperature of the lidocaine. We strongly believe that the information used for this sample size re-estimation - the variability of the outcome in the treatment arms - is not meaningfully influenced by the fact that in the lidocaine arm, the medicament temperature was not monitored correctly. Therefore, we deem the estimate of the variability generalizable to the new data which is collected now monitoring is assured.

We resampled data from the first 34 patients. Note that in the resampling procedure,the pain and morphine value of each patient were kept together as a pair, so that the correlation between both variables was kept intact.

Note that the statistician performing this analysis was blind to the treatment arm labels during the analyses. For both pain and morphine, the arm-means were subtracted from the each value. This has two advantages: 1) If we would simply resample the raw values across arms, our simulation would be

based on too large a variance if there truly were a difference between the treatment arms. 2) The subtraction of the arm means assures that the data analyst is really blind to eventual effects in the data while performing the sample size re-estimation.

The result of the resampling analysis is shown in Figure 1. The figure shows the total number of evaluable patients (both arms together, on the y-axis) required to reach different levels of power (separate lines), given a range of true effect sizes in terms of theta (x-axis). The Figure is based on samples with replacement from the interim data set, where in each simulation, the treatment effect on morphine use was set to *theta* and the effect on pain to 0.75 * theta.

We can see that, based on the data collected up to this sample size re-estimation, the required sample size has changed: The original estimation suggested that a total of 56 evaluable patients sufficed to achieve an 80% power of detect a difference as large as theta = 2 (where the treatment effect on morphine intake is of size theta and the effect on pain is of size 0.75 times theta). The updated analysis suggests that 42 evaluable patients are needed, i.e., 21 per treatment arm. To achieve this number of evaluable patients, and given the updated drop-out rate of 30 %, 59 patients should be recruited.

To reach a power of 90%, data of 79 participants is needed, in order to have 55 evaluable patients, given the updated drop-out rate of 30 %.

11.4 Statistical criteria of termination of trial

No such criteria are defined.

11.5 Planned Analyses

11.5.1 Primary Analysis

The primary endpoint of this study is the SIA score as described in Dai et al.[14]. The SIA score integrates total morphine consumption in mg within the first 24 hours post surgery and Pain (VAS) in the first 24 hours after surgery. Pain is assessed several times. The average of all measurements taken in a patient will be used to calculate the SIA score.

The SIA score will be analyzed in a linear model. Treatment arm will be included as two-level factor ("lidocaine" vs "placebo"). Duration of surgery and number of trocars will be included as covariates.

Model validation will be performed by checking residuals and leverages. The residuals will be checked by visual inspection using a plot of the residuals vs the fitted values and a Normal Q-Q plot. In case of substantial violations of model assumptions, transformations or the use of a generalized linear model will be considered. The estimated treatment effect, the 95% confidence interval thereof and the p-value will be presented. The analysis will be performed using α=0.05 (two-sided).

The analysis will be performed on the ITT set.

A sensitivity analysis will be performed on the PP analysis set and compared to the main analysis in order to investigate the influence of protocol deviations.

