Universitätsspital Basel

Lidocaine and ketamine levels in plasma after simultaneous lidocaine/ketamine infusions. An observational assessment of therapy effects and side-effects.

Research legislation:	Ordinance on human research with the exception of Clinical trials (HRO).
Type of Research Project:	Research project involving human subjects
Risk Categorisation:	Category A
Sponsor Investigator:	Wilhelm Ruppen, Prof. Head of the Pain Unit Department of Anaesthesiology University Hospital of Basel (USB) Spitalstrasse 21 CH - 4031 Basel Phone: +41 61 328 64 96 Fax: +41 61 265 57 20 E-mail: wilhelm.ruppen@usb.ch
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PROTOCOL SIGNATURE FORM

Study Title	Lidocaine and ketamine levels in plasma after simultaneous lidocaine/ketamine infusions. An observational assessment of therapy effects and side-effects.

The project leader has approved the protocol version ***[1.1 (dated 02.05.2023)]*** and confirms hereby to conduct the project according to the protocol, the Swiss legal requirements, current version of the World Medical Association Declaration of Helsinki and the principles and procedures for integrity in scientific research involving human beings.

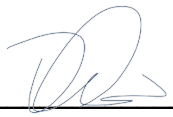
Sponsor Investigator:

Name: Wilhelm Ruppen, Prof.

Date: 8th of May 2023 Signature: 

Project Leader and Principal Investigator:

Name: Tobias Schneider, MD

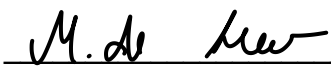
Date: 08.05.2023 Signature: 

Co-Investigators:

Name: Flavia Flepp, pract. med.

Date: 08.05.2023 Signature: 

Name: Matthijs de Leeuw, pract. med.

Date: 08.05.2023 Signature: 

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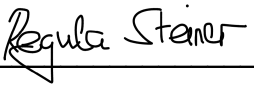
Date: 5.5.2023 Signature: 

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GLOSSARY OF ABBREVATIONS

AE	*Adverse Event*
BASEC	*Business Administration System for Ethical Committees*
BDI-II	*Beck Depression Inventory - 2*
CRF	*Case report form*
FOPH	*Federal Office of Public Health*
HRA	*Human Research Act*
HRO	*Ordinance on Human*
NRS	*Numeric rating scale*
PI	*Principal Investigator*
SAE	*Serious Adverse Event*
SF-MPQ	*Short form – McGill Pain Questionnaire*
USB	*University Hospital Basel*
USZ	*University Hospital Zurich*

132 STUDY SYNOPSIS

Sponsor / Sponsor-Investigator	Wilhelm Ruppen, Prof. Head of the Pain Unit Department of Anaesthesiology University Hospital of Basel (USB) Spitalstrasse 21 CH - 4031 Basel Phone: +41 61 328 64 96 Fax: +41 61 265 57 20 E-mail: wilhelm.ruppen@usb.ch
Study Title:	Lidocaine and ketamine levels in plasma after simultaneous lidocaine/ketamine infusions. An observational assessment of therapy effects and side-effects.
Short Title / Study ID:	LiKe-Level-Trial
Protocol Version and Date:	Version 1.1 (dated 02/05/2023)
Trial registration:	The study will be registered at clinicaltrials.gov and the Swiss National clinical trial portal (SNCTP) upon ethical approval.
Study category and Rationale	Category A: Participants in this study will be exposed to minimal additional risks.
Background and Rationale:	Around 20% of the European population suffers from chronic pain. In addition to the huge emotional and physical burden of chronic pain, the financial impact on society is also enormous, currently estimated at more than €200 billion each year in Europe and $150 billion each year in the USA. [1] However, there are many different treatment strategies for chronic pain, suggesting difficulties in effectively treating these patients. [2] In addition, a substantial number of patients do not respond to first-line treatment. [5] Medications that are frequently prescribed for pain (e.g., NSAIDs, acetaminophen, metamizole, opioids, antidepressants and antiepileptics) often have limiting side effects. [6] Opioids have the additional problem that they have a high potential for abuse and addiction. [7, 8] One possible treatment strategy, especially for therapy-resistant pain, is intravenous infusions with certain pharmacological agents, such as lidocaine and ketamine. [9] Studies have shown that treatments with lidocaine and ketamine have an immediate effect on the one hand, and can also result in longer-lasting pain relief on the other. [10-13] Lidocaine-ketamine infusions (every 4-6 weeks) have been performed at the University Hospital Basel (USB) for almost 20 years. In our pain unit, we combine the positive properties of lidocaine and ketamine by administering infusions of the two agents simultaneously. Internationally, however, safety concerns have been raised following some case studies reported serious side effects [17-19] and the death of a young mother reported in the British media after lidocaine infusion [20]. Therefore, in 2021, an international expert consensus was conducted on the efficacy and safety of intravenous lidocaine for postoperative pain. [21] The elaborated statement includes recommendations for the safe use of lidocaine infusions in the perioperative setting, such as: - A loading dose of no more than 1.5mg/kg lidocaine given as an intravenous infusion over 10 minutes is recommended - After the initial loading dose, an intravenous infusion of 1.5mg/kg/h lidocaine is recommended - No more than 120mg/h of lidocaine should be infused intravenously

