Serratus planus block after minimally invasive cardiac surgery: a prospective randomized study

Serratusblockade nach kardiochirurgischen Eingriffen mit (Mini)Thorakotomie: eine prospektiv randomisierte Studie

doctoral thesis project: XX

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List of Abbreviations

ICU (intensive care unit)
LOS (length of stay)
LVAD (left ventricular assist device)
MIHS (minimal invasive heart surgery)
PACU (post anesthesia care unit)
SAPB (Serratus anterior plane block)
ERAS (early recovery after surgery)
ESB (Erector spinae block)
VAS (visual analogue scale)
LAST (local anesthesia systemic toxicity)
ABP (arterial blood pressure)
SpO2 (arterial oxygen saturation)

Protocol Synopsis

TITLE	***Serratus planus block after minimal invasive cardiac surgery: a randomized comparison of two methods of analgesia***
OBJECTIVES	**Primary Objective** To demonstrate treatment efficacy of ultrasound guided serratus anterior plane block as currently performed in our department in reducing surgical post-thoracotomy pain, as compared to also currently administered intravenous analgesic therapy only. **Secondary Objectives** • To assess postoperative morphine equivalent requirements in the first 12, 12-24, 24-48 hours SAPB or standard i.v. analgesia in patients with and without serratus anterior block • To assess duration of mechanical ventilation, LOS in cardiovascular ICU, postoperative LOS in hospital in patients with and without serratus plane block • To assess complications from block, anesthesia or surgery compared to no block - (pain induced) respiratory complications (reintubation, atelectasis, pneumothorax), PONV, hematoma, LAST • To assess (pain induced) pulmonary dysfunction by means of preoperative and postoperative FEV1
DESIGN / PHASE	*Prospective, single center, randomized, double-blind study*
STUDY PLANNED DURATION	**First patient** *1.1.2023* **Last patient** *31.01.2025*
CENTER(S) / COUNTRY(IES)	*1 center in Austria*
PATIENTS / GROUPS	*66 patients in 2 groups* *33 patients per group* *Randomization ratio 1:1*
INCLUSION CRITERIA	• ≥18 years of age • patients after elective cardiac surgery performed via minithoracotomy (mitral valve, tricuspid valve, ASD or PFO closure) • treated in the cardiothoracic 16 bed ICU 13B-HTG • treated in the 4 bed PACU AWR 1-HTG
EXCLUSION CRITERIA	• patients requiring full sternotomy or emergency surgery • Allergy to amid-type local anesthetics • patients less that 18 years of age at the time of surgery • patients intubated >48h prior to surgery • Infection at the site of the Serratus Anterior Plane Block • Known bleeding diathesis with increased risk of hematoma at the block site

	• Known opioid abuse • Allergy to metamizole AND acetaminophen OR hydromorphone AND Piritramide • Active pulmonary infection at the time of surgery • Patient refusal prior to surgery • Inability to communicate • BMI ≥40 • Patients with known dementia or/and a legal guardian for medical issues • Patients unable to understand the study measures and are not able to complete pain assessment forms. • Known pregnancy • Severe cardiorespiratory disturbances such as high respiratory support (>0,7 FiO2 or driving pressure >25mbar) or high catecholamine support (>0,5mcg/kg/min Norepinephrine and/or >5IE Vasopressin/h) making fast track intensive care with extubation in the first 48 hours after arrival in the ICU and ERAS impossible • Patients with unanticipated prolonged intubation >48h after arrival in the ICU • Postoperative ECMO support
STUDY PERIODS	• 1.1.2023 – 31.1.2025
INVESTIGATIONAL DRUG	***MED 1:*** Ultrasound guided Serratus anterior block will be performed according to the analgetic standard in our department using an ultrasound guided transducer to inject 2mg/kg of 0.5% ropivacaine. A sterile plaster will be placed on the puncture site after performing the block. Patients will receive i.v. analgesia according to the analgesic standard of care in our department.
COMPARATIVE DRUG /CONTROL CONDITION	A sterile plaster will be placed on an appropriate site to blind ICU and PACU personnel of the intervention. Patients will receive i.v. analgesia according to the analgesic standard of care in our department.
CONCOMITANT MEDICATION	**allowed** analgetic standard at our department: Metamizol 3x1g/d 1st choice, Acetaminophen 3x1g/d in case of known allergy against Metamizol or neutropenia before operation and opioid treatment (Piritramid, Hydromorphon), use of rescue NSAR (Diclofenac 75mg 2x/d) or rescue-SAPB, Pethidin for shivering is allowed but will be documented **Not allowed** Other regional anesthesia procedures such as thoracic epidural anesthesia or erector spinae block, bilateral SABP (in case of bilateral minithoracotomy), other opioids
EFFICACY ENDPOINTS	Postoperative Pain Score: VAS 0-10 (Time Frame: from SAPB up to 48 hours thereafter) Pain scores reported 2, 4, 6,8,10,12,18,24, 48 hours after SAPB if possible.

TOLERABILITY / SAFETY ENDPOINTS	• Complications from block, anesthesia or surgery compared to no block - hematoma - occurrence of PONV within the first 24h after surgery - occurrence of LAST (local anesthetic systemic toxicity) - occurrence of delirium in the ICU - need for rescue NSAID (diclofenac) analgesia - need for block repetition on the day after the operation • In case of rare, potential intolerable pain necessitating repetition of SABP, erector spinae block (ESB), thoracic epidural anesthesia, such measures (although rarely necessary in our ICU) may be performed according to our current standard of care from the first postoperative day or later to prevent ropivacaine overdose. The procedure (SABP, ESB, thoracic epidural anesthesia) will be documented.
PHARMACOKINETIC / PHARMACODYNAMIC ENDPOINTS	-
QUALITY OF LIFE / PHARMACOECONOMIC ENDPOINTS	-
STATISTICAL METHODOLOGY	**Primary Endpoint** Mean difference in VAS of 2 points (20%) in the first 12 hours after SAPB compared to standard intravenous analgesia (no SAPB) in the ICU. **Null and alternative hypotheses:** *H_0: SAPB significantly reduces VAS after MIHS compared to no SAPB* *H_1: SAPB does not reduce VAS after MIHS compared to no SAPB* Type-I error: 0,05 Type -II error: 0.2, power: 0,8. Type -II error: 0.1, power: 0,9. **Sample size calculation** Based upon similar investigations by other authors, we are expecting a mean reduction of VAS of 2 points (20%) of VAS measured at 2,4,6,8,10,12 hours and then averaged over the first 12 hours after application of the serratus block to be statistically significant [1,2]. Based on our own unpublished preliminary investigations we are expecting a mean or median VAS to be significantly higher in our ICU than the VAS described by the authors above. Their retrospective analysis showed a median difference of 2.5 points on a VAS with a standard deviation (SD) of 2.62. An interim analysis is planned after half of the planned patients have been treated, using the Lan DeMets spending function that approximates the O'Brien Fleming boundaries, with a nominal one-sided significance level of 0.025. Using the R-package Rpact, we calculated that 28 patients per group are required under these

