Official Title of the study:

Prospective, Randomized Comparative Study of an Anesthesiological, Ultrasound-Guided „Erector Spinae Plane Block“ (ESPB) Versus a Surgical, Thoracoscopically-Guided „Intercostal Nerve Block“ (ICNB) in „Video-Assisted Thoracoscopic“ (VATS) Procedures, Evaluating Postoperative Analgesic Consumption, Postoperative Pain Perception, and Duration of the Procedure

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Responsibilities

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Registration according to Article 35 Declaration of Helsinki in a publicly accessible study registry:
The planned study will be registered at ClinicalTrials.gov after approval by the ethics committee.

Scientific Background

Current state of research (with literature references):

Effective postoperative pain management is essential after thoracic surgery. Insufficient analgesia may lead to pain-related shallow breathing and insufficient coughing effort with increased risk of pulmonary complications such as atelectasis and pneumonias. „Video-assisted thoracoscopic” (VATS) procedures are minimally invasive procedures that are already associated with significantly less pain than open thoracotomies. Nevertheless, postoperative pain is not insignificant.
In recent years, regional anesthesia has become increasingly established for perioperative pain therapy, since it enables a reduction of systemic opioid consumption.
For thoracic surgery, neuraxial procedures or various chest wall blocks are suitable as adjuncts to general anesthesia.

In VATS procedures, chest wall blocks are considered the preferred method due to their lower invasiveness and more favorable risk profile in relation to its effectiveness.
Two procedures that are nowadays frequently used in VATS procedures are the „Erector Spinae Plane Block" (ESPB) and the „Intercostal Nerve Block" (ICNB).
The ESPB was first described in 2016 [1] and is now regarded as one of the most established and most frequently performed chest wall blocks in VATS procedures. Under ultrasound-guidance, local anesthetic is applied into the subfascial space beneath the M. erector spinae. Due to the cranio-caudal spread, multiple dorsal spinal nerve branches can be reached with a single puncture [2]. It is usually performed unilaterally on the operation side in awake, seated patients preoperatively. In randomized studies, the ESPB in VATS procedures has been shown to significantly reduce postoperative opioid consumption and pain intensity [3,4,5].
The technique of the ICNB dates back to the beginning of the 1900s. The local anesthetic is injected into the intercostal space between the M. intercostalis internus and the membrana endothoracica, where a blockade of the intercostal nerves takes place. In 1995, Temes et al. described a performance under thoracoscopic visualization [6]. This enables a direct visual control of the application of the local anesthetic. An additional advantage of this procedure is that a thoracoscopic visualization of the inner rib space is required anyway for the upcoming operation and no additional positioning of the patient is necessary. Studies show a significant reduction of pain in the first 24 hours [7]. In this context, a percutaneous procedure showed a significantly lower opioid requirement and better patient satisfaction than the transthoracic approach [8].
There are already first studies comparing ESPB and ICNB with regard to postoperative analgesic effectiveness. However, the results are inconsistent. Gams et al. could demonstrate a lower opioid consumption in patients with continuous ESPB compared to ICNB [9]. However, Zhang et al. and Sung et al. could not demonstrate a significant difference in pain intensity and opioid consumption within 12-48 hours [10,11]. The studies do not provide direct comparability to the present project, since catheter techniques for continuous local anesthetic administration were used or ICNB was only performed under sonographic and not thoracoscopic visual control.