	The dosage regimens proposed in this recommendation are clearly exceeded by the standard regime at our pain unit (i.e. 4mg/kg lidocaine over 30 minutes). For note the new consensus statement addresses perioperative use of lidocaine in acute postoperative pain, and our treatment regime is based on previous studies investigating chronic pain. [9, 22] In addition, during a previous retrospective study at our Pain Unit, no serious adverse events were registered during 2995 infusions performed, rendering it a safe procedure. [23] Nevertheless, Foo, Macfarlane et al. defined a toxic lidocaine concentration in plasma as >5µg/ml. In order to assess whether this concentration is exceeded at the USB, the aim of this pilot project is to measure the lidocaine plasma level in a limited number of patients to generate explorative data on inter- and intrapersonal stability and safety of drug plasma levels. Beyond safety issues, we are interested in dosing and effects of our treatments. In the literature, there is evidence that higher doses of ketamine are associated with greater and longer pain relief, which is also consistent with the data from our retrospective study. [23, 24] As a standard regime of our infusion therapies, we increase the ketamine dose from 0.15mg/kg at the first infusion to 0.25mg/kg at the second infusion and 0.5mg/kg at the third infusion. Therefore, another aim of this study is to investigate whether higher plasma levels of ketamine can be correlated with a better analgesic effect.
Objective(s):	The primary objective of this study is to measure the concentration of lidocaine in the plasma of patients at the USB after an intravenous infusion with 4mg/kg lidocaine over 30 minutes. We hypothesize that lidocaine concentrations in plasma of patients at the USB are inter- and intrapersonal stable and do not exceed 5µg/ml by the end of the applied infusions. The secondary objectives of this study include the prospective side effects assessment of lidocaine and ketamine as well as the measurement of plasma levels of ketamine. Further, to correlate the plasma levels with the analgesic efficacy and change in possible depressive symptoms, due to the infusions.
Outcome(s):	The primary endpoint of our study is the concentration of lidocaine in the plasma of patients who received an intravenous infusion with 4mg/kg lidocaine and 0.15 – 0.5mg/kg ketamine over 30 minutes at the time directly after the infusion. The secondary endpoints of our study are the recorded side-effects typical for lidocaine and ketamine reported by questionnaires and patient monitoring. A further endpoint of interest is the concentration of ketamine in the plasma of patients directly after the infusion. Development of pain and mood as assessed by the Short form - McGill Pain Questionnaire (SF-MPQ) and Beck Depression Questionnaire II (BDI-II), respectively.
Study design:	This study is designed as monocentric observational study at the University Hospital Basel.

Inclusion / Exclusion criteria:	**Inclusion Criteria:** - Patient is a new recipient of lidocaine-ketamine infusions - Patient is 18 years of age or older - Patient is able to provide Informed Consent **Exclusion Criteria:** - Contraindication to blood sampling (on arm **not used** for infusion) - Insufficient knowledge of German language - Inability to give consent - Patient is under 18 years of age - Contraindication to treatment with lidocaine and/or ketamine
Measurements and procedures:	**Standard procedure of lidocaine/ketamine infusions at USB** Patients with therapy refractory chronic pain are scheduled for Infusion therapies on a four-week interval basis, by their treating pain physician. Before each infusion, a brief medical history interview takes place, during which compliance with the fasting time (6 hours for solid food, 2 hours for clear liquids) in particular is queried. Subsequently, installation of monitoring (10-minute blood pressure measurement, continuous 5-lead ECG, and continuous SPO2 measurement) and placement of venous access. Lidocaine and ketamine are infused over a 30-minute period (detailed dosing schedules are provided in the protocol). After infusion, patients are monitored for at least another half hour, discharged in company, and instructed not to operate heavy machinery or motor vehicles for at least 24 hours. Over the first three infusions the Ketamine dose is adjusted up to 0.5mg/kg/bw, the Lidocaine dose is stable at 4mg/kg/bw during the infusions. Beyond the third infusion dose adjustments are only made if needed (c.f. side-effects) Study procedures Recruitment and consent to participate in the study will take place in the consultation prior to the first infusion. (c.f. 3.2) During the infusion, the patients' vital signs will be monitored as usual (10-minute blood pressure measurement, continuous SPO2 and 5-lead ECG are recorded, c.f. 3.3.2). As a part of this study, at the end of the first, second and third infusion, side effects will be screened using customized questionnaires. (c.f. eCRF forms document). In addition, blood will be collected during each of the first three infusion appointments. The blood collection itself will take place within 3 minutes after termination of the infusion, as we assume the highest plasma levels at that point in time. [25, 26] For blood collection we will use a Butterfly cannula (BBraun Venofix® Safety 23G, PZN 08839883, B. Braun Melsungen AG) which will be inserted on the "non-infusion arm" and two green 7.5ml Lithium-Heparin monovettes (S-Monovette® Lithium-Heparin, liquid, preparation: lithium heparin, liquid, 7.5 ml, membrane screw cap, closure green, color code ISO, (LxØ) without closure: 92 x 15 mm, with paper label, label/printing: green Sarstedt AG & Co. KG, Nümbrecht). Patients will complete the Short form - McGill Pain Questionnaire (with additional recording of pain on the numeric rating scale (NRS) from 0 (no pain at all) to 10 (worst pain imaginable)) and Beck Depression Questionnaire directly prior to the first three infusions. The SF – MPQ is a validated instrument for measures of clinical pain that capture its sensory, affective and other qualitative components. [27] The BDI-II provides a validated psychological test procedure that assesses the severity of

