Comparing Analgesic Efficacy of Systemic Lidocaine against Placebo in General Anesthesia in Bariatric Surgery: prospective, randomized, double-blinded, placebo controlled, monocenter study

Clinical Study Protocol

COMPARING ANALGESIC EFFICACY OF SYSTEMIC LIDOCAINE AGAINST PLACEBO IN GENERAL ANESTHESIA IN BARIATRIC SURGERY: A PROSPECTIVE, RANDOMIZED, DOUBLE-BLINDED, PLACEBO CONTROLLED, MONOCENTER STUDY
[EVALUATING ANALGESIC EFFICACY OF SYSTEMIC LIDOCAINE IN BARIATRIC SURGERY IN A PROSPECTIVE, RANDOMIZED, DOUBLE BLINDED, PLACEBO CONTROLLED STUDY]

STUDY TYPE

Prospective, randomized, double-blinded, placebo controlled

STUDY CATEGORIZATION

In this clinical trial the analgesic effect of intravenously administrated lidocaine is compared with placebo. Despite longstanding use as an antiarrhythmic agent and its use in many clinical trial as analgesic, lidocaine is not licensed for this indication and application. Therefore, the study is assigned as category B.

STUDY REGISTRATION

The study will be registered in both the national (kofam.ch) and international (clinicaltrials.gov) clinical trial databases prior to start.

SPONSOR, SPONSOR-INVESTIGATOR OR PRINCIPAL INVESTIGATOR

The Sponsor and Sponsor/Investigator is Prof. Dr. med. Miodrag Filipovic, Vice-Chairman, Klinik für Anästhesiologie, Intensiv-, Rettungs- und Schmerzmedizin, Kantonsspital St. Gallen, St. Gallen, Switzerland.

Study coordination and contact information:

Prof. Dr. med. Miodrag Filipovic, Kantonsspital St. Gallen, Klinik für Anästhesiologie, Intensiv-, Rettungs- und Schmerzmedizin, Rorschacher Strasse 95, CH-9007 St. Gallen, Switzerland

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INVESTIGATIONAL PRODUCT

Lidocaine, systemic application

PROTOCOL VERSION AND DATE

Version 2.0, 12 / 2018

CONFIDENTIAL

SIGNATURE PAGE

Study number: CTU 17/026

Study title: Comparing Analgesic Efficacy of Systemic Lidocaine against Placebo in General Anesthesia in Bariatric Surgery: prospective, randomized, double-blinded, placebo controlled, monocenter study

The Sponsor/Investigator and trial statistician have approved the protocol version 2.0, and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines if applicable and the local legally applicable requirements.

SPONSOR/INVESTIGATOR

Prof. Dr. med. Miodrag Filipovic

Kantonsspital St. Gallen

Klinik für Anästhesiologie, Intensiv-, Rettungs- und Schmerzmedizin

_____

Place/Date

_____

Signature

STATISTICIAN

Not named yet

_____

Place/Date

_____

Signature

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Study synopsis

Sponsor / Sponsor/Investigator

Prof. Dr. med. Miodrag Filipovic

Study Title

Comparing analgesic efficacy of systemic lidocaine in general anesthesia in bariatric surgery

Short Title / Study ID

Systemic lidocaine versus placebo

Protocol Version and Date

2.0, 12 / 2018

Trial registration

outstanding submission to kofam.ch

Study category and rationale

As a clinical trial, we are comparing lidocaine 1% I.V. as an additional analgesic therapy to placebo with minimal expected additional risks to the participants due to our intervention, this study is assigned to category B. Lidocaine 1% I.V. is authorized in Switzerland but not used according to the approved indication.

Clinical Phase

Phase III

Background

Postoperative pain is a common problem in today`s surgery, although pain management techniques have improved in the last years. Systemic application of lidocaine has gained interest since several studies have shown its analgesic, anti-inflammatory and anti-hyperalgesic properties. This study will be conducted to evaluate the analgesic efficacy of systemic lidocaine in addition to total intravenous anesthesia in morbidly obese patients undergoing laparoscopic bariatric surgery.

Objective

To investigate if intravenous administration of lidocaine in patients undergoing bariatric surgery reduces postoperative pain intensity within the first four hours after completion of surgery.

Hypothesis

Perioperative treatment of patients undergoing bariatric surgery with lidocaine reduces the proportion of those suffering from more intensive pain (any development of VAS/NRS score > 3, in hourly measurements*) within the first four hours from currently 65% to 35%.*

Outcome

Primary: proportion of patients suffering from higher pain intensity (any development of VAS/NRS score > 3, in hourly measurements*) within the first four hours after completion of bariatric surgery.*

Secondary: average maximal pain intensity during first four hours and during 48 hours, total opiate consumption, postoperative nausea and vomiting, time to first defecation and length of hospitalization.

Study design

Prospective, randomized, double blinded, placebo controlled trial

Inclusion / Exclusion criteria

Inclusion: elective laparoscopic bariatric surgery, ASA classification I – III, age 18 – 80, informed consent

Exclusion: no written consent, allergy to the investigational product, cardiac arrhythmia (pacemaker), liver dysfunction (Child-Pugh classification A, B or C)*, pregnancy, central nervous disease, chronic pain and pre-existing opiate prescription, expected non-compliance, drug/alcohol abuse*

Study Product / Intervention

"lidocaine group"

- *1.5 mg/kg lean body mass lidocaine (lidocaine 1%) bolus I.V. as general anesthesia steady state concentration is accomplished*
- *1.5 mg/kg lean body mass/h lidocaine I.V. with beginning of surgical procedures*
- *after completion of surgery: transfer to PACU, pain evaluation (VAS/NRS score questionnaire, see appendix for detailed questionnaire) for 48 hours, nurse –based pain treatment as appropriate*
- *duration of intervention: lidocaine infusion up to four hours from completion of surgery, or till transfer to surgical ward*

Control Intervention

"placebo group"

- *0.15 ml/kg lean body mass saline 0.9% bolus I.V. as general anesthesia steady state concentration is accomplished*
- *0.15 ml/kg lean body mass/h saline 0.9% I.V. with beginning of surgical procedure*
- *after completion of surgery: transfer to PACU, pain evaluation (VAS/NRS score questionnaire) for 48 hours, nurse –based pain treatment as appropriate*
- *duration of intervention: saline infusion up to four hours from completion of surgery, or till transfer to surgical ward*

Number of Participants

63 participants per group + 10% to account for drop-outs (sum. 140 patients),

χ^2 test (allocation of VAS/NRS score ≤ 3 to 65% of interventional group), p-value 0.05, power 90%

Study Duration

Estimated duration for the main investigational plan (from start of screening of first participant to last participant processed and finishing the study) will be approximately two years

Investigator

Prof. Dr. med. Miodrag Filipovic

Kantonsspital St. Gallen

Klinik für Anästhesiologie, Intensiv-, Rettungs- und Schmerzmedizin

Study Centre

Single center, Kantonsspital St. Gallen

Klinik für Anästhesiologie, Intensiv-, Rettungs- und Schmerzmedizin

Rorschacher Strasse 95

CH-9007 St. Gallen

Switzerland

Statistical Considerations:

Sample size of 63 subjects per group was estimated to achieve 90% power and to detect 65% redistribution of VAS/NRS score ≤ 3 in favour of the "lidocaine group".

To account for drop-outs, 140 subjects were recruited and randomized.