References:
1. Forero et al. The Erector Spinae Plane Block: A Novel Analgesic Technique in Thoracic Neuropathic Pain Regional Anesthesia & Pain Medicine 2016;41:621-627.
2. Bang et al. The erector spinae plane block for effective analgesia after lung lobectomy: Three cases report. Medicine (Baltimore). 2019 Jul;98(29):e16262.
3. Ciftci et al. Comparison of ultrasound-guided erector spinae plane block and paravertebral block in VATS: A randomized controlled trial. J Cardiothorac Vasc Anesth. 2020.
4. Liu et al. Effects of ultrasound-guided erector spinae plane block on postoperative analgesia and plasma cytokine levels after uniportal VATS: a prospective randomized controlled trial. J Anesth 35, 3–9 (2021).
5. Yao et al. Impact of ultrasound-guided erector spinae plane block on postoperative quality of recovery in video-assisted thoracic surgery: A prospective, randomized, controlled trial. J Clin Anesth 2020; 63: 109783.
6. Temes et al. Thoracoscopic intercostal nerve blocks. Ann Thorac Surg. 1995;59(3):787–788.
7. Ökmen et al. Rhomboid Intercostal and Serratus Anterior Interfascial Plane Blocks for the Treatment of Post-Operative Pain after Video-Assisted Thoracoscopic Surgery: A Retrospective Propensity-Matched Study. Turk J Anaesthesiol Reanim. 2021; 49(3): 211-217
8. Hui et al. Comparison of analgesic effects of percutaneous and transthoracic intercostal nerve block in video-assisted thoracic surgery: a propensity score-matched study. J Cardiothorac Surg. 2024 Jan 30;19(1):33.
9. Gams et al. Erector spinae plane block versus intercostal nerve block for postoperative analgesia in lung cancer surgery. Radiology and Oncology, vol. 57, no. 3, Sciendo, 2023.
10. Zhang et al. Comparison of Rhomboid Intercostal Block, Erector Spinae Plane Block, and Serratus Plane Block on Analgesia for Video-Assisted Thoracic Surgery: A Prospective, Randomized, Controlled Trial. Int J Clin Pract. 2022 Jun 23;2022:6924489
11. Sung et al. Comparisons in analgesic effects between ultrasound-guided erector spinae plane block and surgical intercostal nerve block after video-assisted thoracoscopic surgery: A randomized controlled trial. J Clin Anesth. 2024 Aug;95:111448

Formulation of the research question (Rationale):

The perioperative pain management strategy for VATS procedures in our clinic provides that every patient receives an additive regional anesthesia perioperatively. If time and resources are sufficient and practical skill and knowledge are available, ESPB is performed by the anesthesiology department during anesthesia induction.
The ICNB under thoracoscopic view by the surgical department is performed if the responsible anesthesiological medical staff is not skilled in the ultrasound-guided ESPB technique or if the transition time is limited. In this study setting, randomization determines the respective procedure. We expect ESPB to be non-inferior to ICNB.
Therefore, the aim of the present monocentric, prospective, randomized study is to test the non-inferiority of ESPB compared to ICNB with regard to postoperative analgesic effectiveness and procedural duration.

Justification of the necessity of a human trial:

The research question of the study can only be answered by means of a human trial. The analgesic effectiveness in humans as well as the duration of the procedure cannot be validly assessed by animal experimental models, simulations or retrospective analyses. Furthermore, both methods are firmly implemented clinical standards and are routinely performed at our clinic. A systematic prospective comparison with regard to the procedure and postoperative analgesic effectiveness has not yet been carried out.

Project objectives

Primary objective:

Postoperative analgesic requirement or consumption within the first 24 hours after surgery.

Secondary objective:

- Postoperative pain perception or intensity of pain, measured using the NRS scale, within the first 24 hours after surgery.
- Time required to perform the chest wall block, defined as the period from initial needle insertion to completion of the full local anesthetic dose administration.

Endpoint / Outcome measures

Endpoint / Outcome measures:

The outcome measures include the recording of analgesic intake within the first 24 hours after surgery as well as the recording of postoperative pain perception using the NRS pain scale. Additionally, the duration of the chest wall block, defined as the period from initial needle insertion to completion of the full local anesthetic dose administration, is documented. The incidence of PONV as well as of other complications are additionally recorded in both groups. The standardized assessment of pain and analgesic consumption after surgery is carried out by the in-house anesthesiology pain service using a standardized pain questionnaire and at predefined time points (1 hour, 2 hours, 12 hours, 24 hours). The anesthesiology pain service remains blinded to the intervention performed.

Hypothesis(es):

Primary hypothesis:
The anesthesiological, ultrasound-guided ESPB is non-inferior to the surgical, thoracoscopically-guided ICNB with regard to postoperative analgesic consumption.
Secondary hypothesis:
The anesthesiological, ultrasound-guided ESPB is non-inferior to the surgical, thoracoscopically-guided ICNB with regard to postoperative pain perception and duration of performance, defined as the period from initial needle insertion to completion of the full local anesthetic dose administration.