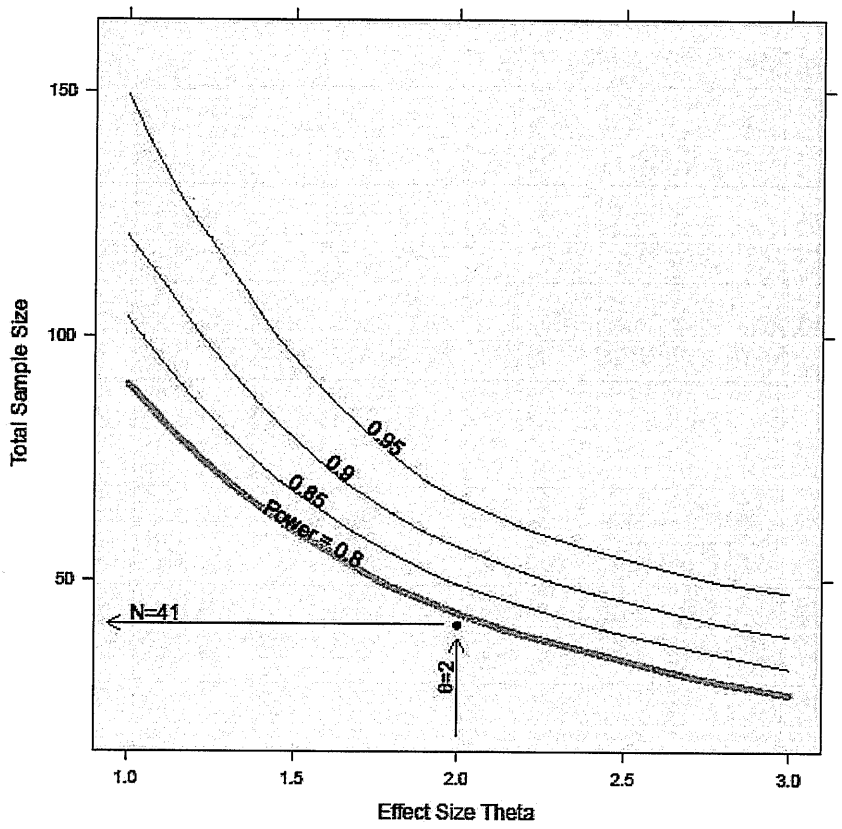


Figure 1: The total number of evaluable patients (both arms together, on the y-axis) required to reach different levels of power (separate lines), given a range of true effect sizes in terms of theta (x-axis). The figure is based on simulations, where in each simulation, the treatment effect on morphine use was set to theta and the effect on pain to 0.75 * theta.

11.5.2 Secondary Analyses

Endpoints Secondary endpoints comprise:

Morphine consumption: morphine consumption within the first 48 hours post surgery in mg.

Pain intensity: measured using a visual analogue scale (VAS), measured up to 6 months after skin closure..

Time to hospital discharge: The duration of hospital stay will be defined as the time in days from the date of surgery until the date of discharge from hospital in days.

Pain intensity and morphine consumption are measured at 1, 2, 4, 8, 16, 24, and 48 hours after skin closure. Pain is additionally measured after 2 weeks as well as 3 and 6 months after skin closure.

Method of analysis

All secondary analyses will be performed on the ITT analysis set. However, patients with missing value in a secondary endpoint will not be included in the corresponding analysis. No imputations for the secondary endpoint will be performed.

To decompose the effect on SIA as studied in the primary analysis, we analyze the treatment effect ("lidocaine" vs "placebo") on pain and morphine consumption during the first 24 hours also as separate variables. Duration of surgery and number of trocars will be included as covariates. In case of substantial violations of model assumptions, we will use a poisson model. In case of over dispersion a negative binomial model will be used.

Time to hospital discharge will be analysed in a Cox-proportional hazards model. Treatment arm will be

included as two-level factor ("lidocaine" vs "placebo"). Duration of surgery and number of trocars will be included as covariables.

11.5.3 Safety analysis

Safety will be assessed via a rigorous and detailed examination of serious adverse events.
The proportion of participants with an adverse event or a serious adverse event will be estimated by trial arm, and reported together with 95%-confidence intervals, calculated according to Blaker (2000)[15].
All safety analyses will be performed on the FAS.

11.5.4 Deviation(s) from the original statistical plan

If substantial deviations of the analysis as outlined in this section are needed for whatever reason, the protocol will be amended. All deviations of the analysis from the protocol or from the detailed analysis plan will be listed and justified in a separate section of the final statistical report.

11.6 Handling of missing data and drop-outs

It is assumed that there are no missing values in the amount of morphine a patient consumed in the first 24 hours. If the morphine consumption is not available for a patient, the patient will not be included in the analyses. Data is collected until the required number of evaluable patients is reached.

For isolated missing measurements in the pain score, a value estimated by linear interpolation of the measurements before and after the missing value will be imputed. If the first measurement (recorded at the arrival at the PACU) of pain is missing, the first available recording will be imputed. If more than three consecutive measurements are missing, the patient will not be included in the analysis.

12. QUALITY ASSURANCE AND CONTROL

12.1 Data handling and record keeping / archiving

12.1.1 eCase Report Forms

The investigators will use paper Worksheets one for each enrolled study participant, to be filled in with all relevant data pertaining to the participant during the study. All participants who either entered the study or were considered not-eligible or were eligible but not enrolled into the study additionally have to be documented on a screening log. The investigator will document the participation of each study participant on the Enrolment Log. All requested information in the worksheet should be completed in a neat legible manner. Use of a black ball pen is recommended to ensure clarity of reproduced copies in the Worksheet . All corrections in a paper Worksheet must be made in a way that does not obscure the original entry. The correct data must be inserted, dated and initialed by the investigator Data that are not available or not done should be made clear by adding NA or ND. A declaration ensuring accuracy of data recorded in the case report forms must be signed by the investigator.
CRFs must be kept current to reflect participant status at each phase during the course of study. Participants must not to be identified in the CRF by name. Appropriate coded identification (e.g. Participant Number) must be used.
It must be assured that any authorized person, who may perform data entries and changes in the CRF, can be identified. A list with signatures and initials of all authorized persons will be filed in the study site file and the trial master file, respectively.
Documented medical histories and narrative statements relative to the participant's progress during the study will be maintained. These records will also include the following: originals or copies of laboratory and other medical test results (e.g. ECGs, etc.) which must be kept on file with the individual participants CRF. The CRF makes provision for the person entering the data to be identified. The investigators assure to perform a complete and accurate documentation of the participant data in the CRF. All data entered into the CRF must also be available in the individual participant file either as print-outs or as notes taken by either the investigator or another responsible person assigned by the investigator.
Essential documents must be retained for at least 10 years after the regular end or a premature termination of the respective study (KlinV Art. 45).
Any patient files and source data must be archived for the longest possible period of time according to the feasibility of the investigational site, e.g. hospital, institution or private practice.