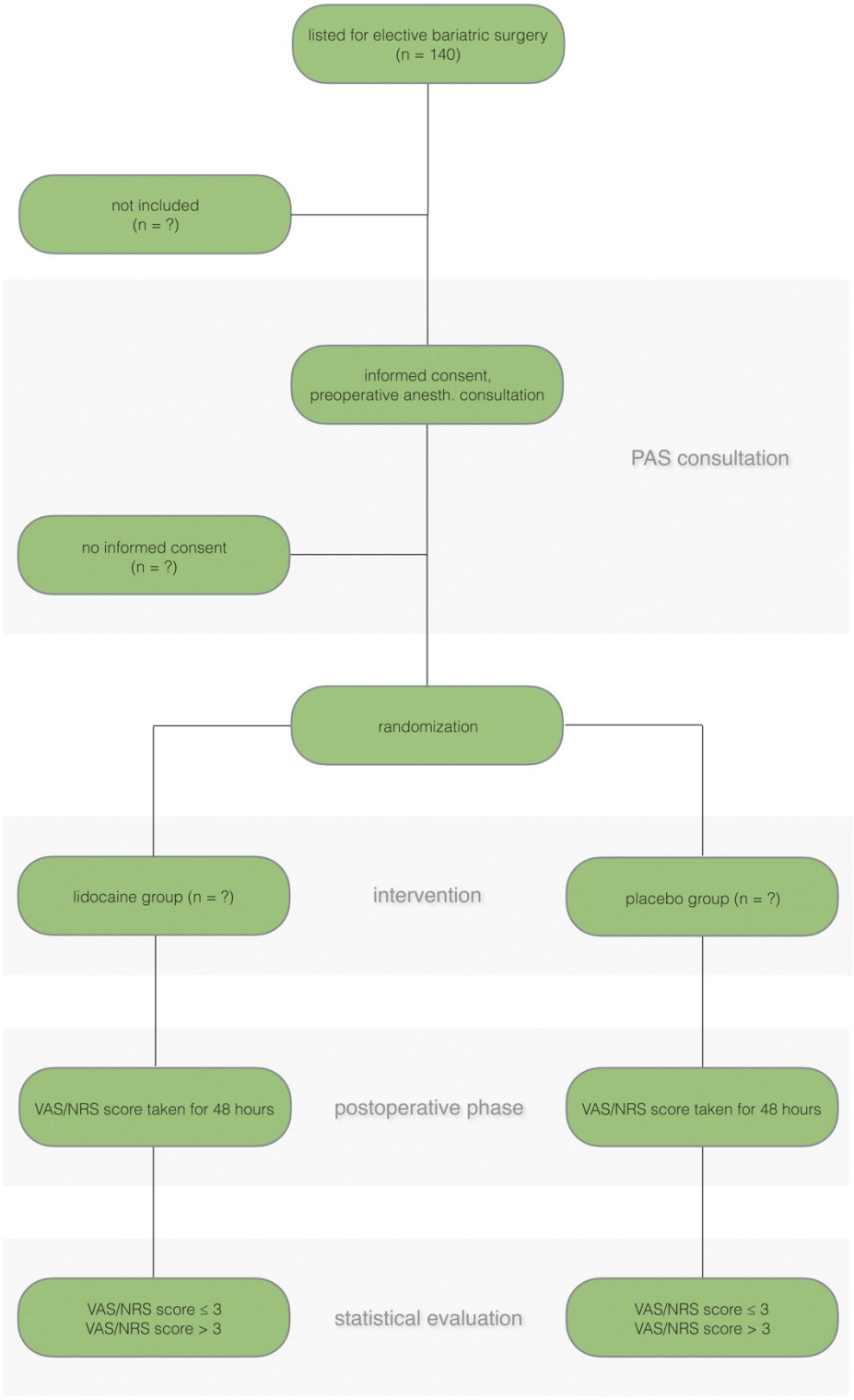
GCP Statement

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

AE Adverse Events
ASA American Society of Anesthesiologists
BMI Body Mass Index
CA Competent Authority (e.g. Swissmedic)
CEC Competent Ethics Committee
CRF Case Report Form
eCRF Electronic Case Report Form
CTCAE Common terminology criteria for adverse events
EKOS Ethikkommission Ostschweiz
GCP Good Clinical Practice
GMP Good Manufactoring Practice
HFG Humanforschungsgesetz (Law on human research)
HMG Heilmittelgesetz
HRA Federal Act on Research involving Human Beings
ICU Intensive Care Unit
IL-6 Interleukin-6
IMC Intermediate Care Unit
IMP Investigational Medicinal Product
LBM lean body mass
MD Medical Device
MEGX Monoethylglycinexylidide
NMDA N-Methyl-D-Aspartat
NRS Numeric Rating Scale
OSA obstructive sleep apnea
PACU post anesthesia care unit
PONV Postoperative Nausea and Vomiting
SAE Serious Adverse Event
SDV Source Data Verification
SIRS Systemic Inflammatory Response Syndrome
SOP Standard Operating Procedure
SPC Summary of product characteristics
SUSAR Suspected Unexpected Serious Adverse Reaction
TIVA Total Intra Venous Anesthesia
TMF Trial Master File
VAS Visualized Analogue Scale

Compendious Flow Chart



1. STUDY ADMINISTRATIVE STRUCTURE

1.1 Sponsor, Sponsor-Investigator

The Sponsor and Sponsor/Investigator is Prof. Dr. med. Miodrag Filipovic, Vice-Chairman, Klinik für Anästhesiologie, Intensiv-, Rettungs- und Schmerzmedizin, Kantonsspital St. Gallen, St. Gallen, Switzerland.

1.2 Monitoring Institution

The Monitoring Institution is the Clinical Trials Unit, Kantonsspital St. Gallen, St. Gallen, Switzerland.

1.3 Data Safety Monitoring Committee

A Data Safety Monitoring Committee will not be required.

2. ETHICAL & REGULATORY ASPECTS

2.1 Study registration

The study will be registered in both the national (kofam.ch) and international (clinicaltrials.gov) clinical trial databases prior to start.

2.2 Categorization of study

As a clinical trial, we are comparing lidocaine 1% I.V. as an additional analgesic therapy to placebo with minimal expected additional risks to the participants due to our intervention, this study falls is assigned to category B. Lidocaine 1% I.V. is authorized in Switzerland but not used according to the approved indication.

2.3 Competent Ethics Committee (CEC)

Prior to beginning the clinical study, the Principal Investigator shall ensure that approval has been obtained from the Competent Ethics Committee (Ethikkommission Ostschweiz (EKOS)). All significant changes in the conduct of the study and any unanticipated problems posting risks to the participants shall be reported to the CEC. Interruption or premature termination of the study shall be reported within 15 days to the CEC. The regular end of the study shall reported within 90 days, with submission of the final study report within one year after study end.

2.4 Competent Authorities (CA)

The trial was categorized as “Category B Clinical Trial”, being a trial evaluating a therapeutic product, which is authorized in Switzerland but not used according to the approved indication. Therefore, the trial requires an authorization from a Competent Authority (Swissmedic). The study will begin once approval from required authorities has been received.

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 anual safety and interim reports and be informed about study stop/end in agreement with local requirements.

2.6 Declaration of interest

None of the involved parties have any relevant conflicts of interest to disclose.