Study population

Included study population: Patients ≥ 18 years

Handling of non-German-speaking persons: Only patients with sufficient proficiency in German are to be included in the planned investigation.

Inclusion criteria:

- Provision of written informed consent
- Adults (≥ 18 years)
- Elective video-assisted thoracoscopic surgery (VATS) for pulmonary resection (e.g., lobectomy, segmentectomy, wedge resection)

Exclusion criteria:

- Lack of informed consent
- Language barrier
- Pregnancy or breastfeeding
- Known allergy to local anesthetics used in the study
- Infection at the injection site(s)
- History of complex chest wall surgery
- Revision surgery with a prior operation within the last 6 months
- Intraoperative conversion to open thoracotomy
- Chronic pain syndrome
- Fibromyalgia
- Chronic opioid use
- Chronic alcohol abuse
- Chronic substance abuse (e.g., THC, amphetamines, cocaine)
- History of psychiatric disorders (e.g., depression, schizophrenia)
- Impaired consciousness, cognition, or ability to communicate
- Known coagulopathy (including platelet count < 80,000/µL or prolonged PTT/aPTT >1.5× the upper limit of normal)
- Ongoing therapeutic anticoagulation

Number of study participants:

In order to be able to compensate for a loss to follow-up of up to 10%, we plan, with a calculated sample size of 66 patients, the recruitment of 72 patients (36 per study arm).

Recruitment measures:

Patients who present for the planned operation and meet the above criteria are recruited.

Information and consent process:

Ultrasound-guided ESPB and thoracoscopically-guided ICNB in VATS procedures are already routinely performed and explained in our clinic by anesthesiologists and surgeons.
As part of the regular preoperative informed consent discussion, patients receive an information sheet and additional information about participation in the study from the informing anesthesiologist. The reflection period corresponds to the reflection period for the anesthetic procedure.

Expense allowance: none

Insurance: none

Methods

Single-/multi-center: single-center

Study design:

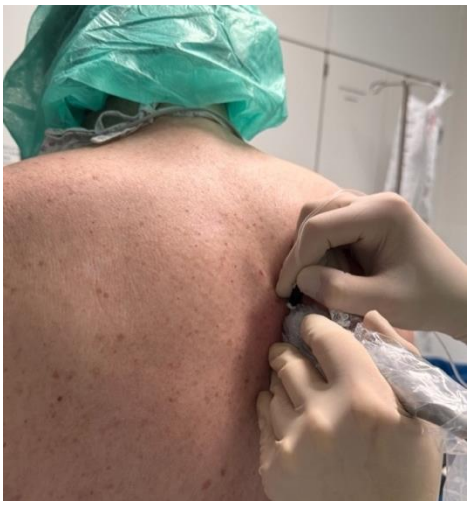
Single-center, prospective, randomized non-inferiority study with two parallel study arms.

Study procedure:

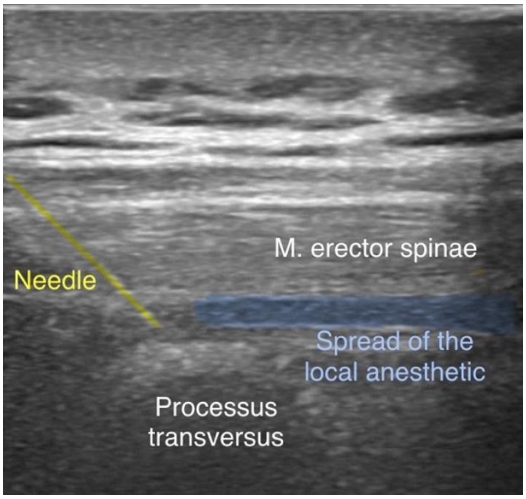
Randomization process:
After proper information and consent, patients are randomized preoperatively using a sealed envelope system and assigned to one of the two intervention groups.