	assumptions to prove an overall power of 80%. Investigation can be stopped at the interim analysis in case of a very large observed treatment effect (observed mean reduction of VAS of 3.23 points within the first 12 hours, if the observed standard deviation corresponds to the planning assumption of 2.62) which seems possible since median treatment effect was 2.5 points in earlier, retrospective analyses [2] . Such substantial treatment effect would enable us to detect a significant treatment effect with 14 patients per group and therefore avoid withholding such an effective treatment from a number of patients in the control group. The local adjusted one-sided significance levels are 0.001525 at interim and 0.0245 at the final analysis. The power for stopping at interim under the planning assumptions is 13%. The probability to continue at interim and stop with a significant result at the final analysis is 67% and the overall power is 80%. To compensate for a possible dropout rate of up to 15% we therefore choose a maximal sample size of n=66 (n= 33 per group). **Statistical methodology** Continuous variables will be compared with the t-test or Mann–Whitney U-test, and categorical variables with the Chi-squared test or Fisher's exact test, as appropriate. Multiple comparisons of opioid consumption at specific intervals will be corrected with the Bonferroni method. Proportions of responders will be compared between groups using a Chi-square test. SPSS (ver. 24; SPSS Inc., Chicago, IL, USA) will be used for all calculations. Metric variables will be described by medians and interquartile ranges or, where appropriate, by means and SDs. Frequencies will be reported as counts and percentages. All analyses will be based on the intention-to-treat principle. The key secondary outcome, the difference in morphine equivalents, will be tested in hierarchical manner, only performing a formal hypothesis test at the one-sided significance level of 0.025 once the null hypothesis for the primary endpoint was rejected. The earlier investigation showed a mean difference of 9.23mg and a SD of 2.79 in the block group and of 5.14 in the standard treatment group [1]. Conservatively assuming a SD of 5.14 in both groups, a sample size of n=14 per group at interim will enables us to detect a difference in the mean of 5.7mg, which is considerably smaller than the difference of 9.23 observed in [1], with a power of 80%. At the final analysis with n=28 per group the power for the same effect will be 98%. Secondary endpoints: • Morphine equivalents administered within the first 12, 12-24 and 24-48 hours after SAPB compared to no block • Mean difference in VAS of 2 points (20%) at 2, 4, 6, 8, 10, 12, 24, 48 hours after SAPB compared to no block

	Other secondary endpoints: • Duration of Mechanical Ventilation compared to no block • Duration of ICU stay compared to no block • Evaluation of pulmonary function by means of a bed side spirometer according to our current standards before surgery and on postoperative day 1 and 2 • Duration of postoperative hospital stay • 30d mortality after MIHS

Introduction

The popularity of minimally invasive cardiac surgery (MIHS) is rising due to a number of positive effects on postoperative wound infection rates, reduced hospital length of stay (LOS), facilitation of postoperative rehabilitation and aesthetic reasons compared to cardiac surgery performed by full median sternotomy [3] .
The one major adverse effect of MIHS, particularly when surgical access by mini-thoracotomy is performed for aortic valve, mitral valve or tricuspid valve surgery or PFO closure has been shown to be severe pain during the postoperative period. Several strategies have been suggested to tackle this problem and to facilitate early recovery after surgery (ERAS) limiting postoperative pain as well as unwanted side effects of opioids like oversedation or postoperative nausea and vomiting (PONV) [4] . Thoracic epidural anesthesia, the gold standard for pain management after thoracotomy has been associated with increased risk for epidural hematoma due to systemic heparinization in the context of cardiac surgery in case reports [5] .
A relatively recent and side-effect limiting alternative to central neuraxial or thoracic paravertebral blocks is performing truncal plane blocks distantly from the spinal column providing hemithoracic analgesia such as erector spinae or serratus anterior plane block [6,7] .
Ultrasound guided Serratus Anterior Plane Block (SAPB) provides long lasting paresthesia (750-840min) anesthesia to the anterolateral chest wall between T2 and T12 by blockage of the lateral cutaneous branches of the thoracic intercostal nerves and has successfully performed for analgesia after breast surgery, thoracic surgery, analgesic management of rib fractures and analgesia for chest tube placement [7–9].
The use of novel ultrasound devices with good resolution has made these field blocks highly efficient and minimizes complications due to direct visualization of fascia and muscles layers.
Data on the effectiveness after cardiac surgery is limited. After minimally invasive cardiac surgery SAPB has been associated with significantly reduced opioid requirements as well as reduced LOS in ICU and in hospital compared to surgical wound infiltration in a retrospective French study [6] .
An Italian observational cohort study showed significant reduction of pain scores and opioid consumption 48 but not 24 hours after minimally invasive mitral valve surgery [1].
A group from India found significantly reduced pain scores and opioid requirements through in the SABP group compared to placebo in a small randomized, but not double blind study after minimally invasive direct coronary artery bypass (MIDCAB) surgery [10].

Study Description

1.1 Primary Objective

To evaluate the efficacy of ultrasound guided serratus anterior plane block as performed according to our department's standard in reducing surgical post- thoracotomy pain scores (mean numerical rating scale during the first 12 hours after admission to the ICU), as compared to standard intravenous analgesic therapy. Efficacy will be evaluated using Pain Scoring by visual analogue scale (VAS) in the early postoperative period according to our current protocol in the ICU.

1.2 Key Secondary Objectives

To evaluate the following in patients after minimally invasive cardiac surgery with ultrasound guided serratus planus block:

- Measurement of opioid exposure (parenteral morphine equivalents) in the early postoperative period (12h, 12-24h and 24-48h) in the block group compared to the standard i.v. analgesia group
- Measurement of difference in VAS at 2, 4, 6, 8, 10, 12, 16, 24, 48 hours after application of the serratus block (SAPB) compared to no SAPB according to our current clinical standard in the ICU.

1.3 Other Secondary Objectives

To evaluate the following in patients after minimally invasive cardiac surgery with ultrasound guided serratus planus block:

- Descriptive data about patients and surgery compared to standard postoperative pain therapy
- Duration of Mechanical Ventilation compared to standard postoperative pain therapy
- Duration of Cardiovascular ICU stay compared to standard postoperative pain therapy
- 30d Mortality after MIHS
- Duration of postoperative hospital stay
- Complications from block, anesthesia or surgery compared to no block
  - hematoma, pneumothorax
  - occurrence of PONV within the first 24h after surgery
  - respiratory complications (reintubation, atelectasis)
  - delirium in the ICU
  - local anesthesia systemic toxicity (LAST)
- Evaluation of pulmonary function by means of a bed side spirometer as done routinely before surgery and on postoperative day 1 and 2 in the ICU
- Evaluation of difference in biomarkers for inflammation and myocardial stress (CRP, PCT, IL6, CK, CK-MB, TropT, pBNP) according to our current standards on day 0,1,2
- after cardiac surgery between block and no block

2.3 Study Rationale

Many patients receiving MIHS suffer from significant postsurgical pain. While systemic analgesic therapy has been proven to be insufficient in a great number of patients, significant unwanted side effects might occur. Therefore, the investigation of peripheral nerve blocks such as SAPB with potential for high benefit and low risk for adverse effects as new treatment options for thoracotomy-pain is relevant. Previous randomized double-blind investigations of this novel technique are lacking. At this moment our department's current standard of care is that, SAPB is performed in patients after MICS in our department if the treating anesthetist is experienced in the procedure and the patient receives i.v. analgesia only without nerve block is he or she is not. If we are able to show a benefit for patients in the SAPB arm, the nerve block may constitute a new standard of care for all MIHS patients at our department.