	depressive symptoms in adolescents 13 years of age and older and adults. [28] In addition, these questionnaires will also be completed at the time points 7 days after, and 14 days after the first, second and third Infusion. The participants will receive a link by e-mail so that they can fill in the questionnaires online. According to the license agreement, the BDI-II will be filled out in paper form and the results will be subsequently transferred to REDCap. If desired by the participant, these questionnaires can also be completed during a telephone survey conducted by the study staff. The surveys will be conducted with REDCap. After the third infusion, this online questioning will take place additionallyafter 28 days (c.f. Appendix 1). After this questioning, the study ends for the participants. **Investigated variables** **Demographic** Variable: Age Categories: Age at beginning of therapy (recorded in years) Variable: Gender Categories: female / male / diverse Variable: Nationality Categories: Recorded as free text Variable: Diagnosis that led to the indication for lidocaine/ketamine infusion Categories: Main pain-related diagnosis coded with ICD11, free text Variable: Dosage Categories: Weight (recorded in kg) / Height (recorded in cm) / Dosage of lidocaine (recorded in mg) / Dosage of ketamine (recorded in mg) **Effects and Side effects** Variable: Depressive Symptoms Categories: Recorded by BDI-II at the beginning of the infusion, 7 days after and 14 days after Variable: Pain Categories: Recorded by SF-MPQ-2 at the beginning of the infusion, 7 days after and 14 days after, and by NRS (Number from 0 to 10) at the beginning of the infusion, 7 days after and 14 days after Variable: Vital sings Categories: blood pressure (recorded in mmHg) / heart rate (recorded in bpm) / saturation of oxygen under infusion (recorded as percentage) / Respiratory rate (recorded in breaths per minute), recorded at the start of the infusion and subsequently during a period of 60 minutes Variable: ECG Categories: Heart rate (recorded in bpm), regular sinus rhythm (recorded as yes or no), PQ interval (recorded in ms), QRS-complex (recorded in ms), ST segment (recorded as conspicuous/inconspicuous), T wave (recorded as conspicuous/inconspicuous), QTc (recorded in ms), Extrasystolies (recorded as number), other anomalies (recorded as free text) at start of infusion and at the end of infusion (minute 30) Variable: Side effects at end of infusion (patient recorded)

	Categories: Injection site pain, dysphoria, euphoria, nervousness, anxiety, dyspnea, nausea, hypersalivation, nightmares, hallucinations, visual disturbances, tinnitus, hyperacusis, paresthesias, numbness, dizziness (recorded as present/absent). Variable: Side effects at end of infusion (patient observation by physician, monitoring) Categories: Exanthema, redness injection site, vomiting, tremor, dysarthria, nystagmus, convulsions, dissociation, disorientation, restlessness, agitation (recorded as present/absent) Variable: Medication plasma levels Categories: Lidocaine and ketamine plasma levels are recorded specified in mg/l al the end of infusions **Laboratory Analysis** Samples were analyzed on a Thermo Scientific™ Orbitrap Exploris™ 240 Mass Spectrometer coupled to reversed phase liquid chromatography with an LLOQ of 0.1 µmol/L for lidocaine and 0.1 mg/L for ketamine. The methods were fully validated according to EMA guideline.
Number of Participants with Rationale:	A total of max. 15 patients (10 + Drop-out of 50%) will be included.
Study Duration:	In total, we expect a study duration of 7 months. Study duration for each individual participant will be 12 weeks.
Study Schedule:	First-Participant-In: 06/2023 Last-Participant-Out: 12/2023
Principal Investigator and Project Leader:	Wilhelm Ruppen, Prof. Leiter der Schmerzklinik Klinik für Anästhesiologie Universitätsspital Basel (USB) Spitalstrasse 21 CH - 4031 Basel Telefon: +41 61 328 64 96 Fax: +41 61 265 57 20 E-mail: wilhelm.ruppen@usb.ch Tobias Schneider, MD Senior Physician Department of Anaesthesiology University Hospital of Basel (USB) Spitalstrasse 21 CH - 4031 Basel Phone: +41 61 328 65 43 Fax: +41 61 265 57 20 E-mail: tobias.schneider@usb.ch

Co-Investigator(s):	Flavia Flepp, pract. med. Doctoral candidate Department of Anaesthesiology University Hospital of Basel (USB) Spitalstrasse 21 CH - 4031 Basel Phone: +41 61 556 55 73 Fax: +41 61 265 57 20 E-mail: flaviabarla.flepp@usb.ch Matthijs de Leeuw, pract. med. Doctoral candidate Department of Anaesthesiology University Hospital of Basel (USB) Spitalstrasse 21 CH - 4031 Basel Phone: +41 61 328 59 14 Fax: +41 61 265 57 20 E-mail: matthijsjan.deleeuw@usb.ch Regula Steiner, Dr. sc. nat. Head of Laboratory for Therapeutic Drug Monitoring and Toxicology Institute for Clinical Chemistry University Hospital of Zurich (USZ) OPS D29 Rämistrasse 100 CH - 8091 Zurich Phone: +41 43 253 06 09 E-mail: regula.steiner@usz.ch
Study Centre(s):	University Hospital of Basel (USB) Spitalstrasse 21 CH - 4031 Basel
Statistical Considerations:	Patients characteristics regarding to age, gender, pharmacological treatment, medical diagnosis will be analyzed exploratively/ descriptively. **Primary outcome:** The primary outcome (Lidocaine plasma level) of our study is explorative and not comparative, therefore, no H0 or H1 are formulated no power analysis is performed and only descriptive/ explorative statistics are reported. We plan to include 10 patients with complete data sets, meaning, full data of three infusions with stable dose of lidocaine (4mg/kg/BW) and escalating dose of ketamine (0.15 – 0.5mg/kg/BW). This corresponds to thirty measures of lidocaine plasma concentrations at a dose of 4mg/kg/BW). Patients without full data sets will be replaced but data from patients with preliminary study termination will be reported in the final protocol. **Secondary outcomes:** 1. Ketamine plasma levels are assessed according to lidocaine levels. 2. H0: dose escalation of ketamine has no effect on pain (outcome measure: SF-MPQ-2) and mood (outcome measure: BDI-II. H1: we hypothesize that ketamine dose has an effect on both outcome measures. For repeated measurements, an ANOVA will be separately calculated for outcome measures of pain and mood as dependent variable. This analysis will be performed separately for intermediate (one and two weeks) and

	long term effects (four weeks). For comparative outcomes a level of significance of 0.05 will be used. In case of multiple testing a correction factor (in case of ANOVA: Bonferroni) for multiple testing is applied. 3. Side effects during treatment will be primary analyzed descriptively. 4. Multiple exploratory linear regressions will be calculated to evaluate the impact of dose and plasma levels of lidocaine and ketamine on pain and mood as well as occurrence of side-effects. SPSS Version 25 will be used for data analyzation and graph pad PRISM Version 9 for data visualization. The investigators, Flavia Flepp and Tobias Schneider, will perform all analysis steps. If needed, statistical guidance will be applied by statisticians of the Clinical Trial Unit (CTU) of the USB. **Handling of missing data:** Dropouts will be replaced. We do not plan data imputation.
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements.