Anesthesiological procedure for both intervention groups:
- Check of preoperative checklist (patient ID, surgery, side of surgery, fasting status, etc.)
- Placement of i.v. access
- Standardized cardiorespiratory monitoring (ECG, SpO2, blood pressure)
- Preoxygenation until etO_2 > 90% & standardized i.v. induction of anesthesia (sufentanil 0.3 µg/kg, propofol 2-3 mg/kg, rocuronium 0.6 mg/kg)
- Mask ventilation, followed by oral endotracheal intubation (male: DLT 39.0, female: DLT 37.0, if necessary size adapted according to body height according to SOP) & initiation of pressure-controlled ventilation (PCV)
- Standard monitoring of ventilatory parameters ($etCO_2$, FiO_2, PEEP, Pinsp, respiratory rate, I:E ratio, plateau duration)
- Standardized maintenance of anesthesia using TIVA: sufentanil as needed, propofol infusion according to depth of anesthesia (target SE 40-60, target BSR 0%), rocuronium according to relaxometry
- Standard i.v. analgesia: metamizole 1 g i.v. (at least 30 min before emergence)
In case of metamizole allergy: paracetamol 1 g i.v. (at least 30 min before emergence)
- Standard administration of 2 i.v. antiemetics: dexamethasone 8 mg i.v. (before incision) & ondansetron 4 mg i.v. (before emergence, if no contraindication)
In case of contraindication to dexamethasone or ondansetron: droperidol 0.625 mg i.v. (before emergence)
- No additional i.v. administration of another opioid (e.g., piritramide or morphine) before extubation
- No additional i.v. administration of adjuvants (such as clonidine) before extubation without justified indication
- No additional local wound infiltration by the surgeon

Intervention:
Chest wall block:
Injection of a total of 25 ml ropivacaine 0.375% into the target compartment before the start of the actual surgical procedure (dose and volumes are identical in both intervention groups)
- Arm 1: Anesthesiological, ultrasound-guided Erector Spinae Plane Block (ESPB):
The anesthesiological, ultrasound-guided Erector Spinae Plane Block (ESPB) is performed by experienced anesthesiologists prior to induction of general anesthesia and before the start of surgery. Broad disinfection and sterile precaution are applied (sterile gloves, sterile ultrasound cover, surgical cap & face mask). One puncture is performed. The fifth and sixth thoracic vertebrae are identified using anatomical landmarks and, if needed, ultrasound guidance. An ultrasound probe is positioned in a paramedian sagittal orientation approximately 2 cm lateral to the spinous process to visualize relevant anatomical structures (M. trapezius, M. rhomboideus major, M. erector spinae and the transverse process). The pleura should not be visualized in this plane. An in-plane puncture is performed with a 10 cm SonoPlex needle (Pajunk®) from cranial to caudal. The needle is visualized along its entire length in the ultrasound image at all times. The target position of the needle tip is the subfascial space beneath the M. erector spinae on the transverse process. The needle is precisely positioned by means of hydrolocation. Fractionated application and spread of the local anesthetic are performed under continuous ultrasound visualization with repeated negative aspiration control for blood. A total of 25 ml of ropivacaine 0.375% is injected.