SAPB was well tolerated in prior clinical trials (see also safety assessment). We therefore consider that the risk-benefit assessment of the current study is favorable.

1.1 Study design

Prospective, Interventional randomized single center, double-blind study

1.2 Study population

66 patients ≥18 years of age, being treated in the cardiothoracic 16 bed ICU or the 4 bed cardiothoracic and vascular PACU after elective cardiac surgery performed via minithoracotomy (mitral valve, tricuspid valve, atrial septal defect closure). Allocation concealment is guaranteed by opening of the concealed envelope and performance of the ultrasound guided SAPB or ultrasound only by medical personnel not involved in any of the study procedures.

Randomization will be carried out by a web-based software ('randomizer,) and patient numbers will be allocated according to their inclusion number in the study in a randomized way. The blinding table will only be unblinded at time of analysis. The intervention will be performed after ICU arrival but under sedation and analgesia before extubation to minimize patient discomfort and to ensure double blinding. The mandatory postoperative observation period will be 24 hours long, a second visit will take place 48 hours after the block has been performed.

Handling of study drug and ultrasound as well as the intervention will be carried out by medical personnel not involved in any of the study assessments or pain therapy for the respective patient.

The total study duration will be 48 hours (irrespectively of patient transfer from the ICU to the ward), mandatory visits will be carried out in person and pain and analgesia requirements will be assessed by members of the study team. Anticipated duration first patient in (FPI) to last patient out (LPO) is 24 months.

1.3 Arms and interventions

Group 1: Block Arm. Patients receive ultrasound guided serratus anterior plane block according to our department's standards between completion of surgery and before extubation as well as non-opioids according to our ICUs standard (Metamizol 3x1g/d 1st choice, Acetaminophen 3x1g/d in case

of known allergy against Metamizol or neutropenia before operation) and opioid treatment (Piritramid, Hydromorphon, Pethidin for shivering)
Serratus anterior block will be performed according to our department's standards using an ultrasound guided transducer to inject 2mg/kg of 0.5% ropivacaine combined with 0.5mcg/kg of dexmedetomidine. A sterile plaster will be placed on the puncture site after performing the block to blind ICU and PACU personnel of the intervention (see below).

Group 2: No block arm. Patients receive non-opioids (Metamizol 3x1g/d 1st choice, Acetaminophen 3x1g/d in case of known allergy against Metamizol or neutropenia before operation) and opioid treatment (Piritramid, Hydromorphon, Pethidin for shivering) only according to our ICUs current standard.

Blocks will be performed by a member of the study team experienced in regional anesthesia under linear ultrasound guidance (HFL38, 13–6 MHz; SonoSite Inc., Bothell, WA, USA), with the participant in a semi-lateral position (right side up and supported by a pillow). After sterile wash, a 70-mm Tuohy-type 22-gauge needle will be advanced beneath the serratus anterior muscle at the fifth and rib in the mid-axillary line. 2mg/kg ropivacaine 0,5% will be injected between serratus anterior and intercostal muscle layers in the 5th ICS. A sterile plaster will be placed on the injection site after completion of the block.

Patients in Group 2 will receive a sterile plaster placed on an appropriate site to blind patients and ICU personnel of the intervention.

1.4 Outcome measures

Primary outcome

Mean postoperative pain score (VAS 0-10) during the first 12 hours (measured according to our ICU's standards 2 hourly wil be compared 2,4,6,8,10,12 hours) after SABP, as compared to standard intravenous analgesic therapy. A mean difference of 20% (2 points on the VAS) will be regarded as significant.

Key secondary outcomes

- Measurement of postoperative opioid demand (Time Frame: From SAPB (or a point of time recorded on which SAPB would have been performed in the standard i.v. analgesia group) to 12, 24 and 48 hours after the intervention) in total morphine equivalents
- Postoperative Pain Score: VAS 0-10 (Time Frame: From arrival to ICU up to 48 hours postoperatively according to our ICUs standards) Pain scores reported immediately after extubation, and if feasible 2, 4, 6,8,10,12,18,24, 48 hours and 5 days after performance of the intervention in the ICU

Other secondary outcomes

- Length of Cardiovascular ICU stay (Time Frame: From admission to the Cardiovascular ICU until discharge ready time from the Cardiovascular ICU up to 30 days)
- Duration of postoperative hospital stay from the end of the operation up to 30 days
- Complications from the block, anesthesia or the surgery up to 24 hours post operatively will be recorded according to our unit's standards:
  - hematoma at puncture site

- PONV
- significant atelectasis right/left side in chest X-ray or diagnosed by ultrasound
- reintubation
- delirium
- (suspected) local anesthesia toxicity (LAST)

- Pulmonary function will be evaluated according to our unit's current standards in an objective manner by means of a bed side flowmeter before the operation and at day 1 and day 2 after extubation: 1 second capacity (VEF1)
- Evaluation of difference in biomarkers for inflammation and myocardial stress (CRP, PCT, IL6, CK, CK-MB, TropT, pBNP) as routinely performed at our department on day 0,1,2 after cardiac surgery

1.5 Inclusion criteria

- 18 years of age or more
- patients undergoing cardiac surgery through a thoracotomy incision
- patients having surgery performed by a Cardiac Surgeon at the Medical University of Vienna
- patients being treated in the 16 bed primary cardiothoracic ICU 13B-HTG at the Medical University of Vienna
- patients being treated in the 4 bed PACU of the cardiothoracic and vascular anesthesia department at the Medical University of Vienna
- signed patient consent prior to surgery

1.6 Exclusion criteria

- patients requiring full sternotomy or emergency surgery
- Allergy to amid-type local anesthetics
- patients less that 18 years of age at the time of surgery
- patients intubated >48h prior to surgery
- Infection at the site of the Serratus Anterior Plane Block
- Known bleeding diathesis with increased risk of hematoma at the block site
- Known opioid abuse
- Allergy to (metamizole AND acetaminophen) OR (hydromorphone AND Piritramide)
- Active pulmonary infection at the time of surgery
- Patient refusal prior to surgery
- Inability to communicate
- BMI ≥40

- Patients with known dementia or/and a legal guardian for medical issues
- Patients unable to understand the study measures and are not able to complete pain assessment forms.
- Known pregnancy
- Severe cardiorespiratory disturbances such as high respiratory support (>0,7 FiO2 or driving pressure >25mbar) or high catecholamine support (>0,5mcg/kg/min Norepinephrine and/or >5IE Vasopressin/h) making fast track intensive care with extubation in the first 24 hours after arrival in the ICU and ERAS impossible
- Patients with unanticipated prolonged intubation >24h after arrival in the ICU
- Postoperative ECMO support

1.7 Legal and ethical aspects

Participation is voluntary, all participants receive detailed written and personal clarification about the study by a medically qualified member of the study team. The collected data are anonymized by use of randomization numbers for further use during the investigation.

