Dissertation

Safety and efficacy of blocking the obturator nerve for regional anaesthesia based on new anatomical findings

Thesis submitted by

Dr. med. univ.

Holger Sebastian SIMONIS, MHBA

for the Academic Degree of

DOCTOR OF MEDICAL SCIENCE

(Dr. scient. med.)

at the

Medical University of Graz

Department of Anaesthesiology and Intensive Care Medicine

under the Supervision of

Univ. Prof. Dr. Andreas SANDNER-KIESLING

2015

Eidesstattliche Erklärung/ Declaration Acknowledgement

Ich erkläre ehrenwörtlich, dass ich die vorliegende Arbeit selbständig angefertigt und abgefasst, und jene Personen und Institutionen, die am Zustandekommen der Forschungsdaten beteiligt waren, namentlich genannt habe. Andere als die angegebenen Quellen habe ich nicht verwendet und die benutzten Quellen wörtlich oder inhaltlich entnommenen Stellen habe ich als solche kenntlich gemacht. Die Arbeit der Dissertation und daraus entstandener Publikationen wurden gemäß den Regeln der „Good Scientific Practice" durchgeführt.

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organizations that have contributed to the research for this thesis. Due acknowledgment has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the guidelines of "Good Scientific Practice".

Graz, 23.06.2015
Dr. med. univ. Holger Sebastian Simonis, MHBA, eh

Acknowledgments

I would like to express my sincere gratitude to my supervisor Prof. Dr. Andreas Sandner-Kiesling for his continuous support of my research, his motivation and guidance, great enthusiasm, and fruitful discussions.

Special thanks to Dr. Helmar Bornemann-Cimenti, Dr. Bernhard Röschel and to all colleagues from the Medical Institute for Statistics that have helped me with their advice and their support whenever needed.

Furthermore, I thank OA Dr. Maria Gries and OA Dr. Thomas Bößner-Weiss for hosting me with this study in their surgical theatre during the study. I thank the chair of our division for their support during the last years.

My warmest thanks go to my family and friends for being there for me at any hour, and to my girlfriend for her precious and never-ending support.

Contents

Abbreviations and Definitions

AL	adductor longus
ASA Score	Physical status classification system of the American Society of Anaesthesiologists
ASIS	anterior superior iliac spine
ASRA	American Society of the Regional Anaesthesia and Pain Medicine
ATP	Adenosine triphosphate
CI	Confidence interval
CRF	Case Report Form
DHHS	US Departments of Health and Human Services
e.g.	exempli gratia (for example)
IL	inguinal ligament
IRB	Institutional Review Board
IUPAC	International Union of Pure and Applied Chemistry
mm HG	millimetre of mercury (monomeric unit of pressure)
MUG	Medical University of Graz
NaCl	Sodium chloride
NRS	11-point Numeric Rating Scale
OBN	Obturator nerve block
OHRP	Office for Human Research Protections
ON	Obturator nerve
PT	pubic tubercle
SC	spermatic cord
SD	Standard deviation
VOB	Vertical Obturator Nerve Block

List of Figures

List of Tables

Abstract in German

Hintergrund und Ziele

Am anatomischen Institut der Medizinischen Universität Graz wurde ein neuer Zugangsweg für eine Nervus-obturatorius-Blockade entwickelt (Vertical Obturator Nerve Block; VOB). Vielversprechende Ergebnisse an 88 Leichen (=176 untere Extremitäten) ermutigten uns die neue Technik an lebenden Patienten in täglicher klinischer Praxis zu testen.

Methoden

Eine prospektive, 2:1 (Verum/Kontroll-Gruppe, n=30) randomisierte, doppelblind, parallel designte Pilotstudie wurde von unsere Ethikkommission zugelassen und unter clinicaltrail.gov (NCT01875289) registriert. Alle Patienten bekamen einen VOB. In der Verum-Gruppe bekamen die Patienten 5 ml 0,75% Ropivacain (37,5 mg) und in der Kontroll-Gruppe bekamen die Patienten 5 ml einer 0,9 % NaCl-Lösung appliziert. Der primäre Endpunkt der Studie war der Kraftverlust der Beinadduktoren 15 Minuten nach Injektion und der Unterschied zwischen den beiden Studiengruppen. Die Kraft wurde mit einer manuellen Blutdruckmanschette gemessen.