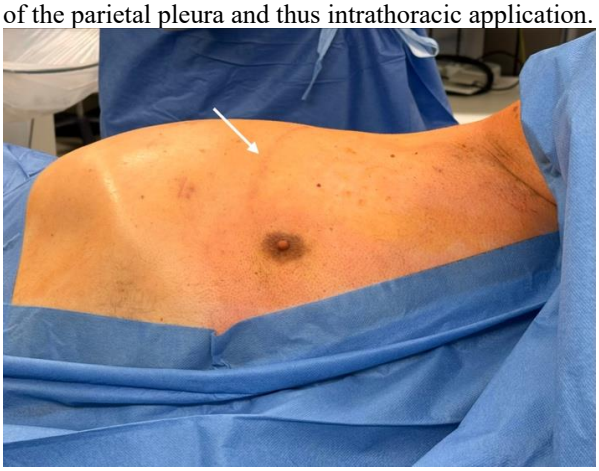


Clinical image of ESPB

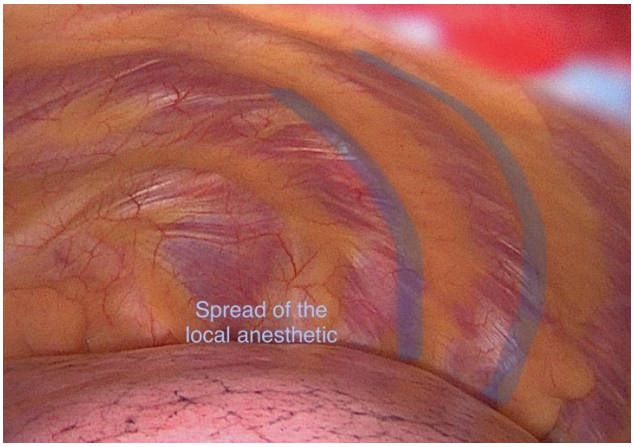


Ultrasound image of ESPB

- Arm 2: Surgical, thoracoscopically-guided Intercostal Nerve Block (ICNB):
The surgical, thoracoscopically-guided ICNB is performed by the surgeon intraoperatively immediately after insertion of the thoracoscope and before the start of surgery. The puncture is performed percutaneously with a sharp needle (20G x 2 ¾ inch 0.9 x 70 mm, Sterican®). The needle is introduced from the outside under continuous thoracoscopic visual control. The target position of the needle tip is the level of the neurovascular bundle in the costal groove (between M. intercostalis internus and membrana endothoracica). Injections are performed at the level of trocar insertion and two intercostal spaces cranial and caudal to it. A volume of 5 mL is administered per level, resulting in a total of 25 mL of ropivacaine 0.375%. The spread of the local anesthetic is performed under continuous visual control and should cause bulging of the parietal pleura. Visual control should prevent perforation of the parietal pleura and thus intrathoracic application.



Patient positioning and needle direction of ICNB



Thoracoscopic image depicting the parietal pleura

In both study arms, the duration of performance of the chest wall block, defined as the period from initial needle insertion to completion of the full local anesthetic dose administration, is documented. The standardized assessment of pain and analgesic consumption after surgery is carried out by the in-house anesthesiology pain service using a standardized pain questionnaire and at predefined time points (1 hour, 2 hours, 12 hours, 24 hours). The anesthesiology pain service remains blinded to the intervention performed.

Data sources:

Medical records, standardized pain questionnaires

List/description of the data to be collected:

- Age
- Sex
- Body measurements (weight, height)
- Relevant comorbidities
- ASA status
- Premedication protocol
- Anesthesia protocol, in particular vital parameters and administered
- Surgical report
- Duration of block procedure (from initial needle insertion to full local anesthetic dose administration)
- Length of stay in recovery room
- Pain perception in the first 24 hours (NRS 0-10) at predefined time points (1, 2, 12 and 24 hours)
- Total consumption of analgesics within the first 24 hours
- Occurrence of postoperative nausea and/or vomiting (PONV)
- Occurrence of muscle shivering after anesthesia (shivering)
- Occurrence of unexpected adverse effects

Timeline:

The chest wall block is performed as part of the surgical treatment. Postoperatively, pain is assessed by the anesthesiology pain service 1 hour, 2 hours, 12 hours and 24 hours after surgery using a standardized pain questionnaire.

Expected study completion:

After approval by the local ethics committee, we expect a duration of 12 months to reach the planned sample size.

Benefit-risk assessment

Individual benefit:

These regional anesthesia procedures are already routinely explained to and performed in patients independently of this study. The reduction of pain perception and analgesic consumption contributes to improved patient satisfaction and is therefore an integral part of modern multimodal pain therapy.
Participation in this study does not provide any additional direct benefit beyond this.

Group or third-party benefit:

The study results will very likely contribute to improved treatment of other patients in the future.

Risks and burdens:

In addition to the risks of the surgical procedure and general anesthesia, the following potential risks exist in the context of a chest wall block:
Allergic reaction/anaphylaxis to the local anesthetic, local anesthetic toxicity due to accidental intravascular injection or increased systemic absorption, bleeding/hematoma, infection, pneumothorax, injury to nerves/vessels in the puncture area, failure of analgesic effect. Since the procedure is already an established method in our clinic, no additional complications beyond the standard risks are expected.