2.7 Patient Information and Informed Consent

The investigators will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits, any discomfort it may entail and grant enough time for consideration. Each participant will 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 assistance and treatment. The participant must be informed that his/her medical records may be examined by authorised individuals other than their treating physician.

All participants for the study will be provided a participant information sheet and a consent form describing the study and providing sufficient information for participant to make an informed decision about their participation in the study.

The patient information sheet and the consent form will be submitted to the CEC and to the competent authority to be reviewed and approved. The formal consent of a participant, using the approved consent form, must be obtained before the 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 and it will be retained as part of the study records.

Please refer to appendix for a copy of the Patient Information Brochure.

2.8 Participant privacy and confidentiality

The Investigator affirms and upholds the principle of the participants' 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 utilizing subject identification code numbers to correspond to treatment data in the computer files.

For data verification purposes, authorized 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,
- safety issues,
- alterations in accepted clinical practice, making the continuation of a clinical trial unwise
- early, strong evidence of benefit or harm of the experimental intervention

2.10 Protocol amendments

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 & RATIONALE

3.1 Investigational product - Lidocaine

The systemic application of lidocaine and other local anesthetics has been restricted to a few indications for a long time, for example the treatment of cardiac arrhythmias (1,12). For several years, systemic use of local anesthetics experiences a revitalization due to their approved and beneficial effects in daily routine of anesthesiology and treatment of chronic pain (2 - 4). Primarily, lidocaine has been known for its blocking effect on voltage-gated sodium channels and the associated inhibition of neuronal transmission, basis for anti-arrhythmic and anti-nociceptive properties (5 - 9). Furthermore, it shows so-called alternative effects, which require considerably lower dosage as the mentioned effect on voltage gated sodium channels (10, 11). These specific drug concentrations can be found in patients` blood after receiving either an epidural injection or systemic application of lidocaine (3, 13, 14). Anti-hyperalgesic, anti-inflammatory properties and the reduction of bronchial hyperactivity are among these alternative effects (15 - 19). In addition, perioperative hypercoaguability seems to be reduced (20). Most of these qualities apply for all local anesthetics, but have just been suitable for lidocaine in clinical practice due to its advantageous features and the well reviewed potential of side effects during the treatment of cardiac arrhythmias (21, 22, 52). Anti-nociceptive and anti-hyperalgesic properties might be a result of G-protein receptor modification, as well as an interaction with glyceinergic synaptic neurons and an inhibition of NMDA receptors. This might also be an explanation for the influence on inflammatoric and hemostatic mediators (6, 23, 24). Lidocaine conducts a modification of an excessive inflammatory response due to surgical intervention and hereby induced postoperative complications as suppressed gastrointestinal function, pain and sepsis (25 - 27). Careful titration allows a high degree of selectivity in the inhibition of sensory neurons, in contrary to higher concentrations, which also affect other modalities of neuronal signaling. The same principle applies for cardiac actions. Blocking sodium channels in the conduction system, as well as the muscle cells of the heart, raises the depolarization threshold, making the heart less likely sensitive to initiate or conduct early action potentials that may cause an arrhythmia. When used as an injectable, it typically initiates its effect within four minutes and lasts for 30 minutes to three hours. Lidocaine is metabolized by hepatic cells to 95% mainly by cytochrome P450 3A4 to the pharmacologically active metabolites monoethyl-

glycinexylidide (MEGX) and then subsequently to the inactive glycine xylidide. MEGX has a longer half-life than lidocaine, but also is a less potent sodium channel blocker. (47 - 49) Lidocaine elimination in patients with liver cirrhosis was examined by Wojcicki et al.. Their findings indicated higher plasma concentrations of lidocaine and lower concentration of MEGX, dependent on the stage of liver dysfunction (Child-Pugh A to C). (57) Current studies, setting the focus on abdominal surgery, indicated that the systemic application of lidocaine was associated with fewer intensity of pain at rest and during mobilization and resulted in a decrease of patients' opiate consumption. Studies evaluating patients receiving orthopedic and neurosurgical interventions did not show any benefit from lidocaine I.V. (28 - 30). This discrepancy is most likely explained by the different development of inflammation due to visceral and somatic pain induction. Noteworthy is the fact, that local anesthetics can suppress the overreacting immune-signaling due to surgical intervention, without interfering with the physiological immune-signaling. Studies showed an inhibition of white blood cells' priming (as a principle for immune-reaction, the prearrangement of granulocytes to a following inducing signal leads to a up to 20-times exaggerated release of superoxides) due to the implementation of systemic lidocaine. Interestingly, lidocaine impedes the priming, which represents a common reaction to tissue damage induced by surgery, without inhibiting the classic activation of neutrophil granulocytes. (31) A major reason for patients' discomfort, prolonged recovery, length of hospital stay and thereby resulting, higher morbidity and increased financial costs, are post-surgical complications, especially gastrointestinal dysfunction and postoperative nausea and vomiting (PONV) due to surgical inflammation and increased opiate consumption. Average incidence of PONV after abdominal surgery in general anesthesia ranges between 25 – 30%. Pathogenic mechanisms are complex but are traced back to the nerval and inflammatory response and stimulation after surgical interventions. A study by Groudine et al. showed that patients receiving systemic lidocaine during radical prostatectomy regained gastrointestinal motility faster and required less opiates after the intervention compared to an application of placebo during surgery. (32, 33) However, lidocaine seems to be profitable to patients undergoing abdominal surgery as meta analyses demonstrate. Inhibition of myenteric plexus reflex as a target might play a role in the effectiveness of systemically administered lidocaine, as well as a reduction of interleukin-6 (IL-6) which could be significantly reduced in a study examining patients receiving systemic lidocaine during colorectal surgery (32, 34).

3.2 Data currently available

A meta-analysis by Weibel et al. has investigated 45 studies related to the preoperative application of lidocaine referring to a reduction of postoperative pain, early regaining of gastrointestinal motility, length of hospital stay, development of PONV, total opiate consumption, surgical complications and occurrence of adverse effects due to intervention. Most studies compared lidocaine with a placebo, two studies compared the systemic application with epidural analgesia. Findings show that lidocaine was capable to reduce postoperative pain within the first four hours after surgery compared with placebo. However, there was no evidence for reduction of postoperative pain for the time beyond. The positive effect of lidocaine on postoperative pain was just verified in patients receiving major or laparoscopic bowel surgery. Considering that lidocaine had positive effects on regaining gastrointestinal function, length of hospital stay, development of PONV and total opiate consumption in these patients. However, data is lacking for patients with high need for opiates, as commonly seen in bariatric surgery. The occurence of adverse effects was examined in 17 studies, but there was no evidence of higher risk for lidocaine intoxication, cardiac arrhythmias or death. (41) Another meta-analysis from McCarthy et al. also showed a reduction of postoperative pain and total opiate consumption in patients receiving major bowel surgery. Compared to control groups, participants receiving systemic lidocaine required up to 85% less opiates. Positive effects on gastrointestinal function and length of hospital stay could also be confirmed. De Oliveira et al. examined the effects of systemic lidocaine compared to placebo, laying their focus on patients scheduled for bariatric surgery. They also confirmed opiate sparing effects and a higher level of satisfaction after 24 hours of patients treated with lidocaine, however no other study focused on this kind of patient collective. (50) In summary, the systemic application of lidocaine as an additional analgesia is a safe and meanwhile an approved method, also implemented in the perioperative setting of abdominal, thoracic and orthopedic surgery at the Kantonsspital St. Gallen. (3) Although several studies suggested a beneficial outcome for patients treated with systemic lidocaine in major bowel surgery, just few compared its efficacy to an epidural analgesia (EDA). Staikou et al. examined postoperative pain levels, length of hospitalization and gastrointestinal function of patients undergoing large bowel surgery and either treated with systemic lidocaine or EDA and showed that patients treated with lidocaine were not inferior to the analgesic effect of EDA. (35, 36)