1 BACKGROUND AND PROJECT RATIONALE

Around 20% of the European population suffers from chronic pain. In addition to the huge emotional and physical burden of chronic pain the financial impact on society is also enormous, currently estimated at more than €200 billion each year in Europe and $150 billion each year in the USA. [1] Moreover, chronic pain is the most common cause of long-term disability in middle-aged people. [2] Chronic pain is complex and the pathomechanisms behind it are still not fully understood. Nevertheless, it is increasingly regarded not only as a symptom, but as a disease in its own right. This is also visible in the fact that chronic pain can be coded independently for the first time in ICD 11. [3] In recent years, clinical research has shown that chronic pain can occur independently of disease or tissue damage due to increased sensitization of the central or peripheral nervous system. If chronic pain is inadequately treated, it leads to multidimensional adverse effects: Impairments in daily activities and work ability, general health, and social life. [4] However, there are many different treatment strategies for chronic pain, suggesting difficulties in effectively treating these patients. [2] In addition, a substantial number of patients do not respond to first-line treatment. [5] Medications that are frequently prescribed for pain (e.g., NSAIDs, acetaminophen, metamizole, opioids, antidepressants and antiepileptics) often have limiting side effects. [6] Opioids have the additional problem that they have a high potential for abuse and addiction. [7, 8]

One possible treatment strategy, especially for therapy-resistant pain, is intravenous infusions with certain pharmacological agents, such as lidocaine and ketamine [9] Studies have shown that treatments with lidocaine and ketamine have an immediate effect on the one hand, and can also result in longer-lasting pain relief on the other. [10-13] Ketamine is also interesting for pain therapy due to its antidepressant effect [14, 15] since chronic pain is often accompanied by depressive symptoms. [16]

Lidocaine-ketamine infusions (every 4-6 weeks) have been performed at the University Hospital Basel (USB) for almost 20 years. In our pain unit, we combine the positive properties of lidocaine and ketamine by administering infusions of the two agents simultaneously. This allows us to achieve good clinical results in patients who are non-responders to first- or second-line therapy.

Internationally, however, safety concerns have been raised following some case studies reported serious side effects [17-19] and the death of a young mother reported in the British media after lidocaine infusion. [20] Therefore, in 2021, an international expert consensus was conducted on the efficacy and safety of intravenous lidocaine for postoperative pain. [21] The elaborated statement includes recommendations for the safe use of lidocaine infusions in the perioperative setting, such as:

- A loading dose of no more than 1.5mg/kg lidocaine given as an intravenous infusion over 10 minutes is recommended
- After the initial loading dose, an intravenous infusion of 1.5mg/kg/h lidocaine is recommended
- No more than 120mg/h of lidocaine should be infused intravenously
- For the dose calculation, the ideal body weight should be used

The dosage regimens proposed in this recommendation are clearly exceeded by the standard regime at our pain unit (i.e. 4mg/kg lidocaine over 30 minutes). For note the new consensus statement addresses perioperative use of lidocaine in acute postoperative pain, and our treatment regime is based on previous studies investigating chronic pain. [9, 22] In addition, during a previous retrospective study at our Pain Unit, no serious adverse events were registered during 2995 infusions performed, rendering it a safe procedure. [23] Nevertheless, Foo, Macfarlane et al. defined a toxic lidocaine concentration in plasma as >5µg/ml. In order to assess whether this concentration is exceeded at the USB, the aim of this pilot project is to measure the lidocaine plasma level in a limited number of patients to generate explorative data on inter- and intrapersonal stability and safety of drug plasma levels.

Beyond safety issues, we are interested in dosing and effects of our treatments. In the literature, there is evidence that higher doses of ketamine are associated with greater and longer pain relief, which is also consistent with the data from our retrospective study. [23, 24] As a standard regime of our infusion therapies, we increase the ketamine dose from 0.15mg/kg at the first infusion to 0.25mg/kg at the second infusion and 0.5mg/kg at the third infusion. In cases where patients already experiencing sufficient analgesic effect and/or improvement in quality of life after the 1st or 2nd infusion or if side effects are not tolerated, no further increase of ketamine dosage is made. Therefore, another aim of this study is to investigate whether higher plasma levels of ketamine can be correlated with a better analgesic effect.

2 PROJECT OBJECTIVES AND DESIGN

2.1 Hypothesis and primary objective

The primary objective of this study is to measure the concentration of lidocaine in the plasma of patients at the USB after an intravenous infusion with 4mg/kg lidocaine over 30 minutes.

We hypothesize that lidocaine concentrations in plasma of patients at the USB are inter- and intrapersonal stable and do not exceed 5µg/ml by the end of the applied infusions.

2.1.2 Secondary objectives

The secondary objectives of this study include the prospective side effects assessment of lidocaine and ketamine as well as the measurement of plasma levels of ketamine. Further, to correlate the plasma levels with the analgesic efficacy and change in possible depressive symptoms, due to the infusions.