Statement on (medical) justifiability:

Both chest wall blocks to be compared are clinically established regional anesthesia procedures used in routine care. Known risks such as insufficient analgesia, local anesthetic toxicity or injury to surrounding structures correspond to the usual risk profile of these procedures.
In contrast, there is a clear benefit: in a prospective, randomized design, the study can clarify whether one procedure is superior to the other with regard to analgesia and duration of performance. In this context, the expected benefit outweighs the manageable risk.

Criteria for termination of participation of individual participants:

Participation in the study will be terminated if consent is withdrawn, serious adverse events that make further participation medically unjustifiable occur, or if intra-/postoperative changes impede adherence to the protocol. Further reasons for termination are new contraindications or serious protocol violations.

Criteria for (premature) termination of the entire study:

The study will be terminated prematurely if new scientific findings make continuation unjustifiable or if serious unexpected safety problems occur. Further reasons are organizational circumstances that prevent implementation. The decision on termination is made by the investigator in consultation with the principal investigator, taking into account the recommendations of the ethics committee.

Biometry

Exact definition of endpoints:

The primary endpoint of the study is the postoperative analgesic consumption within the first 24 hours after surgery. The non-inferiority margin is defined as $\Delta = 5$ mg piritramide over 24 hours. $\Delta = 5$ mg piritramide was chosen because this corresponds to the upper limit of the bolus dose (3-5 mg) commonly used in our routine in the recovery room and thus represents a clinically well interpretable dose level.

Secondary endpoints are postoperative pain intensity within the first 24 hours measured using the numeric rating scale, as well as the procedural duration of the chest wall block, defined as the period from initial needle insertion to completion of the full local anesthetic dose administration

Sample size justification:

The aim of the study is to demonstrate non-inferiority of the anesthesiological, ultrasound-guided application compared to the surgical, thoracoscopically-guided application with regard to the primary endpoint (24h piritramide consumption).

The non-inferiority margin (Δ) is defined at 5 mg piritramide over 24 hours. Δ = 5 mg was chosen because this corresponds to the upper limit of the bolus dose (3-5 mg) commonly used in our clinical routine in the recovery room and thus represents a clinically well interpretable dose level.

For the estimation of the variance of the primary endpoint, data from the study by Sung et al. [11] are used. In Table 2 of this study, the 24h opioid consumption is reported as morphine consumption in the form of median and interquartile range (3 mg [0–6] vs. 0 mg [0–5], each n = 50). Since a standard deviation is required for sample size calculation, group-specific standard deviations are estimated from the median and interquartile range according to Wan et al. [12]. This results in standard deviations of SD ≈ 4.58 mg and SD ≈ 3.82 mg morphine as well as a pooled standard deviation of SD_pooled ≈ 4.21 mg morphine.

Since the non-inferiority margin in the protocol is defined in piritramide, a conversion is carried out to harmonize the units based on a defined equivalence factor (0.75 mg morphine = 1 mg piritramide). This results in a pooled standard deviation of SD_pooled ≈ 5.61 mg piritramide; conservatively, the larger group-specific standard deviation is additionally taken into account (maximum ≈ 6.11 mg piritramide).

Assuming a one-sided significance level of $\alpha = 0.025$, a target power of $1-\beta = 0.90$ and a 1:1 randomization, this results, depending on the assumed variance, in a required sample size of n = 28 patients per group (using the pooled standard deviation) or n = 33 patients per group (conservative). Taking into account a dropout of 10%, recruitment of 31–36 patients per group is planned (corresponding to 62–72 patients in total).