3.3 Dose Rationale

Though varying dosages are described in current studies, updated literature recommends a bolus of 1.5 mg/kg bodyweight lidocaine 1% for induction of anesthesia followed by a continuous infusion with 1.5 mg/kg bodyweight/h until transfer to the PACU. Determination of dose adjustment in obese patients has been described in literature by Janmahasatian et al. Total bodyweight or BMI measurement will not give reliable information about biological activity and metabolism. Therefore, an approach to measure body composition via lean body mass (LBM) function has been recommended. (58) Based on these recommendations, dosage of lidocaine in our study will be determined via scaled LBM, assuming a standard patient with 70 kg weight and 170 cm height. A detailed version of the calculator can be found in the appendix. Furthermore, originally indicated for treatment of major arrhythmias and status epilepticus, the use of systemic lidocaine 1% I.V. is authorized in Switzerland but not used according to the approved indication. (10, 37 - 40, 52)

3.4 Explanation for choice of placebo

A placebo, a pharmaceutically inert agent, will be used to detect and prove superiority of a new treatment, i.e. investigation of additional analgesic agents in opposition to no additional treatment. A placebo-controlled trial is regarded as the gold standard to detect efficacy of a new treatment. Participants of the study will be fully informed of the risks involved in assignment to the placebo group, though management in the placebo group equals our current clinical routine and no standard treatment will be withheld from this group of patients. This is specifically true for the analgesic regime. The agent used as placebo will be saline 0.9% as an injectible. Adverse effects due to rapid infusion can be neglected, as participants will receive minor volumes of saline 0.9%. Further information about saline 0.9% will be provided in the summary of product characteristics in the appendix.

3.5 Risks and Benefits

Just a few studies described the occurrence of adverse effects in patients treated with systemic lidocaine. A recently published work showed a comparable incidence of adverse effects in patients treated with systemic lidocaine versus treatment with placebo. (51) Historically, treatment of cardiac dysrhythmias after myocardial infarction was per-

formed with lidocaine I.V. and studies described minor side effects like dizziness and „ear ringing“ after continuous infusion of 2 up to 6 mg/min lidocaine 2%. (52) Anyway, indication for systemic lidocaine needs to be strictly evaluated and, according to patients` risk potential for advert effects thoroughly selected. Contraindications for the application of systemic lidocaine comprise identified allergies to local anesthetics, a reduction in hepatic function as well as serious cardiac arrhythmias. First signs of intoxication occur after reaching plasma levels of 5 µg/ml and more. Based on their effect on voltage gated sodium channels, neurological and central nervous stimulation become apparent, followed by inotropic and bathmotropic effect-related cardiac failure. (42, 43) Based on anti-inflammatory effects, a higher susceptibility to infection has been discussed and has been confirmed in small investigations with rats. However, most studies showed a sufficient function of leucocytes and furthermore postulated anti-bacterial properties in vitro and in vivo. (44 - 46) Further information about expectation of adverse effects and safety reference information can be found in the prescribing information for lidocaine 1%, provided by Streuli Pharma. Obesity is a major factor for postoperative respiratory complications, especially in patients with confirmed or suspected obstructive sleep apnea (OSA). Increased risk of perioperative morbidity and mortality developes because of potential difficulty in maintaining patients` airway. Aggravation of OSA due to sedation, analgesia or extended effects and accumulation of narcotic agents, especially opiates, has been described. (53) Generally, regional analgesic techniques, like epidural analgesia should be considered to reduce or eliminate the requirement for systemic opiates, however difficulties in location and correct placement of epidural catheters can occure due to impeded anatomical proportions in obese patients. Practice guidelines for the management of patients with OSA, have been published by the American Society of Anesthesiologists, recommending well-considered use of sedatives and opiates for the peri- and postoperative course in this group of patients. (54) The application of lidocaine as an additional analgesia during bariatric surgery gives hope to reduce the before mentioned complications and adverse effects due to increased opiate consumption, to assure a postoperative phase more comfortable and less branded by side effects for the patient. Therefore, the study was designed to investigate if the proportion of patients suffering from higher pain intensity (any development of VAS/NRS score > 3, in hourly measurements) within first four hours after bariatric surgery can be reduced by preoperative lidocaine infusion. Secondary endpoints will include the total opiate consumption of patients,

occurence of adverse effects due to opiates, time to first defecation and total length of hospitalization.

3.6 Standardized procedures

Since our institute cares for anesthesia in up to 150 patients per year in bariatric surgery, we want to optimize the outcome and postoperative analgesia for patients and guarantee a phase free of pain and other complications. The intervention is usually proceeded laparoscopically, with an average length of 120 minutes. Overweight patients with a mean BMI of 38 points, receive general anesthesia (TIVA and initial fentanyl application of 0.6 - 1.0 mg I.V.). After completion of surgery, patients are transferred to PACU for further observation and treatment. Emphasizing, these patients require almost double amount of opiates in the perioperative setting, than patients receiving laparoscopic appendectomy or hemicolectomy, as well as during the postoperative phase. The adverse effects of an increased opiate consumption like nausea, vomiting, hypopnea, pruritus and reduced gastrointestinal function are commonly aggravating the symptoms of pre-existing diseases like sleep apnea syndrome, reduced functional residual capacity, due to higher intraabdominal mass and thereby caused dyspnoea. Based on increased pain levels, these patients receive up to 1.0 mg fentanyl during the first four hours after completion of surgery to cope with pain. Additionally, PONV, induced by opiates, presents a major discomfort for these patients.

4. STUDY OBJECTIVES

4.1 Primary study objective

To investigate if intravenous administration of lidocaine 1% I.V. in patients undergoing bariatric surgery reduces postoperative pain intensity within the first four hours after completion of surgery.

4.2 Secondary study objective

To investigate if the experienced average maximal pain intensity and the total opiate consumption of patients who underwent bariatric surgery can be reduced during the first four hours and 48 hours by perioperative lidocaine infusion.

4.3 Other objectives of interest

Other objectives of interest are as follows:

- Monitoring of PONV and its distribution between the groups.

- Comparing time to first defecation after completion of surgery in both groups in regard of a beneficial effect in the “lidocaine group”.

- Comparing length of hospitalization of both groups in regard of a beneficial effect in the “lidocaine group”.

5. STUDY OUTCOMES

5.1 Primary outcome

Any development of VAS/NRS score > 3, in hourly measurements within the first four hours after completion of bariatric surgery.

5.2 Secondary outcome

Average experienced maximal pain during the first four hours and 48 hours (in hourly measurements on PACU and in eight-hourly measurements on surgical ward) is assessed by VAS/NRS score. The total amount of opiates (given during surgery and on PACU and administrated on surgical ward).