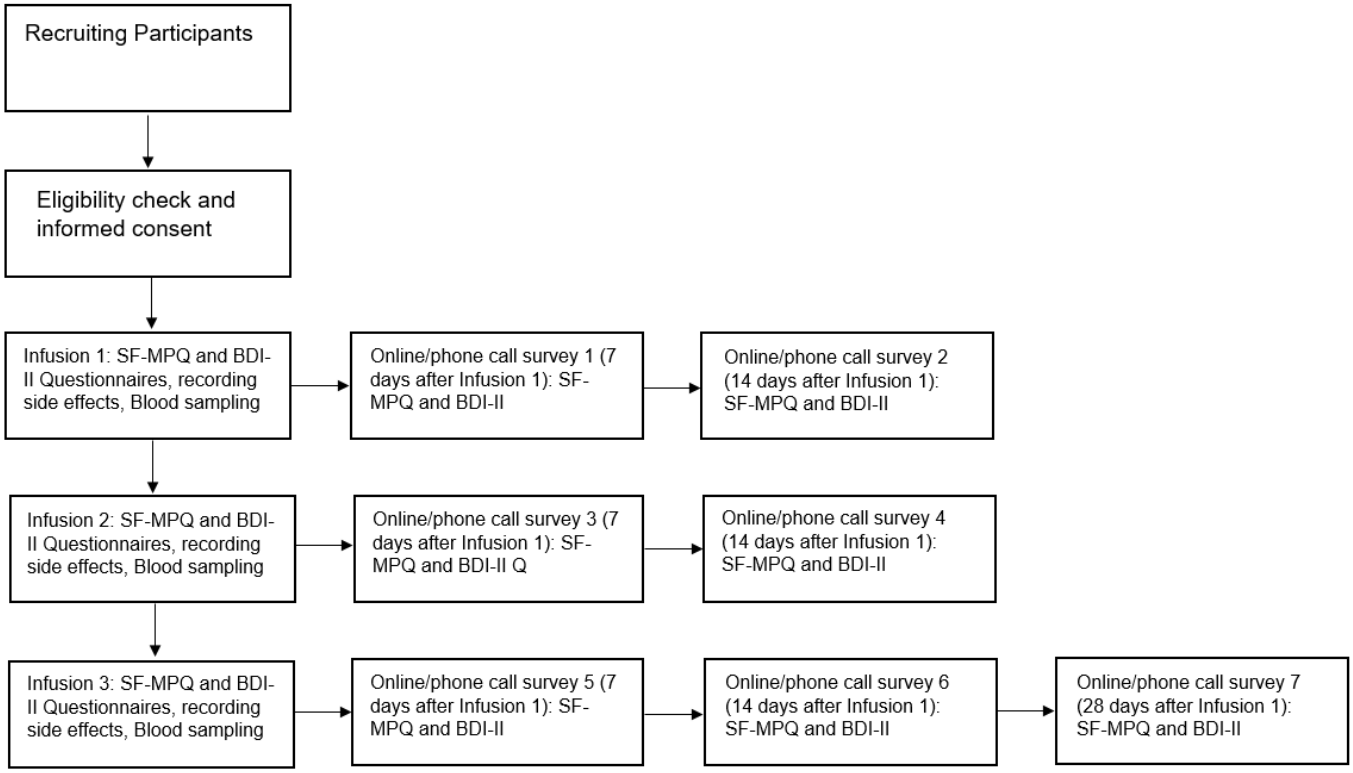
2.2 Primary and secondary endpoints

The primary endpoint of our study is the concentration of lidocaine in the plasma of patients who received an intravenous infusion with 4mg/kg lidocaine and 0.15 – 0.5mg/kg ketamine over 30 minutes at the time directly after the infusion.

The secondary endpoints of our study are the recorded side-effects typical for lidocaine and ketamine reported by questionnaires and patient monitoring. A further endpoint of interest is the concentration of ketamine in the plasma of patients directly after the infusion. Development of pain and mood as assessed by the Short form - McGill Pain Questionnaire (SF-MPQ) and Beck Depression Questionnaire II (BDI-II), respectively.

2.3 Project design

This study is designed as monocentric observational pilot-study at the USB.



3 PROJECT POPULATION AND STUDY PROCEDURES

3.1 Project population, inclusion and exclusion criteria

For our pilot project on drug plasma levels in an ambulatory infusion regime, a total of max. 15 patients (10 + Drop-out of 50%) newly receiving lidocaine-ketamine infusions at the USB will be randomly selected. To minimize selection bias (including only responders, or patients with less side-effects) and because we increase the ketamine dosage normally during the first 3 infusions, we will only include patients who are new to lidocaine/ketamine infusions.

Inclusion Criteria:

- Patient is a new recipient of lidocaine-ketamine infusions

- Patient is 18 years of age or older
- Patient is able to provide Informed Consent

Exclusion Criteria:
- Contraindication to blood sampling (on arm not used for infusion)
- Insufficient knowledge of German language
- Inability to give consent
- Patient is under 18 years of age
- Contraindication to treatment with lidocaine and/or ketamine

3.2 Recruitment, screening and informed consent procedure

All patients who are newly assigned to lidocaine-ketamine infusions at the USB and who meet the inclusion criteria will be asked to take part in the study by their treating physician.

If the patients are willing to participate, they will be informed in verbal and written form by one of the investigators about the study and the blood collection.

All study participants will receive an informed consent form describing the study and providing sufficient information to allow participants to make an informed decision about their participation in the study. Sufficient time (at least 24 hours) will be given to the potential participants to make a decision about participation.

Formal informed consent will be obtained from a participant using the approved consent form before the participant undergoes any of the study procedures.

The consent form will be signed and dated by the investigator or his/her designee concurrently with the participant's signature. A copy of the signed consent form will be given to the study participant. The informed consent form will be retained as part of the study records.