Referenzen:
11. Sung et al. Comparisons in analgesic effects between ultrasound-guided erector spinae plane block and surgical intercostal nerve block after video-assisted thoracoscopic surgery: A randomized controlled trial. J Clin Anesth. 2024 Aug;95:111448
12. Wan et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014 Dec 19;14:135

Statistical formulation of the main research questions:

Primary non-inferiority hypothesis:

The anesthesiological, ultrasound-guided ESPB is non-inferior to the surgical, thoracoscopically-guided ICNB with regard to postoperative analgesic consumption. The non-inferiority margin is Δ = 5 mg piritramide. This means that the anesthesiological, ultrasound-guided ESPB is considered non-inferior if the mean 24h piritramide consumption compared to the thoracoscopically-guided ICNB is not increased by more than 5 mg.

Analysis methods for the main research questions (confirmatory approach):

The statistical data analysis is performed using GNU R 4.3.1 (or newer).

The descriptive data presentation is carried out depending on scale level and distribution. Continuous data are reported as mean with standard deviation if normally distributed, otherwise as median with interquartile range. Frequencies of nominally scaled data are presented as absolute frequencies and percentages. Normal distribution is tested, among other things, using the Shapiro-Wilk test.

The primary evaluation is carried out as a non-inferiority analysis with a one-sided significance level of $\alpha = 0.025$. The difference in mean 24-hour piritramide consumption (ESPB group minus ICNB group) is estimated and a one-sided 97.5% confidence interval is calculated. Non-inferiority will be concluded if the upper bound of this confidence interval lies below Δ = 5 mg piritramide. The primary analysis is performed in the intention-to-treat population; additionally, a per-protocol analysis is planned as a sensitivity analysis.

Secondary endpoints are compared – depending on the distribution of the data – using t-test (normally distributed) or Wilcoxon-Mann-Whitney test (non-normally distributed/ordinal). Nominal variables are compared using χ^2 test or – in case of small expected cell counts – Fisher's exact test. If randomized patients differ in relevant baseline characteristics, additional adjusted sensitivity analyses (e.g., regression models; if applicable IPTW) are planned.

Data management and data protection

Legal basis for data processing:

The legal basis for data processing is the voluntary consent of the patients (Art. 6 para. 1 lit. c GDPR).

Controller responsible for data processing for the purposes of the GDPR:

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Collected personal data:

Personal data such as age, sex, body measurements, relevant comorbidities and ASA status are collected in pseudonymized form. In addition, perioperative and health-related data are recorded, including type and duration of surgery, premedication and anesthesia protocol, surgical report, duration of performance of the chest wall block, postoperative pain perception (NRS 0-10), analgesic consumption, PONV, shivering as well as, if applicable, unexpected adverse effects. All data are used exclusively for the scientific evaluation of the study.

Form of data storage (type, location, duration)**:**

All study data are stored in pseudonymized form both in a password-protected Word document and on paper in locked archives. Access is restricted exclusively to authorized study personnel and changes to the electronic document are logged. The data are stored for at least 10 years after completion of the study and are subsequently deleted or destroyed in accordance with data protection regulations.

Measures for data security:

Patient data are treated confidentially and pseudonymized at all times. A pseudonymization list is stored at the study center. This list is stored separately and is subject to technical and organizational measures that ensure that unauthorized persons have no access to personal data. Only the responsible investigators have access.

Pseudonymized data storage:

All study participants receive a study code at the beginning, which is linked to identity data in a separate pseudonymization list. The list is created by authorized study personnel and is accessible exclusively to this group of persons. Only the codes are used in the data collection forms. Personal identifying characteristics are not recorded. The pseudonymization list is securely archived after completion of the study and retained in accordance with applicable data protection regulations. The data are stored for at least 10 years after completion of the study and are subsequently deleted or destroyed in accordance with data protection regulations.

Data transfer:

No data are transferred to third parties.

Procedure in case of withdrawal:

In the event of withdrawal of study participation by patients, no further data are collected. Already collected pseudonymized data are retained for scientific evaluation, since traceability to the person is excluded. The pseudonymization list is continued unchanged so that data integrity and anonymity are ensured. Withdrawal only affects further participation and data collection, not the use of already collected pseudonymized data.

Data deletion or anonymization:

The pseudonymization list is deleted in accordance with data protection regulations after completion of the study and expiry of the retention period of 10 years. The pseudonymized study data continue to be stored in order to enable scientific evaluation.

Signature of the principal investigator

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