A delegation log will assign responsibilities for the different tasks, e.g. data entry, data sign-off, monitoring.

Data will be entered from the CRF into a database (secuTrial®).

12.1.2 Specification of source documents

The following documents are considered source data, including but not limited to:

- SAE worksheets
- Nurse records, records of clinical coordinators, and
- Medical records from other department(s), or other hospital(s), or discharge letters and correspondence with other departments/hospitals, if participant visited any during the study period and the post study period.

Source data must be available at the site to document the existence of the study participants and substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the participant.

The following information (at least but not limited to) should be included in the source documents:

- Demographic data (age, sex)
- Inclusion and Exclusion Criteria details
- Participation in study and signed and dated Informed Consent Forms
- Visit or telephone interview dates
- Medical history and physical examination details
- Key efficacy and safety data (as specified in the investigation plan)

- Additional analgesic medication
- Results of relevant examinations
- Laboratory printouts
- Reason for premature discontinuation
- Randomization number

12.1.3 Record keeping / archiving

All study data must be archived for a minimum of 10 years after study termination or premature termination of the clinical trial.
Location of storage – In a lockable cupboard in the Department of Thoracic Surgery.
IMP: Archiving for 10 years

12.2 Data management

12.2.1 Data Management System

The clinical trial data will be collected in electronic data capture (EDC) system, named secuTrial®.

The EDC system runs on a server maintained by the IT-department of the University Hospital Basel.

The electronic CRF (eCRF) is implemented (set-up and adjusted) by the datamanagement group at the Clinical Trial Unit (CTU) at the University Hospital Basel.

12.2.2 Data security, access and back-up

The EDC system is accessible via a standard browser on a WWW-connected device.

Password protection ensures that only authorized persons can enter the system to view, add or edit data according to their permissions.

User administration and user training is performed by the CTU according to predefined processes.

Back-up of secuTrial study data is performed according to the processes of the IT-department of the University Hospital Basel.

12.2.3 Analysis and archiving

The EDC will be locked after all data was monitored and all raised queries have been resolved.

Data is exported and transferred to the investigator by the CTU according to

internally defined processes.

Data will be archived by the investigator.

12.2.4 Electronic and central data validation

Data is entered into the eCRF and can be validated for completeness and discrepancies automatically.

An audit trail system maintains a record of initial entries and changes (reasons for

changes, time and date of changes, user identification of entry and changes).

12.3 Monitoring

A monitor from the CTU Basel will raise queries using the query management system implemented.

Designated investigators have to respond to the query and confirm or correct the corresponding data.

Thereafter the monitor can close the query.

12.4 Audits and Inspections

A quality assurance audit/inspection of this study may be conducted by the competent authority or CEC, respectively. The quality assurance auditor/inspector will have access to all medical records, the investigator's study related files and correspondence, and the informed consent documentation that is relevant to this clinical study.
The investigator will allow the persons being responsible for the audit or the inspection to have access

to the source data/documents and to answer any questions arising. All involved parties will keep the patient data strictly confidential.

12.5 Confidentiality, Data Protection

The participants name or other personal identifiable data are not recorded in the CRF as well as study database. Each participant will be coded using a unique identifier (Patient-ID). The relation between Patient-IDs and personal identifiable data is recorded in a separate document which is restricted to the PI.

Direct access to source documents will be permitted for purposes of monitoring, audits and inspections (12.4)
The research team, CEC and CA will have access to the protocol.
The sponsor-investigator, PI and study coordinator will have access to the dataset, statistical code, etc. during and after the study.

13. PUBLICATION AND DISSEMINATION POLICY

The results of the analysis shall be published in a Journal with peer review dedicated to thoracic surgery and be presented to the clinical and scientific community on dedicated meetings. All publication or dissemination of data will only be done in anonymized manner.

14. FUNDING AND SUPPORT

14.1 Funding

Financial support for the trial: University Hospital Basel, Department of Thoracic Surgery and Department of Anesthesia, Surgical Intensive Care, Prehospital Emergency Medicine and Pain Therapy, University Hospital Basel.