The patients themselves have no direct advantage from participating in the study. The risk resulting from an additional venepuncture is to be considered minimal. The typical risks of inserting an indwelling venous cannula are already part of the infusion information. However, patients are explicitly informed that taking part in the study includes three additional venous punctures.

3.3 Study procedures

Recruitment and consent to participate in the study will take place in the consultation prior to the first infusion. (c.f. 3.2) During the infusion, the patients' vital signs will be monitored as usual (10-minute blood pressure measurement, continuous SPO2 and 5-lead ECG are recorded, c.f. 3.3.2).

As a part of this study, at the end of the first, second and third infusion, side effects will be screened using customized questionnaires (c.f. eCRF forms document). In addition, blood will be collected during each of the first three infusion appointments. The blood collection itself will take place within 3 minutes after termination of the infusion, as we assume the highest plasma levels at that point in time. [25, 26] For blood collection we will use a Butterfly cannula (BBraun Venofix® Safety 23G, PZN 08839883, B. Braun Melsungen AG) which will be inserted on the "non-infusion arm" and two green 7.5ml Lithium-Heparin monovettes (S-Monovette® Lithium-Heparin liquid, preparation: lithium heparin, liquid, 7.5 ml, membrane screw cap, closure green, color code ISO, (LxØ) without closure: 92 x 15 mm, with paper label, label/printing: green Sarstedt AG & Co. KG, Nümbrecht).

Patients will complete the Short form - McGill Pain Questionnaire (with additional recording of pain on the numeric rating scale (NRS) from 0 (no pain at all) to 10 (worst pain imaginable)) and Beck Depression Questionnaire directly prior to the first three infusions. The SF – MPQ is a validated instrument for measures of clinical pain that capture its sensory, affective and other

qualitative components. [27] The BDI-II provides a validated psychological test procedure that assesses the severity of depressive symptoms in adolescents 13 years of age and older and adults. [28]

In addition, these questionnaires will also be completed at the time points 7 days after, and 14 days after the first, second and third Infusion. The participants will receive a link by e-mail so that they can fill in the questionnaires online. According to the license agreement, the BDI-II will be filled out in paper form and the results will be subsequently transferred to REDCap. If desired by the participant, these questionnaires can also be completed during a telephone survey conducted by the study staff. The surveys will be conducted with REDCap. After the third infusion, this online questioning will take place additionally after 28 days (c.f. Appendix 1). After this questioning, the study ends for the participants.

3.3.1 Investigated variables

Demographic

Variable: Age
Categories: Age at beginning of therapy (recorded in years)

Variable: Gender
Categories: female / male / diverse

Variable: Nationality
Categories: Recorded as free text

Variable: Diagnosis that led to the indication for lidocaine/ketamine infusion
Categories: Main pain-related diagnosis coded with ICD11, free text

Variable: Dosage
Categories: Weight (recorded in kg) / Height (recorded in cm) / Dosage of lidocaine (recorded in mg) / Dosage of ketamine (recorded in mg)

Effects and Side effects

Variable: Depressive Symptoms
Categories: Recorded by BDI-II at the beginning of the infusion, 7 days after and 14 days after

Variable: Pain
Categories: Recorded by SF-MPQ-2 at the beginning of the infusion, 7 days after and 14 days after, and by NRS (Number from 0 to 10) at the beginning of the infusion, 7 days after and 14 days after

Variable: Vital sings
Categories: blood pressure (recorded in mmHg) / heart rate (recorded in bpm) / saturation of oxygen under infusion (recorded as percentage) / Respiratory rate (recorded in breaths per minute), recorded at the start of the infusion and subsequently during a period of 60 minutes

Variable: ECG
Categories: Heart rate (recorded in bpm), regular sinus rhythm (recorded as yes or no), PQ interval (recorded in ms), QRS-complex (recorded in ms), ST segment (recorded as conspicuous/inconspicuous), T wave (recorded as conspicuous/inconspicuous), QTc (recorded in ms), Extrasystolies (recorded as number), other anomalies (recorded as free text) at start of infusion and at the end of infusion (minute 30)

Variable: Side effects at end of infusion (patient recorded)
Categories: Injection site pain, dysphoria, euphoria, nervousness, anxiety, dyspnea, nausea, hypersalivation, nightmares, hallucinations, visual disturbances, tinnitus, hyperacusis, paresthesias, numbness, dizziness (recorded as present/absent).

Variable: Side effects at end of infusion (patient observation by physician, monitoring)
Categories: Exanthema, redness injection site, vomiting, tremor, dysarthria, nystagmus, convulsions, dissociation, disorientation, restlessness, agitation (recorded as present/absent)

Variable: Medication plasma levels
Categories: Lidocaine and ketamine plasma levels are recorded specified in mg/l al the end of infusions

3.3.2 **Standard Procedure of lidocaine-ketamine infusions at the Pain Unit of USB**

During a short medical history interview Patients are briefly asked about their current pain situation before each infusion. For safety reasons, additional questions are asked about weight changes, compliance with fasting (= no solid food for 6 hours, no drinks for 2 hours) and allergies.

Monitoring is then installed (10-minute blood pressure measurement, continuous SPO2 and 5-lead ECG are recorded) and venous access is established. Lidocaine and ketamine are infused over a period of 30 minutes. The dosage of lidocaine is 4mg/kg is maintained throughout the infusions, and the dosage of ketamine is increased within the first three infusions from 0.15mg/kg at the first, to 0.25mg/kg at the second and 0.5mg/kg at the third infusion. In case patients already experiencing sufficient analgesic effect and/or improvement in quality of life after the 1st or 2nd infusion or if side effects do not allow a further dose increase, no further step up of ketamine dosage is made. We define a sufficient effect as a significant pain reduction (more than 50%) for at least 2 weeks and/or better quality of life with improved functionality during at least 2 weeks.