1.8 Sample size calculation

The sample size calculation was provided by Dr. Robin Ristl from the statistical department of the Medical University of Vienna.

Based upon similar investigations by other authors we are expecting a mean reduction of VAS of 2 points (20%) of VAS measured at 2,4,6,8,10,12 hours and then averaged over the first 12 hours after application of the serratus block to be statistically significant.[1,2] Based on our own unpublished preliminary investigations we are expecting a mean or median VAS to be significantly higher in our ICU than the NRS described by the authors above. Their retrospective analysis showed a median difference of 2.5 points on a NRS with a standard deviation (SD) of 2.62.

An interim analysis is planned after half of the planned patients have been treated, using the Lan DeMets spending function that approximates the O'Brien Fleming boundaries, with a nominal one-sided significance level of 0.025. Using the R-package Rpact, we calculated that 28 patients per group are required under these assumptions to proved an ovaerall power of 80%. Investigation can be stopped at the interim analysis in case of a very large observed treatment effect (observed mean reduction of VAS of 3.23 points within the first 12 hours, if the observed standard deviation corresponds to the planning assumption of 2.62) which seems possible since median treatment effect was 2.5 points in earlier, retrospective analyses.[2] Such substantial treatment effect would enable us to detect a significant treatment effect with 14 patients per group and therefore avoid withholding such an effective treatment from a number of patients in the control group. The local adjusted one-sided significance levels are 0.001525 at interim and 0.0245 at the final analysis. The power for stopping at interim under the planning assumptions is 13%. The probability to continue at interim and stop with a significant result at the final analysis is 67% and the overall power is 80%. To compensate for a possible dropout rate of up to 15% we therefore choose a maximal sample size of n=66 (n= 33 per group).

2.9.2 Statistical considerations

Continuous variables will be compared with the t-test or Mann–Whitney U-test, and categorical variables with the Chi-squared test or Fisher's exact test, as appropriate. Multiple comparisons of opioid consumption at specific intervals will be corrected with the Bonferroni method. Proportions of responders will be compared between groups using a Chi-square test. The Cochran–Armitage test will be used for satisfaction score analysis. SPSS (ver. 24; SPSS Inc., Chicago, IL, USA) will be used for all calculations. Metric variables will be described by medians and interquartile ranges or, where appropriate, by means and SDs. Frequencies will be reported as counts and percentages. All analyses will be based on the intention-to-treat principle. The key secondary outcome, the difference in morphine equivalents will be tested in hierarchical manner, only performing a formal hypothesis test at the one-sided significance level of 0.025 once the null hypothesis for the primary endpoint was rejected. The earlier investigation showed a mean difference of 9.23mg and a SD of 2.79 in the block group and of 5.14 in the standard treatment group {Toscano:2020ce}. Conservatively assuming a SD of 5.14 in both groups, a sample size of n=14 per group at interim will enables us to detect a difference in the mean of 5.7mg, which is considerably smaller than the difference of 9.23 observed in {Toscano:2020ce}, with a power of 80%. At the final analysis with n=28 per group the power for the same effect will be 98%. In the table below all outcome parameters and the appropriate statistical analysis method will be described en detail.

	outcome variable	**unit**	**statistical test**
primary outcome	mean NRS within 12h after ICU admission	VAS 0-10	t-test
secondary outcome	mean/median NRS 2h, 4h, 6h, 8h, 10h, 12h, 16h, 24h, 48h after ICU admission	VAS 0-10	t-test / Mann-Whitney U test
secondary outcome	mean/median morphine equivalents 12h, 12-24h, 24-48h after ICU admission	PME	t-test / Mann-Whitney U test
secondary outcome	complications: pneumothorax, atelectasis, hematoma, PONV, delirium, LAST	yes/no	Chi square test
secondary outcome	pulmonary function test (FEV1) preoperative, POD1, POD2	ml/sec	t-test / Mann-Whitney U test
secondary outcome	postoperative biomarkers (CRP, PCT, Trop.T, CK, CK-MB)	mg/dl, ng/ml, U/L	t-test / Mann-Whitney U test
secondary outcome	patient satisfaction with postoperative analgesia	5 point scale	t-test / Mann-Whitney U test
secondary outcome	length of stay (LOS) in the ICU, LOS in hospital	days	t-test / Mann-Whitney U test
secondary outcome	length of mechanical ventilation	hours	t-test / Mann-Whitney U test
secondary outcome	hospital mortality		Chi square test

Randomization, Stratification and Blinding

After arrival in the ICU or PACU after respiratory weaning has been initiated and before extubation, patients that have been previously included in the study will be allocated according to their inclusion number into the study to serratus anterior plane block, or no block, in a 1:1 ratio using a computer-generated sequence, with allocations sealed in opaque envelopes. An investigator opens the envelope after confirming the patient's participation in the study, after weaning has been initiated but before extubation and will perform the serratus anterior plane block in the manner depicted under "arms and interventions". The patient, ICU nursing staff, ICU physicians in charge, surgeons, and data analysts will not be informed of the group assignment and will leave the room during the performance of the procedure or ultrasound only respectively. The study medication and other equipment necessary for performing the block is readily available and frequently used in our ICU. The blinding table (see below) will be held at our clinic by the member of staff responsible for randomization and not involved in any study procedures. Unblinding will only be carried out at time of analysis or in case of emergency unblinding (see "emergency unblinding").

If emergency unblinding is necessary the blinding table will be locked but available at all times through the consultant physician on duty at our clinic.

Interim analysis (see methods/statistics). Patient list after interim analysis as follows:

Intervention

After screening, inclusion, arrival in the ICU or PACU informed consent and randomization, patients in the intervention group will receive the ultrasound guided SAPB according to our department's standards.

Table 1. weight adapted SAPB dose scheme

	patient weight (kg	Naropin 0,5%	Naropin 0,5% (ml)	Maximum dose Naropin (mg	Maximum dose Naropin (ml)
≥	50	100mg	20	150	30
≥	60	120mg	24	180	36
≥	70	140mg	28	210	42
≥	80	160mg	32	240	48
≥	90	180mg	36	270	54
≥	100	200mg	40	300	60
≥	110	200mg	40	330	66

In the no-SABP group, an appropriate block site in the no-SABP group will be covered by a sterile plaster after the intervention to ensure blinding of patients and ICU staff.