5.3 Other outcomes of interest

- any event of postoperative nausea and vomiting (subdivided by event of no nausea (PONV = 0), event of nausea without vomiting (PONV = 1) and event of nausea with vomiting (PONV = 2)) during first 48 hours after completion of surgery

- time to first defecation (quantified in hours)

- duration of hospitalization (quantified in days)

5.4 Safety outcomes

Vital parameters (blood pressure, pulse rate, oxygen saturation) will be recorded digitally by the electronic acute care patient data management system (ACPDMS) during the peri- and postoperative phase and according to institutional standards. Incidence of any potential adverse events (AE) requiring treatment attributable to lidocaine (e.g. local skin reactions, nausea, vomiting, dizziness, ear ringing, etc.), serious adverse events (SAE) (cardiac arrhythmia with relevant hemodynamic outcome, cardiac arrest) or adverse

events related to opiates (respiratory adverse events, ileus). Other outcomes of interest, precisely PONV will not be accounted for an AE.

6. STUDY DESIGN

6.1 General study design and justification of design

The study design will be randomized, double blinded and placebo controlled. All patients complying our inclusion criteria will be included to the selection procedure. Patients will be informed about the study sequence during preoperative anesthesiological consultation to give their informed consent. Patients` data will be subsequently integrated to the eCRF. Each participant will be linked with a unique identification code which will be used for continuing process. Furthermore, information about sex, date of birth, date of surgery, indication, BMI, ASA classification, medical history and allergies will be recorded. Patients denying informed consent will be excluded from the pool of selected patients.

The intervention to be studied will either be the additional application of systemic lidocaine 1% dosed 1.5 ml/kg LBM to general anesthesia in bariatric surgery or the application of placebo. Patients, randomly assigned to one study group, will be surveyed for 48 hours after completion of surgery, experienced pain, occurrence of PONV, time to first defecation and length of hospitalization will be monitored. The population to be studied will include 140 patients listed for bariatric surgery at the Kantonsspital St. Gallen and fulfilling criteria for inclusion, respectively without criteria for exclusion. Patients, medical practitioner, nurses and investigators will be blinded by utilization of equal appearance and packing of IMPs, which will be fabricated individually for each patient and on request one to two days before surgery by the pharmacy of the Kantonsspital St. Gallen. Each patient will self-evaluate his maximal experienced pain eight-hourly during a sequence of 48 hours after completion of surgery. Study observation ends with study nurses` final visit on second postoperative day 2pm respectively +/- 30 minutes.

6.2 Methods of minimizing bias

Measures taken to minimize or avoid bias include randomization and blinding of participants after they have given their informed consent. Blinding of medical practitioner and medical personel will be conducted by provision of equal looking and packing of IMPs,

which will be fabricated individually for each patient and on request one to two days before surgery by the pharmacy of the Kantonsspital St. Gallen.

6.3 Randomization

Patients selected to participate will be randomized automatically after giving their informed consent using a computerized block randomization process (10 patients per block). Patients will be randomized 1:1 to either “lidocaine group” or “placebo group”.

6.4 Blinding procedures

All patients will be blinded to their randomization. Attending physician and other personnel responsible for patients` care (peri- and postoperative) will be blinded. Syringes used for application of interventional drugs will be blinded, labelled as “interventional drug”. Unblinding, in case of SAE or suspected unexpected serious adverse reactions and to guarantee patients safety, will be executed by the Principal Investigator.

6.5 Unblinding procedures

Should it be necessary to unblind a patient for safety or regulatory reasons, the Principal Investigator shall look up the randomization, which will be kept in a separate envelope, containing information about randomization and leads back to specific IMP of each participant of the study.

7. STUDY POPULATION

7.1 Inclusion

Adult patients listed for elective laparoscopic bariatric surgery, age between 18 – 80 will be screened for inclusion.

7.2 Exclusion

The presence of any of the following exclusion criteria will lead to exclusion of the participant:

- Patients without informed consent, contraindication to the class of drugs under study, e.g. known hypersensitivity or allergy to class of drugs or the investigational product, cardiac arrhythmias, liver dysfunction (Child-Pugh classification A, B or C)

- Women who are pregnant or breast feeding
- Patients suffering from central nervous diseases, which affect structure and function of the brain or the spinal cord (including autism, bipolar disorders, catalepsy, depression, encephalitis, epilepsy, locked-in syndromes, meningitis, multiple sclerosis, myelopathy Tourette's syndrom and neurodegenerative disorders like Alzheimer's disease, Huntington's disease and Parkinson's disease)
- Chronic pain with pre-existing enteral or transdermal opiate prescription or any known drug or alcohol abuse.
- Patients with previous enrolment into the current study, enrolment of the investigator, his/her family members, employees and other dependent persons will be excluded from the screening

7.3 Recruitment and informed consent

Patients' recruitment will take place during preoperative anesthesiological consultation, which regularly takes place two to three weeks prior hospitalization. Patients will be screened for eligibility using a checklist based on inclusion and exclusion criteria and previous medical history. Informed consent will be obtained in all patients prior to inclusion to the study and randomization process. Patients denying inclusion to the study will be documented as having been screened.

7.4 Assignment to study groups

Patients given their informed consent will be randomly assigned to either the "lidocaine group" or the "placebo group". Randomization will be conducted by the statistician of the study using a computerized block randomization process (10 patients per block). Patients will be randomized 1:1 to either "lidocaine group" or "placebo group".

7.5 Criteria for withdrawal / discontinuation of participants

The criteria for withdrawal of participants are either the request of participants to be withdrawn from the study or SAE, related to exercise of IMPs or other medication aplli-cated during general anesthesia, including signs of cardiac arrhythmia or other evidence of drug incompatibility resulting in hemodynamic instability.

8. STUDY INTERVENTION

8.1 General information

Patients will randomly be allocated either to the “lidocaine group“, or the “placebo group”. The only difference between both groups will be the implementation of a systemic lidocaine infusion during perioperative phase. Allover management and techniques of anesthesia will be handled as described in the current “Standard Anaesthesie KSSG”. It includes detailed description of anesthesiological procedures for specific surgical interventions. Patients listed for bariatric surgery receive detailed information about anesthesiological techniques, course and management of adverse effects due to medical side effects or surgical complications during the preoperative anesthesiological consultation. On the day of surgery, the patient will receive premedication of 1 mg paracetamol p.o. one hour before planned intervention. Apart from the study intervention, standard anesthetic technique and pain management (related to practice of the anesthesiological standard of the Kantonsspital St. Gallen will be used in all the patients at the discretion of the attending anesthesiologist (use of alternative aminoamid local anesthetics, as additional analgesic will be prohibited during treatment and hospitalization of patients included to the study). After securing intravenous line, monitoring will be installed. Baseline parameters will be observed and recorded in the ACPDMS. Fentanyl (≈ 0.002 … 0.003 mg/kg) will be given intravenously two minutes before the induction of anesthesia in both groups. Airway management in patients with a mean BMI > 35 kg/cm^2 is performed by fiberoptic nasal intubation in awake condition. Nasal drops (0.25 ml cocainhydrochloride 10%) will be applicated and transcricoidal application of 2 ml lidocaine 1% for anesthesia of the upper airway will be performed before advancing the fiberscope into the trachea. As soon as vocal cords are crossed, induction of general anesthesia will be induced with etomidate 0.2 mg/kg bodyweight. Thereafter the nasotracheal tube is placed. Anesthesia will be maintained by target controlled infusion of propofol 1% and remifentanil 40 µg/ml according to institutional standards in all patients. Neuromuscular blockade will be achieved by bolus followed by continuous administration of rocuronium as clinically necessary.