After the infusion, patients are monitored for at least another half hour, are discharged in company and are instructed to not run heavy machines and motor vehicles for at least 24 hours.

3.3.3 Laboratory Analysis

Plasma concentrations of lidocaine and ketamine are determined at the Institute of clinical chemistry at University Hospital Zurich under ISO/IEC 17025:2017 accreditation.

The Plasma lidocaine and ketamine concentrations are measured using liquid chromatography coupled to high-resolution accurate mass-spectrometry (LC-MS).

For lidocaine measurement, 100uL of plasma samples are precipitated with 100uL acetonitrile (containing internal standard) and centrifuged. Supernatant is diluted with 5mM ammonium format buffer pH 3 for analysis.

For ketamine measurement, 1 mL of plasma samples are diluted with 0.5mL H2O and 0.5 mL ethanol (containing internal standard) extracted using e 150 µl 1 M NaOH in H2O and 5 ml n-Hexan/Dichlormethan (4+1, v+v). Supernatant was separated and dried down under steam of N2. For measurement, samples are reconstituted with acetonitrile and 10 mM ammonium acetate buffer.

Samples were analyzed on a Thermo Scientific™ Orbitrap Exploris™ 240 Mass Spectrometer coupled to reversed phase liquid chromatography with an LLOQ of 0.1 µmol/L for lidocaine and 0.1 mg/L for ketamine. The methods were fully validated according to EMA guideline.

Both methods were fully validated according to EMA guideline.

3.4 Withdrawal and discontinuation

Patients may withdraw from the study at any time and for any reason (stating reason is not

required). No further data will be collected after withdrawal. Unless otherwise requested, the data collected up to that point will still be evaluated in encrypted form and anonymized after the evaluation.

The following reasons result in withdrawal:

- SAE
- AE challenging the health of the subject if continuing the study

Drop-outs will be replaced by new patients and will be reported in the final publication.

4 STATISTICS AND METHODOLOGY

4.1. Statistical analysis plan

Patients characteristics regarding to age, gender, pharmacological treatment, medical diagnosis will be analyzed exploratively/ descriptively.

Primary outcome:

The primary outcome (Lidocaine plasma level) of our study is explorative and not comparative, therefore no H0 or H1 are formulated no power analysis is performed and only descriptive/ explorative statistics are reported.

We plan to include 10 patients with complete data sets, meaning, full data of three infusions with stable dose of lidocaine (4mg/kg/BW) and escalating dose of ketamine (0.15 – 0.5mg/kg/BW). This corresponds to thirty measures of lidocaine plasma concentrations at a dose of 4mg/kg/BW). Patients without full data sets will be replaced but data from patients with preliminary study termination will be reported in the final protocol.

Secondary outcomes:

1. Ketamine plasma levels are assessed according to lidocaine levels.

2. H0: dose escalation of ketamine has no effect on pain (outcome measure: SF-MPQ-2) and mood (outcome measure: BDI-II. H1: we hypothesize that ketamine dose has an effect on both outcome measures. For repeated measurements, an ANOVA will be separately calculated for outcome measures of pain and mood as dependent variable. This analysis will be performed separately for intermediate (one and two weeks) and long term effects (four weeks). For comparative outcomes a level of significance of 0.05 will be used. In case of multiple testing, a correction factor (in case of ANOVA: Bonferroni) for multiple testing is applied.

3. Side effects during treatment will be primary analyzed descriptively.

4. Multiple exploratory linear regressions will be calculated to evaluate the impact of dose and plasma levels of lidocaine and ketamine on pain and mood as well as occurrence of side-effects.

SPSS Version 25 will be used for data analyzation and graph pad PRISM Version 9 for data visualization. The investigators, Flavia Flepp and Tobias Schneider, will perform all analysis steps. If needed, statistical guidance will be applied by statisticians of the Clinical Trial Unit (CTU) of the USB.

4.2. Handling of missing data

Dropouts will be replaced (c.f. 3.4). We do not plan data imputation.

5 REGULATORY ASPECTS AND SAFETY

5.1 Local regulations / Declaration of Helsinki

This research project will be conducted in accordance with the protocol, the Declaration of Helsinki [3], the principles of Good Clinical Practice, the Human Research Act (HRA) and the Human Research Ordinance (HRO) [1] as well as other locally relevant regulations. The project leader acknowledges his responsibilities as both the project leader and the Sponsor.

5.2 Notification of safety and protective measures (HRA Art. 15, HRO Art. 20)

If, during the research project, circumstances arise which could jeopardise the safety or health of the participants or lead to a disproportionate relationship between the risks and burdens and the benefits, all the measures required to ensure protection are to be taken without delay.
The project leader is promptly notified (within 24 hours) if immediate safety and protective measures have to be taken during the conduct of the research project. The Ethics Committee will be notified via BASEC of these measures and of the circumstances necessitating them within 7 days.

5.3 Serious events (HRO Art. 21)

If a serious event occurs, the research project will be interrupted and the Ethics Committee notified on the circumstances via BASEC within 7 days according to HRO Art. 21[1].

5.4 Amendments

Substantial changes to the project set-up, the protocol and relevant project documents will be submitted to the Ethics Committee for approval according to HRO Art. 18 before implementation.

5.5 End of project

Upon project completion or discontinuation, the Ethics Committee is notified within 90 days. All biological materials and health-related data are anonymized upon termination of data analysis.

5.6 Insurance

In the event of project-related damage or injuries, the Sponsor will be liable, except for damages that are only slight and temporary; and for which the extent of the damage is no greater than could be expected according to the current state of scientific knowledge (Art. 12 HRO).