Safety Assessment Ropivacain for SAPB

The SAPB will be performed according to our department's current standard. After performing the block for several years using these standards, only block failure has been recorded, no other complication (LAST, hematoma, pneumothorax) occurred. A great number of clinical studies have been investigating Ropivacain for a great number of different nerve blocks. There is a risk for local anesthesia associated toxicity (LAST) through spread into the systemic circulation, mainly in high risk blocks and without ultrasound guidance of 1-11 per 10.000 patients receiving nerve blocks. The risk can be further minimized by performing aspiration before injection and using agents with low systemic toxicity such as Ropivacain. (Safety Committee of Japanese Society of Anesthesiologists: 2019dt)
This risk can be minimized by skilled operators with experience in performing ultrasound guided blocks and by staying well below the maximal safe dose for Ropivacain as shown in table 1. All nerve blocks at our department are performed by experienced consultants. Additionally, all our patient after cardiac surgery receive invasive blood pressure monitoring and continuous monitoring of heart rate, ECG, arterial oxygen saturation as well as dept and rate of breathing and have a central venous catheter in situ for rapid infusion of medication into the central circulation. There is no better monitoring or safer place for any patient than an ICU or PACU and the monitoring described above. Additionally, a study investigating Ropivacain continuous infusions after knee surgery found no local anesthesia associated complications. [11]

Dexmedetomidine, which is to be used as an adjuvans to Ropivacain according to our department's standards with 0.5mcg/kg patient weight has been administered countless times in clinical practice and in clinical studies to increase block duration due to its alpha-2 agonistic effects. Potential adverse events could therefore be bradycardia and hypotension, however in our postoperative setting with 100% of postsurgical patients being on catecholamine (vasopressor) infusions and having epicardial pacemaker support in situ such potential side effects are luckily irrelevant. In a large metaanalysis of 9 RCTs it could be shown to be free of adverse events apart from dryness of the mouth and showed rapid onset and prolonged block duration in patients receiving epidural anesthesia [12].
A Review of 9 RCTs using Dexmedetomidine for nerve blocks showed improved analgesia, block duration and reduced need for opioid analgesia at the expense of (clinically irrelevant)

hypotension[13]. Other trials using Dexmedetomidine showed no significant hemodynamic effects but a significantly reduced need for morphine and a prolonged block duration through use in a field block [14].
Unsurprisingly, there is increasing evidence that sparing (reducing) of opioid analgesia in cardiac surgery by using dexmedetomidine may increase outcome by avoiding its numerous and deleterious side effect [15].

Concerning SABP, a number of studies have investigated the efficacy and safety of SAPB for thoracic surgery and MIHS and potentially due to use of novel and highly effective ultrasound devices with live and direct visualization of the blocking needle and spread of local anesthetic, investigators have found no block related complications [6,16].

The block was efficient in patients after breast surgery, thoracic surgery and MIHS leading to significantly reduced pain scores and reduced morphine consumption in a nonrandomized cohort study [1]. The medication is approved for intrathecal and peripheral nerve blocks.
SAPB is performed routinely in our department for several years and no complication including LAST occurred.

Necessity of Patient Study-ID

In Austria Ropivacain ist not a scheduled narcotic. It is freely available and can be purchased legally. Ropivacain or is not tested for in any drug test panel in use. Therefore a specific study ID aimed at avoiding legal consequences in case of a positive drug test is not warranted.

Study medication

Ropivacain 0,5% (5mg/ml)

Active agent and characteristics: Ropivacainhydrochloride Monohydrate 10mg/ml in 10ml of H2O + 10ml NaCl out of sterile plastic vials creating Ropivacainhydrochloride Monohydrate 5mg/ml in 20 ml solution used for central and peripheral nerve and field blocks

Trade name of the agent: Ropivacain Sintetica 10mg/ml 10ml

Manufacturer: Ropivacain used is manufactured by Sintetica GmbH, Münster

Drug supply: Sintetica GmbH, Münster,

Storage Instructions: Ropivacain Sintetica sterile plastic vials are stable for 3 years at room temperature <25°C.

Route of administration: peripheral nerve block

Dexmedetomidine (adjuvans to Ropivacain)

Active agent and characteristics: Dexmedetomidine 100mcg/ml in 2ml of H2O in sterile glass vials used as an adjuvans to local anesthetics to prolong block duration in central, peripheral nerve and field blocks

Trade name of the agent: Dexmedetomidin Ever Pharma 100mcg/ml

Manufacturer: Dexmedetomidine used is manufactured by Ever Pharma GmbH, Jena

Drug supply: Ever Neuro Pharma GmbH

Storage Instructions: Dexmedetomidin Ever Pharma sterile glass vials are stable for 4 years at room temperature protected from light.

Route of administration: mixed in very small doses with Ropivacain to increase nerve and field block duration

Dosage and administration

All Ropivacain doses are administered according to our existing department's standard as single shot doses with a maximal dose of 200mg/d and reduced doses for patients according to body weight

Initial (single shot) dose:

	patient weight (kg	Naropin 0,5%	Naropin 0,5% (ml)	Maximum dose Naropin (mg	Maximum dose Naropin (ml)
≥	50	100mg	20	150	30
≥	60	120mg	24	180	36
≥	70	140mg	28	210	42
≥	80	160mg	32	240	48
≥	90	180mg	36	270	54
≥	100	200mg	40	300	60
≥	110	200mg	40	330	66

block interruption or avoidance

Since the planned intervention is a single shot nerve block temporarily interrupting or permanently discontinuing the study drug is not appropriate, rather interrupting the nerve block during the process or avoiding a planned injection completely is appropriate if continued administration of the study drug is believed to be contrary to the best interests of the patient.

Interrupting the injection during the process or avoiding a planned injection of the study drug completely might be triggered by an AE, a diagnostic or therapeutic procedure, an abnormal assessment, or for administrative reasons, in particular withdrawal of the patient's consent before anesthesia.

The reason for injection interruption or avoidance of performance of the block must be documented in the CRF.

block interruption, permanent avoidance due to an adverse event

If the reason for premature permanent discontinuation of study treatment is an AE, the patient will have a "Premature End of Study (EOS)" visit with all the assessments performed whenever possible.

block interruption, permanent avoidance due to another reason than adverse event

If the reason for premature permanent discontinuation of study treatment is not an AE, the patient should be withdrawn from the study (withdrawal of consent) and have the end of study (EOS) visit with all the assessments whenever possible.

block repetition

In case of patient discomfort due to pain and continued stay in the ICU block repetition is possible at the treating physician's and the patient's discretion. Repetition of the block will be performed with Naropin 5mg/ml, there will be no randomization or plaster-only group. Repetition of the block will be documented in the CRF.