Study intervention: Patients in the “lidocaine group” will receive 1.5 mg/kg lean body mass of lidocaine 1% bolus intravenously after induction of general anesthesia (as soon

as general anesthesia's steady state is accomplished), followed by a continuous infusion of lidocaine 1% with 1.5 mg/kg lean body mass/h during surgery and continued for four hours after completion of surgery or until the discharge from the PACU, whatever comes first. Patients in "placebo group" will receive 0.15 ml/kg lean body mass of saline 0.9% bolus I.V. after induction of general anesthesia (as soon as general anesthesia's steady state is accomplished), followed by continuous infusion of NaCl 0.9% I.V. with 0.15 ml/kg lean body mass/h during surgery and continued for four hours after completion of surgery or until the discharge from the PACU, whatever comes first. Maintenance of general anesthesia and optional application of additional opiates for pain treatment (fentanyl 0.1 - 0.2 mg as an intravenous bolus) during surgery is under discretion of the attending anesthesiologist and is related to the practice of standardized pain management and will be equal in both groups. Similarly, postoperative treatment in the PACU and further on the surgical ward, are under discretion of the clinically responsible physicians, relating to current practice of standardized pain management at the Kantonsspital St. Gallen (Schmerzkarte KSSG).

A detailed graphical version of study sequences is provided in german as follows:

Periode		Ort	Intervention		Details
Anmeldung		Studien-koordination	Screening		Ein- / Ausschlusskriterien evaluieren
			I		
			erfüllt		
			I		
PAS Termin		PAS	Informed consent		Aufklärung und Einwilligung durch Patienten
			I		
			erfüllt		
			I		
PAS Termin		PAS	Randomisierung		Zuteilung zur Gruppe Lidocain oder Placebo
			I		
OP Datum		OPS 03	Intervention COALAS		- IMP Bolus ab AN steady state - anschliessend Beginn IMP Perfusor - Datenerfassung ACPDMS (Medis, Vitalparameter) - AE, SAE, ADR erfassen
			Transfer		
POD 0		PACU	VAS Monitoring VAS Evaluationsbogen		- IMP Perfusor bis 4 Std. ab "OP-Ende" od. Transfer auf Abteilung - VAS 1.,2.,3.,4. Std. - Datenerfassung ACPDMS (Medis, Vitalparameter) - Prim./Sek. Variablen im CRF erfassen - AE, SAE, ADR erfassen
			Transfer		
POD 0		ABTEILUNG	VAS Monitoring 2pm, 10pm Studienvisite 10am, 2pm		- Erinnerung des Pat. durch Pflege- Studienpersonal - Prim./Sek. Variablen im CRF erfassen - AE, SAE, ADR erfassen
POD 1		ABTEILUNG	VAS Monitoring 6am, 2pm, 10pm Studienvisite 10am, 2pm		- Erinnerung des Pat. durch Pflege- Studienpersonal - Prim./Sek. Variablen im CRF erfassen - AE, SAE, ADR erfassen
POD 2		ABTEILUNG	VAS Monitoring 6am, 2pm Studienvisite 10am, 2pm (Safety follow-up)		- Erinnerung des Pat. durch Pflege- Studienpersonal - Prim./Sek. Variablen im CRF erfassen - AE, SAE, ADR erfassen
POD X		Studien-koordination	Safety follow-up		- telefonisch / ambulant - AE, SAE, ADR erfassen

table 2: study sequence describing process and daily course, POD X will be postoperative day seven or day of patients discharge

8.2 Identity of Investigational Products

Lidocaine hydrochloride 1% by Streuli Pharma is a sterile, nonpyrogenic solution of lidocaine hydrochloride in water for injection for parenteral administration. Dosage of 1.5 mg/kg LBM will be calculated individually. Injection of 1.5 mg/kg LBM bolus will be performed as soon as steady state concentration of general anesthesia is accomplished. Steady infusion of lidocaine 1.5 mg/kg/h LBM will be initiated with the beginning of surgical procedures and estimated duration of infusion will be four hours after completion of surgery (expecting an average of two hours of surgery and four hours monitorization in PACU till transfer to surgical ward). Dosage and average duration of application represents references in current literature.

Additional IMP in placebo group will contain saline (Natrii chloridum 0.9%), which will be provided by Grosse Apotheke Dr. G. Bichsel AG. Dosage of 0.15 ml/kg LBM will be calculated individually and represents an equivalent amount (in ml) of IMP used in the interventional group. Injection of 0.15 ml/kg LBM bolus will be performed as soon as steady state concentration of general anesthesia is accomplished. Steady infusion of NaCl 0.9% 0.15 ml/kg/h LBM will be initiated with the beginning of surgical procedures and estimated duration of infusion will be four hours after completion of surgery (expecting an average of two hours of surgery and four hours monitorization in PACU till transfer to surgical ward).

8.3 Packaging, Labelling and Supply

Lidocaini hydrochloridum (Lidocaine Streuli®) will be provided by Streuli Pharma AG, Switzerland (Swissmedic registration number: 300 16).

Saline (Natrii chloridum 0.9%) will be provided by Grosse Apotheke Dr. G. Bichsel AG, Switzerland (Swissmedic registration number: 298 00).

Syringes and ampulles containing the IMPs (Lidocaine 1% or Saline 0.9%) used during the study will be labelled notably. Distinct labels for ampulles and syringes include information about IMPs`origin, charge number, dedicated patient`s ID, fabrication and expiration date (see appendix for a detailed graph of IMP labels). Blinded personel (practitioner, nurses, surgeon, etc.) will not be able to distinguish between the containing IMPs

due to identical appearance and labeling. An additional code to reproduce its origin will also be visible. No special storage conditions are needed for the IMPs. Prepackaging, assembly, blinding procedure and labeling of syringes will be organized by the pharmacy of the Kantonsspital St. Gallen. Personel related to the peri- and postoperative course (anesthesiology, surgery, PACU, follow-up on surgical ward) will be blinded by the above-mentioned methods. Study specific labeled syringes will be fabricated individually for each patient and on request one to two days before surgery and will be delivered to the OR on the day of surgery and preparation of syringes (connection to syringe pump) will be conducted by anesthesiological employees.

To ensure product safety for human consumption/application, Good Manufactoring Practice will be conducted.

8.4 Administration of experimental and control interventions

Experimental Intervention („lidocaine group“)

Lidocaine 1% will be administered I.V., 1.5 mg/kg lean body mass will be given as bolus when general anesthesia steady state concentration is accomplished, 1.5 mg/kg lean body mass/h will be given as continuous infusion with beginning of surgical procedures and up to four hours from completion of surgery, or till transfer to surgical ward.

Control Intervention (“placebo group”)

The management of patients in the placebo group equals our current clinical routine and no standard treatment is withheld from this group of patients. This is specifically true for the analgesic regime.

Saline 0.9% will be administered I.V., 0.15 ml/kg lean body mass will be given as bolus when general anesthesia steady state concentration is accomplished, 0.15 ml/kg lean body mass/h will be given as continuous infusion with beginning of surgical procedures and up to four hours from completion of surgery, or till transfer to surgical ward.

8.5 Dose modifications

If SAE will be recognized, infusion of investigational product will be stopped and arrangements conducted to treat potential adverse effects and ensure patients` safety. The Principal Investigator will be informed about the incident within 24 hours.