14.2 Other Support

n/a

15. INSURANCE

Any damage developed in relation to study participation is covered by the hospital insurance. So as not to forfeit their insurance cover, the participants themselves must strictly follow the instructions of the study personnel. Participants must not be involved in any other medical treatment without permission of the principal investigator (emergency excluded). Medical emergency treatment must be reported immediately to the investigator. The investigator must also be informed instantly, in the event of health problems or other damages during or after the course of study intervention.
The investigator will allow delegates of the insurance company to have access to the source data/documents as necessary to clarify a case of damage related to study participation. All involved parties will keep the patient data strictly confidential.

16. REFERENCES

1 Branson, R. D. The scientific basis for postoperative respiratory care. *Respir Care*, 2013 Nov, 58(11); 1974-84; doi: 10.4187/respcare.02832

2 Warner, D. O. Preventing postoperative pulmonary complications: the role of the anesthesiologist. *Anesthesiology* **92**, 1467-1472 (2000).

3 Ansari, D., Gianotti, L., Schroder, J. & Andersson, R. Fast-track surgery: procedure-specific aspects and future direction. *Langenbecks Arch Surg* **398**, 29-37, doi:10.1007/s00423-012-1006-9 (2013).

4 Herroeder, S. *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, doi:10.1097/SLA.0b013e31805dac11

5 Kaba, A. *et al.* Intravenous lidocaine infusion facilitates acute rehabilitation after laparoscopic colectomy. *Anesthesiology* **106**, 11-18; discussion 15-16, doi:00000542-200701000-00007 [pii] (2007).

6 Wuethrich, P. Y., Romero, J., Burkhard, F. C. & Curatolo, M. No benefit from perioperative intravenous lidocaine in laparoscopic renal surgery: a randomised, placebo-controlled study. *Eur J Anaesthesiol* **29**, 537-543, doi:10.1097/EJA.0b013e328356bad6 (2012).

7 Martin, F. *et al.* Lack of impact of intravenous lidocaine on analgesia, functional recovery, and nociceptive pain threshold after total hip arthroplasty. *Anesthesiology*, 2008, **109**, 118-123, doi:10.1097/ALN.0b013e31817b5a9b

8 Insler, S. R., O'Connor, M., Samonte, A. F. & Bazaral, M. G. Lidocaine and the inhibition of postoperative pain in coronary artery bypass patients. *J Cardiothorac Vasc Anesth* **9**, 541-546, doi:S1053-0770(05)80138-7 [pii] (1995).

9 Striebel, H. W. & Klettke, U. [Is intravenous lidocaine infusion suitable for postoperative pain management?]. *Schmerz* **6**, 245-250, doi:10.1007/BF02527813 (1992).

10 Slovack, M., Taylor, B., Bryce, R., Ong, D. Does intravenous lidocaine infusion during video-assisted thoracoscopic surgery reduce postoperative analgesia? a randomized controlled study. *Canad. J. Anesth.* **62**, 676--677 (2015).

11 Koppert, W., Weigand, M., Neumann, F., Sittl, R., Schuettler, J., Schmelz, M., Hering, W. Perioperative intravenous lidocaine has preventive effects on postoperative pain and morphine consumption after major abdominal surgery. *Anesth. Analg.* **98**, 1050--1055 (2004).

12 AstraZeneca. Vol. S22876 (ed AstraZeneca GmbH) (Wedel, 2007).

13 Kranke, P., Jokinen, J., Pace, N. L., Schnabel, A., Hollmann, M. W., Hahnenkamp, K., Eberhart, L. H. J., Poepping, D. M., Weibel, S. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery (Review). *The Cochrane Collaboration* (2015).

14 Dai, F., Silverman, D. G., Chelly, J. E., Li, J., Belfer, I., Qin, L. Integration of pain score and morphine consumption in analgesic clinical studies. *The Journal of Pain* **14**, 767--777 (2013).

15 Blaker, H. Confidence curves and improved exact confidence intervals for discrete distributions. *Canad. J. Statist.* **28**, 783--798 (2000).

16 Melzack, R. The short-form McGill Pain Questionnaire. Pain 30 (1987) 191-197

17 Myles PS, Weitkamp B, Jones K, Melick and Hensen S. Validity an reliability of postoperative quality of recovery score: the QoR-40. Br J Anaesth 2000; 84: 11-15

18 Riker, R. R., Picard, J. T., Fraser, G. L. Prospective evaluation of the sedation agitation scale for adult critically ill patient. Crit. Care Med. 1999 Jul; 27(7):1325-9

Article information: https://dx.doi.org/10.21037/jtd-23-1438