Study-drug delivery & drug and equipment storage conditions

Vials containing the study medication are delivered by the hospital pharmacy service to our ICU and are regularly stored in the ICU pharmacy at ambient temperature (≤25°C), protected from light. NaCl to establish the adequate drug concentration is also stored in the ICU pharmacy, the ultrasound machine, needles to perform the nerve block, disinfection solution and sterile gloves, ultrasound gel and sterile sleeves for the ultrasound transducer will be stored in our ICU-equipment storage.

Drug accountability

Performance of the block or ultrasound only will be electronically recorded as "study measure" in the ICU patient data management system (PDMS) and the CRF by the member of the study team performing the intervention and is otherwise not involved in the treatment of the patient.

The study drug is a commonly administered local anesthetic which is in store in our ICUs pharmacy and additional doses will be ordered from the hospital pharmacy in case of stocks running low.

Concomitant medication

The well-being of the patient has the first priority, and modifications of concomitant treatment during the trial are allowed as necessary. They will be documented in the patient's records.

Allowed: All patients will receive the current standard of intravenous analgesia at our department: metamizol 3 x 1g PD as their basic analgesic medication.
Patients will be allowed opioids as Piritramid, Hydromorphon as additional medication according to the WHO-formula for severe pain. Acetaminophen 3x1g/d will be given instead of Metamizol in case of known allergy against Metamizol or neutropenia in the last lab findings before the operation or a history of Metamizol-induced agranulocytosis. In addition, diclofenac up to 2x75mg i.v. may be given in appropriate patients to reduce postthoracotomy pain.

Not allowed: other opioids or NSAIDs other than mentioned above

Emergency procedure for unblinding

'Emergency' is defined as a Serious Adverse Event which is possibly related, probably related or related to the study drug.

A patient's treatment assignment should only be unblinded when knowledge of the treatment is essential to make a decision on the medical management of the patient.

In such case the blinding table, which can be accessed by the anesthesia consultant on duty will be available at all times.

Study procedures

General rules for trial procedures

- No study specific measures like blood sampling and measurements (vital parameters, ECG, etc.) are planned and only data collected during clinical routine after minimally invasive cardiac surgery are used. Vital parameters including invasive blood pressure monitoring, respiration, SpO2, blood gases, central venous pressure and in some cases cardiac output are routinely and continuously measured in our ICU and PACU. Blood samples including cardiac enzymes and inflammation parameters as well as spirometric FEV1 measurements are routinely measured before surgery for risk assessment and routine measurements are performed in our ICU on the first and on the second postoperative day.

Screening investigation

The screening investigation and obtaining informed consent by the patient will be done before the planned MIHS either in the outpatient department at the same time as patient assessment before anesthesia will be performed, consent for anesthesia will be obtained and patients will be informed about the planned measures. In semi-acute cases when assessment in the outpatient clinic is not possible the screening investigation and informed consent will be performed on the ward at the same time as patient assessment before anesthesia will be performed.

Performance of the intervention

After the surgical procedure and after patient arrival in the ICU but before extubation a member of the study team will confirm that none of the exclusion criteria are fulfilled before opening the opaque envelope containing the randomization information and performing the intervention. The intervention will be documented on the paper-CRF and electronically in the ICU-PDMS as “study intervention” with date, time and possible problems.

Interim Investigation

As described under “statistical considerations” and in the synopsis part, an interim analysis is planned after half of the planned patients have been treated, using the Lan DeMets spending function that approximates the O'Brien Fleming boundaries, with a nominal one-sided significance level of 0.025. Using the R-package Rpact, we calculated that 28 patients per group are required under these assumptions to proved an ovaerall power of 80%. Investigation can be stopped at the interim analysis in case of a very large observed treatment effect (observed mean reduction of VAS of 3.23 points within the first 12 hours, if the observed standard deviation corresponds to the planning assumption of 2.62) which seems possible since median treatment effect was 2.5 points in earlier, retrospective analyses. {Aydin:2020bl} Such substantial treatment effect would enable us to detect a significant treatment effect with 14 patients per group and therefore avoid withholding such an effective treatment from a number of patients in the control group. The local adjusted one-sided significance levels are 0.001525 at interim and 0.0245 at the final analysis. The power for stopping at interim under the planning assumptions is 13%. The probability to continue at interim and stop with a significant result at the final analysis is 67% and the overall power is 80%. To compensate for a possible dropout rate of up to 15% we therefore choose a maximal sample size of n=66 (n= 33 per group).

End-of-study (EOS) examination

After treatment period for 24 hours and if possible before transfer to the ward from the ICU, patients undergo the end-of-study examination that entails data routinely collected in the ICU at the first day after cardiac surgery:

VAS-Score at 24 hours, ECG, physical examination, blood pressure, safety laboratory, FEV1 measurment, adverse events and blinding survey.

As described above, repetition of the block in accordance with the physician on duty in the ICU and the patient is a possibility at this point. Apart from documentation of the repetition, further outcome data such as pain scores or opioid consumption >24h after the performance of the first intervention will be collected according to the clinical standard after MIHS in our ICU.

Definition of the end of the trial

The end of the trial is defined as the date of the last visit (EOS investigation) of the last patient undergoing the trial

SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

Adverse events (AEs)

Summary of known and potential risks of the study drug

Please see safety assessment of Ropivacain above.

Definition of adverse events

An AE is any untoward adverse change from the subject's baseline condition, i.e., any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease which is considered to be clinically relevant by the physician that occurs during the course of the study, whether or not considered related to the study drug.

Adverse events include:

- Exacerbation of a pre-existing disease.
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.
- Disease or medical condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study.
- Continuous persistent disease or symptoms present at baseline that worsen following the start of the study.
- Lack of efficacy in the acute treatment of a life-threatening disease.
- Events considered by the Investigator to be related to study-mandated procedures.
- Abnormal assessments, e.g., ECG and physical examination findings, must be reported as AEs if they represent a clinically significant finding that was not present at baseline or worsened during the course of the study.

- Laboratory test abnormalities must be reported as AEs if they represent a clinically significant finding which is not sufficiently explained by lab changes occurring after cardiac surgery, symptomatic or not, which was not present at baseline or worsened during the course of the study or led to dose reduction, interruption or permanent discontinuation of study drug. Adverse events do not include:

    - Pre-planned interventions or occurrence of endpoints specified in the study protocol are not considered AE´s, if not defined otherwise (eg.as a result of overdose)
    - Medical or surgical procedure, e.g., surgery, endoscopy, tooth extraction, transfusion. However, the event leading to the procedure is an AE. If this event is serious, the procedure must be described in the SAE narrative.
    - Pre-existing disease or medical condition that does not worsen.
    - Situations in which an adverse change did not occur, e.g., hospitalizations for cosmetic elective surgery or for social and/or convenience reasons.
    - Overdose of either study drug or concomitant medication without any signs or symptoms. However, overdose must be mentioned in the Study Drug Log.