6 FURTHER ASPECTS

6.1 Overall ethical considerations

Overall, this project is in accordance with the regulatory requirements of the HFG and the HFV. An approval of the local ethic committee is mandatory to conduct this project. The minimal

[1] A serious event is defined as any adverse event where it cannot be excluded, that the event is attributable to the sampling of biological material or the collection of health-related personal data, and which:
a. requires inpatient treatment not envisaged in the protocol or extends a current hospital stay;
b. results in permanent or significant incapacity or disability; or
c. is life-threatening or results in death.

additional risks of an additional venous cannulation for the single patient is outweighed by far due to the additional knowledge we generate about the safety profile and dose adjustments for patients receiving future infusion treatments. As this is an observational study and the blood sample analysis only evaluates the drug plasma levels, we do not expect incidental findings due to study procedures. Especially the screening for depression is a standard procedure at the pain clinics, suspicion of depression would be communicated to the patient independently of study participation. This is also the case for incidental findings during the hemodynamic monitoring during the infusion therapies.

6.2 Risk-Benefit Assessment

Venous catherization brings the risk of bleeding, bruises, swellings with it, as well as the small chance of infection.
In summary, this study will not provide any direct benefit beyond the expected relief by the infusion therapy on pain, to the participating patients, but it may provide valuable insights as a basis from which we can optimize and adopt our infusion regimes up on plasma levels of lidocaine and ketamine correlated with effects and side-effects. Participants will be exposed to minimal additional risks due to the venous cannulation.

7 QUALITY CONTROL AND DATA PROTECTION

7.1 Quality measures

The study will be conducted by a small team of the Pain Unit of the USB. All team members will be trained on all important study related aspects.

For quality assurance the sponsor, the Ethics Committee or an independent trial monitor may visit the research sites. Direct access to the source data and all study related files is granted on such occasions. All involved parties keep the participant data strictly confidential.

7.2 Data recording and source data

Study data will be recorded with electronic CRFs, using a database (RedCap, Research Electronic Data Capture, Vanderbilt University, Tennessee, USA). For each enrolled study participant CRFs will be maintained. Participants will not be identified in the CRF by name or initials and birth date; instead the participant number will be used. The study staff and the PIs are authorized for all CRFs.

Demographic data, visit dates, participation in study and Informed Consent Forms, randomization number, SAEs, AEs and concomitant medication, results of relevant examinations and all CRFs are considered the source documents in the study.

Paper source documents will be archived in folders at the study site with restricted access (Pain Unit USB).

7.3 Confidentiality and coding

Project data will be handled with uttermost discretion and is only accessible to authorized personnel who require the data to fulfil their duties within the scope of the research project. On the CRFs and other project specific documents, participants are only identified by a unique participant number.

The data collection is based on electronic CRFs, other source documents will be on paper. Data from paper forms will then be transferred to the source documentation in a secure database. Only CIs and study team members will be authorized to coordinate CRF entries. Data entry of paper

pencil documents will be checked double after entry into the eCRF. The electronic database is based on the secure web application REDCap (Research Electronic Data Capture) and will be operated with individual user log in, time stamp, and logging of changes with the name of the respective study member. Only authorized personnel will be able to enter the system to view and edit data.

Participants will not be identified in the CRF by name or initials and birth date. Only participant identification codes will be used to track participants. The participant identification list will be stored at the Pain Unit and will be only accessible for the investigators. The data will be locked and therefore protected from unauthorized or accidental disclosure, alteration, deletion, copying and theft.

Biological material in this project is not identified by participant name but by a unique participant number. Biological material is appropriately stored in a restricted area only accessible to authorized personnel. The plasma samples analyzed by the laboratory of the USZ are coded with a unique batch and no personal/ identifying data will be shared with the USZ. The identification list is stored locked and protected from unauthorized access at the Pain Unit USB.

7.4 Retention and destruction of project data and biological material

All study data will be archived for a minimum of 10 years after study termination or premature termination of the clinical trial. All data is archived in folders at the study site with restricted access (Pain unit USB).

Upon conclusion, the database is secured and cannot be changed anymore. The Plasma samples will be disposed by the laboratory of the USZ directly after analysis.

8 FUNDING / PUBLICATION / DECLARATION OF INTEREST

The study is funded by the Clinic for Anesthesia, USB. There is no conflict of interest and the financing party has no influence on the protocol, analysis or publication. We plan to publish the results in a peer-reviewed scientific journal. Upon request, we will provide the full study protocol and data (as required by some journals). The trial results might be presented at scientific congresses. The main publication will be created by Flavia Flepp, Matthijs de Leeuw, Regula Steiner, Tobias Schneider and Wilhelm Ruppen. No unpublished data may be transmitted to a third party without prior written approval by sponsors and PIs. No publication or communication involving the results of the study is authorized without prior written consent from the PIs. In view of patent and confidentiality issues, however, the PIs must accept requirements on the timing of early publication. No use of professional writers is intended. The PIs will have ultimate authority over any of the activities.

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Appendix 1: Schedule of assessments

Time (days)	***>-1 day***	***0***	***+7***	***+14***	***+28***	***+35***	***+42***	***+56***	***+63***	***+70***	***+84***
Visit	*Information*	*Infusion 1*	*Questionnaires online*	*Questionnaires online*	*Infusion 2*	*Questionnaires online*	*Questionnaires online*	*Infusion 3*	*Questionnaires online*	*Questionnaires online*	*Questionnaires online*
oral and written Information	+										
Written consent	+										
check inclusion-/ exclusion criteria	+										
Medical history	+										
Participant Characteristics		+									
Questionnaires Side effects		+			+			+			
Blood Sampling		+			+			+			
Short form McGill		+	+	+	+	+	+	+	+	+	+
Beck Depression		+	+	+	+	+	+	+	+	+	+

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