8.6 Compliance with study intervention

Patients will be informed during preoperative anesthesiological consultation and give their informed consent. Patients denying informed consent will be excluded from the pool of selected patients. During consultation, patients will be informed about general study sequences, process of drug administration, differences between the interventional and placebo group and the postoperative sequence. The detailed version of patients' information is given in the appendix. In addition, general information about risk of anesthesia and perioperative adverse events are explained during the pre-anaesthesia visit and are part of the "Consent to Anaesthesia" ("Patienteneinwilligung") according to institutional practice.

8.7 Trial specific preventive measures

Apart from the study intervention, standard anesthetic technique will be used in all patients at the discretion of the attending anesthesiologist. Medication and treatment plans which are permitted before and/or during the trial include the medication and treatment plans listed in the „Kantonsspital St. Gallen – Standard Anästhesie". Equipment and medication for resuscitation and treatment of adverse events occurring during and after anaesthetic procedures are available in all operation theatres, the PACU and intensive care unit according to institutional standards. In addition, trained personal is continuous available in these locations. Accordingly, no study specific measures are necessary. Vital parameters (blood pressure, pulse rate, oxygen saturation) will be recorded and possible deviations resulting in clinical relevant consequences treated immediately by attending anesthesiologist. Incidence of any potential AE, SAE due to application of IMPs will be documented and treated (e.g. local skin reactions, nausea, vomiting, dizziness, ear ringing, cardiac arrhythmia with relevant hemodynamic outcome or cardiac arrest) or adverse events related to opiates (e.g. hypoventilation).

8.8 Concomitant Interventions (treatments)

Apart from the study intervention, standard anesthetic technique and perioperative medication will be used in all the patients at the discretion of the attending anesthesiologist. Accordingly, different treatment options and drugs are allowed. These include current medical treatment options applied by the Kantonsspital St. Gallen. Patients will be in-

formed about treatment options during preoperative anesthesiological visit. Induction of anesthesia will be performed in line with the „Standard Anästhesie“ of the Kantonsspital St. Gallen. These treatments will have no impact on the effect of the IMPs. Postoperative pain management will be performed according to current clinical standards (Schmerzkarte KSSG).

8.9 IMPs / Medical Device Accountability

IMP Lidocaine will be provided by Streuli Pharma AG, Switzerland and IMP saline will be provided by Grosse Apotheke Dr. G. Bichsel AG, Switzerland. Storage and distribution will be organized by the pharmacy of the Kantonsspital St. Gallen, as well as prepackaging, assembly, blinding procedure and labeling. Adequate records about maintenance, shipment to the site, return or disposal of remaining or expired IMPs, physical location, dates of receipt, expiry, use and return, stock numbers and quantities received, used or destroyed will be recorded, referring to GMP. The pharmacy of the Kantonsspital St. Gallen is certified with the cantonal approval of manufacturing (kantonale Herstellungsbewilligung).

9. STUDY ASSESSMENTS

9.1 Study flow charts / table of study procedures and assessments

Please refer to appendix for a detailed graph of the study procedures and assessment plans.

9.2 Assessments of outcomes

Assessment of Pain

Pain will be assessed by the visual analogue scale (VAS) or the numeric rating scale (NRS), respectively, 0 indicating no pain and 10 maximal possible pain sensation. VAS/NRS scoring systems are validated and frequently used methods to evaluate variations in pain intensity. The VAS/NRS score will be recorded by trained nurse practitioners in the PACU, respectively on the surgical ward, once per hour during the first four hours after completion of surgery. Analysis of the primary outcome (any development of

VAS/NRS score > 3, in hourly measurements within the first four hours after completion of surgery) will be dichotomized accordingly. Thereafter, VAS/NRS score will be assessed by a patient questionnaire for self-evaluation and in addition by trained nurse practitioners during their daily round (10am and 2pm respectively +/- 30 minutes) during the first 48 hours after completion of surgery. Missing postoperative VAS/NRS scores, required for primary and secondary endpoints, will be handled as interpolation values, calculating an average score between last recorded scores before and after the missing value.

Secondary endpoints

- Average maximal pain intensity during first four hours and during 48 hours
- total amount of opiates as documented in the electronical anesthesia records during surgery and on PACU
- total amount of opiates applicated on surgical ward, recorded in the charts. Values will be categorized in total amount in mg, average amount in mg/h and indexed amount in mg/kg bodyweight/h
- any event of postoperative nausea and vomiting (subdivided by event of no nausea (PONV = 0), event of nausea without vomiting (PONV = 1) and event of nausea with vomiting (PONV = 2)) during first 48 hours after completion of surgery
- time to first defecation after completion of surgery (quantified in hours)
- total time spent in hospital after completion of surgery (quantified in days)

9.3 Assessments of safety outcomes

Vital parameters (blood pressure, pulse rate, oxygen saturation) will be recorded digitally by the electronic acute care patient data management system (ACPDMS) during the peri- and postoperative phase and according to institutional standards.. During the entire surgical and anaesthetic procedure and in the PACU trained personnel will be present monitoring vital parameters and the patient clinical status. Every deviation to normal course will be treated and recorded according clinical standards of the institution. SAE related to the administration of the IMP will cause an immediate cessation of the drug administration and will be reported to the Sponsor Investigator not later than 24 hours after the event.

9.4 Procedures at each visit

Each patient will be visited after surgical treatment and transfer to PACU/ICU by a study nurse or the Study Investigator. The VAS/NRS score (registration of any development of VAS/NRS score > 3) will be assessed by trained nurse practitioners in the PACU/ICU in hourly measurements during the first four hours after completion of surgery, respectively until discharge to the surgical ward. Thereafter, VAS/NRS score will be assessed by a patient questionnaire for self-evaluation and in addition by trained nurse practitioners during their daily round (10am and 2pm respectively +/- 30 minutes) during the first four hours and during 48 hours after completion of surgery. VAS/NRS scores and vital parameters will be recorded. Incidental questions about upcoming study process will be answered. Infusion of the investigational product will be stopped four hours after the end of surgery (or before the transfer of the patient from the PACU to the surgical ward, whichever occurs first). Pain evaluation will take place every eight hours by recording the maximum VAS/NRS score experienced within this period. Recording of VAS/NRS scores will be stopped at 2pm respectively +/- 30 minutes on second postoperative day. Completion of study investigation will be finalized by collecting the study documents at study nurses final visit on second postoperative day at 2pm respectively +/- 30 minutes.

10. STATISTICAL METHODS

10.1 Statistical considerations

Determination of sample size was performed by retrospective analysis of 50 patients` records, listed for bariatric surgery at the Kantonsspital St. Gallen in the year 2015. Experienced pain score determined as VAS/NRS score, amount of opiates required and occurence of PONV in the postoperative periode were reviewed and examined. Compared to other laparoscopically performed surgeries, patients undergoing a bariatric intervention reported higher postoperative pain levels and required more opiates. In total, 35 of 50 patients showed an average VAS/NRS score > 3 during the first four hours after surgery. This accounts for 65% regarding the whole population examined. Average VAS/NRS score after eight hours was > 3 in 35% of patients.

10.2 Hypothesis

Null hypothesis: perioperative treatment of patients undergoing bariatric surgery with lidocaine has no impact on postoperative quality of analgesia.

Alternative hypothesis: perioperative treatment of patients undergoing bariatric surgery with lidocaine reduces the proportion of patients suffering from more intensive pain (any development of VAS/NRS score > 3, in hourly measurements) within the first four hours from currently 65% to 35%.