Serious adverse events (SAEs)

A Serious Adverse Event (SAE) is defined by the International Conference on Harmonization (ICH) guidelines and GCP guidelines as any AE fulfilling at least one of the following criteria:

- Results in deaths.
- Life-threatening – defined as an event in which the subject was, in the judgment of the Investigator, at risk of death at the time of the event;
- Requiring subject's hospitalization or prolongation of existing hospitalization
- Resulting in persistent or significant disability or incapacity (i.e., a substantial disruption of a person’s ability to conduct normal life functions).
- Congenital anomaly or birth defect.
- Optional: Is medically significant or requires intervention to prevent at least one of the outcomes listed above

Life-threatening refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

Important medical events that may not immediately result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above. This means an individual case decision.

Hospitalization – Prolongation of existing hospitalization

Hospitalization is defined as an overnight stay in a hospital unit and/or emergency room. An additional overnight stay defines a prolongation of existing hospitalization.
The following is not considered an SAE and should be reported as an AE only:

• Treatment on an emergency or out subject basis for an event not fulfilling the definition of seriousness given above and not resulting in hospitalization.

The following reasons for hospitalizations are not considered AEs, and therefore not SAEs:

- Hospitalizations for cosmetic elective surgery, social and/or convenience reasons.
- Elective treatment of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for chemotherapy for cancer, elective hip replacement for arthritis.

SAEs related to investigational drug

Such SAEs are defined as SAEs that appear to have a reasonable possibility of causal relationship.

Suspected unexpected serious adverse reactions (SUSARs)

SUSARs are all serious adverse reactions with **suspected** causal relationship to the study drug that is **unexpected** (not previously described in the Summary of Product Characteristics or Investigator's brochure) and serious.

Pregnancy

Any pregnancy that occurs during study participation must be reported to the Investigator/sponsor. To ensure subject safety, each pregnancy must be reported to the Sponsor immediately. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the Investigator's attention after the subject has completed the study and considered by the Investigator as possibly related to the investigational product, must be promptly reported to the Investigator/sponsor.

In addition, the Investigator must attempt to collect pregnancy information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study. Pregnancy information must be reported to the Investigator/sponsor as described above.

Severity of adverse events

The severity of clinical AEs is graded on a three-point scale: mild, moderate, severe, and reported on specific AE pages of the CRF.

If the severity of an AE worsens during study drug administration, only the worst intensity should be reported on the AE page. If the AE lessens in intensity, no change in the severity is required.

If an AE occurs during a washout or placebo run-in phase and afterwards worsens during the treatment phase, a new AE page must be filled in with the intensity observed during study drug administration.

Mild

Event may be noticeable to subject; does not influence daily activities; the AE resolves spontaneously or may require minimal therapeutic intervention;

Moderate

Event may make subject uncomfortable; performance of daily activities may be influenced; intervention may be needed; the AE produces no sequelae.

Severe

Event may cause noticeable discomfort; usually interferes with daily activities; subject may not be able to continue in the study; the AE produces sequelae, which require prolonged therapeutic intervention.

A mild, moderate or severe AE may or may not be serious. These terms are used to describe the intensity of a specific event (as in mild, moderate, or severe myocardial infarction). However, a severe event may be of relatively minor medical significance (such as severe headache) and is not necessarily serious. For example, nausea lasting several hours may be rated as severe, but may not be clinically serious. Fever of 39°C that is not considered severe may become serious if it prolongs hospital discharge by a day. Seriousness rather than severity serves as a guide for defining regulatory reporting obligations.

Relationship to study drug

For all AEs, the Investigator will assess the causal relationship between the study drug and the AE using his/her clinical expertise and judgment according to the following algorithm that best fits the circumstances of the AE:

Not related

- May or may not follow a temporal sequence from administration of the study product
- Is biologically implausible and does not follow known response pattern to the suspect study drug (if response pattern is previously known).
- Can be explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

Unlikely

- There is a reasonable temporal relation between the AE and the intake of the study medication, but there is a plausible other explanation for the occurrence of the AE.

Possibly

- The AE has a reasonable temporal relationship with drug administration.
- The AE may equally be explained by the study subject's clinically state, environmental or toxic factors, or concomitant therapy administered to the study subject.
- The relationship between study drug and AE may also be pharmacologically or clinically plausible.

Probably

- There is a reasonable temporal relation between the AE and the intake of the study medication, and plausible reasons point to a causal relation with the study medication.

Related

- Reasonable temporal relation between the AE and the intake of the study medication and
- There is no other explanation for the AE and
- Subsidence or disappearance of the AE on withdrawal of the study medication and

- Recurrence of the symptoms on restart at previous dose (only applies for re-institution of mediation).

Not assessable

- The causal relationship between the study drug and the AE cannot be judged.

Reporting procedures

A special section is designated to adverse events in the case report form. The following details must thereby be entered:

- Type of adverse event
- Start (date and time)
- End (date and time)
- Severity (mild, moderate, severe)
- Serious (no / yes)
- Unexpected (no / yes)
- Outcome (resolved, resolving, not resolved, resolved with sequelae, unknown, fatal)
- Relation to study drug (Related/ Probably/ Possibly/ Unlikely/ Not related/ Not assessable)

  Adverse events are to be documented in the case report form in accordance with the above mentioned criteria.

Reporting procedures for SAEs

In case of a serious adverse event, the Investigator has to use all supportive measures for best patient treatment. A written report is also to be prepared and should at least contain the following:

- Patient number
- Patient: sex
- The suspected investigational medical product (IMP)
- The adverse event assessed as serious
- Short description of the event and outcome

If applicable, the initial report should be followed by the Follow up report, indicating the outcome of the SAE.

Reporting procedures for SUSAR

It must be remembered that the regulatory authorities, and the Institutional Review Board / Independent Ethics Committee (IRB / IEC) must be informed about all SUSAR. Such reports shall be made by the sponsor and should content at least the following details:

- Patient number (study code/screening number)
- Patient: age in years, sex
- Name of Investigator and investigating site
- Period of administration
- The suspected investigational medical product (IMP)
- The adverse event assessed as serious and unexpected, and for which there is a **suspected** causal relationship to the IMP

- Concomitant disease and medication
- Short description of the event:
    - Description
    - Onset and if applicable, end
    - Therapeutic intervention
    - Causal relationship
    - Seriousness criteria or reportable reason

Electronic reporting should be the expected method for reporting of SUSARs to the competent authority. In that case, the format and content as defined by the regulatory requirements should be adhered to. The latest version of MedDRA should be applied. Lower level terms (LLT) should be used.

DOCUMENTATION AND DATA MANAGEMENT

Documentation of study results

A subject screening and identification Log will be completed for all enrolled subjects with the reasons for exclusion. The screening and identification log will be held in a password protected on a desktop computer owned by the medical university of Vienna.

Case report form (CRF)

In the current study paper based CRFs will be used.

For each subject enrolled, regardless of performance of SPB, a CRF must be completed and signed by the Investigator or a designated sub-Investigator. This also applies to those subjects who fail to complete the study. If a subject withdraws from the study, the reason must be noted on the CRF. Case report forms are to be completed on an ongoing basis.

If screening failures should not be documented in the CRF, this has to be clearly defined in the protocol.

CRF entries and corrections will only be performed by study site staff, authorized by the Investigator.

In a paper based CRF all forms should be completed and must be legible. Entry errors have to be corrected according the ICH-GCP Guidelines.

The entries will be checked by trained personnel (Monitor) and any errors or inconsistencies will be checked immediately.

The monitor will collect original completed and signed CRFs at the end of the study. The completed and signed CRFs will remain on site.

Data Manager: Dr. Maximilian Stanger

Department of General Anaesthesia and Intensive Care Medicine, Medical University of Vienna

Maximilian.Stanger@meduniwien.ac.at

Data collection

Data collected at all visits are entered into a paper CRF. The CRFs will be source documents verified following guidelines established before study onset as detailed in the Monitoring Plan.

Safekeeping

The Investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified (according to ICH-GCP “essential documents”). These documents will be classified into two different categories: Investigator's study site file (ISF) with all essential documents regarding the study conduct, and subject clinical source documents.

The Investigator's file will contain all essential documents listed in ICH-GCP Guidelines section 8.

Subject clinical source documents include all patient hospital clinical records in original version, such as original laboratory reports, ECG, X-ray prints and other reports.

These two categories of documents must be kept on file by the Investigator for as long as needed to comply with the regulatory requirements.

Quality control and quality assurance

Periodic Monitoring

The designated monitor will contact and visit the Investigator on a regularly basis and will be allowed to have direct access to all source documents needed to verify the entries in the CRFs and other protocol-related documents provided that subject confidentiality is maintained in agreement with local regulations. It will be the monitor's responsibility to inspect the CRFs at regular intervals according to the monitoring plan throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them.

Monitoring will be performed by Univ. Prof. E. Tschernko

Edda.Tschernko@meduniwien.ac.at

Department of Cardiothoracic and Vascular Anaesthesia and Intensive Care Medicine, Medical University Vienna

4 monitoring visits are scheduled (initiation visit, three routine visits (every 6 months) and a close out visit after the last patient has completed the study)

The monitor will check the source data on the following points for each patient:

1) Informed Consent
2) Adverse Events
3) Primary Endpoint

100% of source data will be inspected in a control sample.

Audit and inspections

Upon request, the Investigator will make all study-related source data and records available to a qualified quality assurance auditor mandated by the sponsor or to competent authority inspectors. The main purposes of an audit or inspection are to confirm that the rights and welfare of the subjects have been adequately protected, and that all data relevant for assessment of safety and efficacy of the investigational product have appropriately been reported to the sponsor.

Reporting and publication

Publication of study results

The findings of this study will be published by the sponsor (Investigators) in a scientific journal and presented at scientific meetings. The manuscript will be circulated to all co-Investigators before submission. Confidentiality of subjects in reports/publications will be guaranteed.

ETHICAL AND LEGAL ASPECTS

Informed consent of subjects

Following comprehensive instruction regarding the nature, significance, impact and risks of this clinical trial, the patient must give written consent to participation in the study.

During the instruction the trial participants are to be made aware of the fact that they can withdraw their consent – without giving reasons – at any time without their further medical care being influenced in any way.

In addition to the comprehensive instructions given to the trial participants by the Investigator, the trial participants also receive a written patient information sheet in comprehensible language, explaining the nature and purpose of the study and its progress.

The patients must agree to the possibility of study-related data being passed on to relevant authorities.

The patients must be informed in detail of their obligations in relation to the trial participants insurance in order not to jeopardize insurance cover.

Acknowledgement / approval of the study

The Investigator (or a designated CRO) will submit this protocol and any related document provided to the subject (such as subject information used to obtain informed consent) to an Ethics Committee (EC) or Institutional Review Board (IRB). Approval from the committee must be obtained before starting the study.

The clinical trial shall be performed in full compliance with the legal regulations according to the Drug Law (AMG - Arzneimittelgesetz) of the Republic of Austria.

An application must also be submitted to the Austrian Competent Authorities (Bundesamt für Sicherheit im Gesundheitswesen (BASG) represented by the Agency for Health and Food Safety (AGES Medizinmarktaufsicht) and registered to the European Clinical Trial Database (EudraCT) using the required forms. The timelines for (silent) approval set by national law must be followed before starting the study.

Changes in the conduct of the study

Protocol amendments

Proposed amendments must be submitted to the appropriate CA and ECs. Substantial amendments may be implemented only after CA/EC approval has been obtained. Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to receiving CA/EC approval. However, in this case, approval must be obtained as soon as possible after implementation.

Study Termination

If the sponsor or the Investigator decides to terminate the study before the planned completion, they will notify each other in writing stating the reasons of early termination. Both the sponsor and the investigator will ensure the protection of the subjects' wellbeing. The sponsor will notify the regulatory authority as well as the ethics committee about the premature termination. Documentation will be filed in the Trial Master File as well as in the Investigator Site File.

Clinical Study Report (CSR)

Within one year after the final completion of the study, a full CSR will be prepared by the sponsor and submitted to the EC and the competent authority.

The Investigator will be asked to review and sign the final study report.

Insurance

During their participation in the clinical trial the patients will be insured as defined by legal requirements. The Investigator of the clinical trial will receive a copy of the insurance conditions of the 'patients insurance'. The sponsor is providing insurance in order to indemnify (legal and financial coverage) the Investigator/center against claims arising from the study, except for claims that arise from malpractice and/or negligence. The compensation of the subject in the event of study-related injuries will comply with the applicable regulations.

Details on the existing patients insurance are given in the patient information sheet.

All subjects participating in clinical studies will be insured through the Department of Anesthesiology and Pain Medicine (master policy, Medical University Vienna) by:

Zürich Versicherungs AG
Address: Schwarzenbergplatz 15, 1010, Wien Telephonnumber: 0043 (01) 50125-0 Insurance Policy Number: 07229622-2

Ethics and good clinical practice (GCP)

The Investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" (as amended at the 64th WMA General Assembly, Fortaleza, Brazil, 2013) and with the laws and regulations of the country in which the clinical research is conducted.

The Investigator of the clinical trial shall guarantee that only appropriately trained personnel will be involved in the study. All studies must follow the ICH GCP Guidelines and the regulatory requirements.

Therefore this study follows the EU Directive embedded in the Austrian drug act

Potential inconveniences and risks for the patients:

- **Drug** Patients will be informed about all potential side effects ropivacaine for serratus block. A detailed safety evaluation is presented above.
- **Block site hematoma** patients will be informed of the possibility of small, cutaneous hematoma formation although this is an extremely rare condition in our ICU since blocks are routinely done by experienced clinicians

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