10.3 Determination of Sample Size

With an expected postoperative VAS/NRS score (any development during first four hours after completion of surgery) of > 3 points in patients undergoing elective bariatric surgery of 65% in the control group, the expected frequency of VAS/NRS score ≤ 3 is 65% in the interventional group. A two group test with a 0.05 two-sided significance level will have 90% power to detect a redistribution of VAS/NRS score ≤ 3 points in favour of interventional group when the sample size in each group is 63. Assuming a 10% dropout rate, 140 subjects will be recruited and randomized. Sample size was calculated according to Jaykaran et al. with a sample size calculation for χ^2 tests using web-based sample size calculator on biomath.info. (55, 56)

10.4 Planned Analyses

Following populations will be analyzed

- Interventional group (patients receiving lidocaine 1% I.V. in addition to general anesthesia)
- Control group (patients receiving saline 0.9% as placebo I.V. in addition to general anesthesia)
- whole population (evaluation of secondary endpoints)

10.5 Primary and secondary endpoint analyses

Potential differences between the two groups in the distribution of dichotomous data will be analysed by χ^2 statistics. Continuous data will be analyzed by parametric or non-parametric test for unpaired comparison as appropriate. Statistics will be calculated with SPSS. We will consider the null hypothesis refuted if p-value is < 0.05.

10.6 Interim analysis

No interim analysis will be performed.

10.7 Deviation from the original statistical plan

Should any deviations from the statistical plan be necessary, these shall be detailed in an amendment to the study protocol and declared in any publications. Unplanned interim analysis, not described in the original study protocol shall be registered in an amendment to the protocol.

10.8 Handling of missing data and drop-outs

Missing postoperative VAS/NRS scores, required for primary and secondary endpoints, will be handled as interpolation values, calculating an average score between last recorded scores before and after the missing value. Missing data for secondary endpoint PONV or time to first defecation will be handled as no occurence of PONV (PONV 0) or no defecation yet. In case of drop-out, data collected till patients drop out will be neglected and not taken into account of statistical consideration of the study.

11. SAFETY ANALYSIS

11.1 Drug studies

During the entire duration of the study, all AE, ADR and all SAE, related to the application of IMPs (severity of possible AE related to lidocaine will be discussed in chapter 11.6) 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 study nurses final visit on second postoperative day at 2pm respectively +/- 30 minutes.

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

An AE is any untoward medical occurrence in a patient or a clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study procedure. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

A **SAE** is classified as any untoward medical occurrence that:

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

In addition, important medical events that may not be immediately life-threatening or result in death, or require intensive care treatment, but may require intervention to prevent one of the other outcomes listed above should also usually be considered serious.

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

11.3 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
Definitly	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

11.4 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.

11.5 Suspected Unexpected Serious Adverse Reactions (SUSAR)

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, unblinding will be carried out by the Sponsor Investigator to re-evaluate the event and eventually classify it a SUSAR. In this case, the Sponsor Investigator will give report including full detail about patient and incident to the local ethics committee within 15 days. In case of fatal SUSAR, reporting to local ethics committee will be given within seven days. Swissmedic will be informed about non-fatal SUSAR within 15 days and in case of fatal SUSAR within seven days.

11.6 Assessment of Severity

Severity of possible AE due to the application of IMPs will be classified as follows.

- Mild: numbness and tingling in the fingers and toes, numbness and unusual sensations around the mouth, a metallic taste in the mouth, ringing in the ears, or lightheadedness and dizziness, local skin reactions (redness, urticaria)

- Moderate: mild side effects with the addition of nausea and vomiting, severe dizziness, decreased hearing, tremors, changes in blood pressure and pulse

- Severe: drowsiness confusion, muscle twitching, convulsions, loss of consciousness, cardiac arrhythmias with hemodynamic instability, cardiac arrest

Events classified as severe adverse reactions due to IMPs will be included to the definition of SAE. Any other event, not applicable to the classification will be documented in the electronic anesthesia protocol and the CRF and assessed by the investigator if discontinuation and/or further treatment is required.

11.7 Reporting of Adverse and Serious Adverse Events

Fatal, life-threatening or relevant events according patients` health will be defined as SAE. Safety outcomes will not be defined as SAE as long as the Investigator considered these events to be exceptional. Primary, secondary and safety events will be recorded on single CRF, though not reported as an SAE, unless the Investigator considered these events to be exceptional.

All events not fitting as primary, secondary or safety outcomes will be reported within 24 hours to the Sponsor Investigator of the study and will again be evaluated by the Sponsor Investigator. Unblinding will be performed by the Sponsor Investigator to evaluate a suspected unexpected serious adverse reaction. SAE resulting in death will be reported to the local Ethics Committee within a week.

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 seven days to the local Ethics Committee (local event via local Investigator) and to Swissmedic due to study category B.

An annual safety report is submitted once a year to the local Ethics Committee via local Investigator and to Swissmedic due to study category B via the Sponsor Investigator. Any amendment or modification in study sequence and resulting in changed safety conditions for participants will be reported.

11.8 Safety follow-up

Regulatory follow-up will take place seven days after surgery (postoperative day seven) or on day of patient`s discharge, whatever comes first (labeled as “POD X” in the study sequence). Follow-up of patients terminating the study (either regulatory or prematurely) with reported ongoing SAE, or any ongoing AEs or vital signs being beyond alert, will be

conducted by the Sponsor Investigator / study nurses. Patients will either be contacted by phone or mail or by consultation of their general practitioner, or in case of hospitalization or out-patient treatment, visited on ward. During follow-up SAE and AE will be evaluated and documented in the CRF. If treatment is necessary, patients will be given an appointment for out-patient treatment or hospitalization.

11.9 Safety SOP

The Sponsor's standard operating procedures (SOP) provide more detail on safety reporting. During the entire duration of the study, all AE and all SAEs are collected, fully investigated and documented in source documents and 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.

12. QUALITY ASSURANCE & CONTROL

12.1 Data Handling and Management

Data collected will be documented and stored in an electronic data system (electronic case report form (eCRF)). All data collected will be treated in confidence and storage system will be validated and compliant to GCP.

12.2 Storage of Data

All data collected will be stored in the eCRF generated by Secu Trial (compliant to GCP, provided by interActive Systems GmbH) and administered by the CTU data manager. Non-electronic data will be stored in the study administration office. Period of data archiving will be ten years (subject to the regulations of article 45 KlinV).

12.3 Monitoring and Auditing

Monitoring will be performed by the CTU St. Gallen according to a Monitoring Plan.

12.4 Confidentiality

The investigator affirms and upholds the principle of the participants' right to privacy and shall comply with applicable privacy laws. Particularly the 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 shall be protected by assigning each participant a unique alphanumerical identifier to be used in lieu of their name in the study database. For data verification purposes, authorized representatives of the Sponsor (Investigator), a competent authority (e.g. Swissmedic), or an ethics committee may require direct access to the medical records relevant to the study, including participants' medical history.

13 PUBLICATION AND DISSEMINATION POLICY

The study will be published in a peer-reviewed scientific journal. This study protocol and the raw dataset will be published as well. The publication process shall be under the direction of the Principal Investigator.

14 FUNDING AND SUPPORT

Funding is being sought from our institution's research fund.

15 INSURANCE

The Kantonsspital St. Gallen will assure that every patient included in the study is insured for any complications developed as a consequence of the study. For further information and insurance certificate see "risk management" of the Kantonsspital St. Gallen.

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