Ergebnisse

Der Unterschied in den Gruppen war nicht signifikant (p=0,074). Dreimal wurde der N. obturatorius erfolgreich in der Verum-Gruppe geblockt, jedoch keinmal in der Kontroll-Gruppe; unter Bezugnahme eines Cut Offs von 50 % Kraftverlust der Beinadduktoren nach der Blockade. Die Zeit für die Vorbereitungen des Blocks betrug 97.5±96.8 Sekunden (Mittelwert; SD) und die der Punktion dauerten 32.4±18.3 Sekunden. Die gesamte Nervenblockade dauerte 129.8±100.7 Sekunden. Der mittlere Schmerz während der Punktion wurde mit 2.9±1.73 auf einer numerischen Schmerzskala (0-10) angegeben. Jeder Patient stimmte einem erneuten Nerv Block für zukünftige Eingriffe zu.

Zusammenfassung

Im Vergleich mit anderen Nervus-obturatorius-Blockaden ist der VOB einfach, schmerzfrei und sehr schnell durchführbar. Die niedrige Erfolgsrate in dieser Studie ließe

sich durch minimale Verbesserungen der Technik nachhaltig verbessern. Für zukünftige Studien werden wir Nervenstimulatoren und/oder ultraschallgezielte Techniken, höhere Lokalanästhetika-Volumina sowie längere Zeiten bis zur operativen Freigabe benutzen um die Erfolgsrate der Nervenblockade zu steigen.

Abstract

Background and Objectives

The Institute of Anatomy at the Medical University of Graz developed a new approach for the obturator nerve block (Vertical Obturator Nerve Block; VOB). Promising results on 88 cadavers (=176 lower limbs) encouraged us to test this new technique in patients in our daily hospital routine.

Methods

A prospective, 2:1 (verum/control group, n=30) randomized, double-blind, parallel designed pilot trial was approved by our Institutional Ethics Committee and registered at clinicaltrials.gov (NCT01875289). All patients received a VOB. We used 5 ml 0.75 % ropivacaine (37.5 mg) in the verum group and 5 ml 0.9 % sodium chloride in the control group. The primary outcome was adductor muscle strength before and 15 minutes after nerve block, and the difference between both groups. The adductor muscle strength was measured with a manual sphygmomanometer.

Results

The difference between groups was not significant (p=0.074). A successful obturator nerve block was observed in the verum group (n = 3), but not in the control group (n = 0), based on a cut off at 50 % decrease in muscle strength. The prep time before needling was 97.5±96.8 seconds (mean; SD). The needle-in-body time was 32.4±18.3 seconds. The whole nerve block took 129.8±100.7 seconds. Mean patient's pain intensity during needling was 2.9±1.73 on a Numeric Rating Scale (0-10). Every patient would be willing to agree to receive this nerve block again in future.

Conclusions

The VOB is a simple, painless and outstanding fast nerve block compared to the common obturator nerve blocks. The low success rate can be improved substantially by minor technical modifications. We will use electro-stimulation plus/minus ultrasound targeting, higher volume of local anaesthetics and additional measurements later after nerve block in future to increase the success rates.

1 Introduction

1.1 The history of obturator nerve block techniques

Several different techniques were described for an obturator nerve block (ONB) over the last century. The first selective ONB was specified by Labat in 1922, using a approach nearby the pubic tubercle (1). Followed by small technique adjustments by Parks in 1967 and Pinnock in 1996 (2,3). In 1993 Wassef (4) specified a new approach for the obturator nerve (ON); an inter-adductor approach, distal of the separation of the ON into the two terminal branches. With the upcoming use of ultrasound, more and more studies reported their promising results of the inter-adductor approach ONBs (5–9).

In 2012, Feigl described a new technique of an ONB at 88 cadavers (=176 lower limbs) (10), using again an approach nearby the pubic tubercle like first described by Labat. This block technique was labelled vertical obturator nerve block (VOB), because of the perpendicularly needle direction to the surface. Comparing to other techniques nearby the pubic tubercle, this new technique does not require a second morphological landmark. No obligate turning of the needle is necessary. Therefore, a fan-like searching for the ON by using electrostimulation-guidance is not required.

1.2 Anatomy of the obturator nerve

The obturator nerve is a branch of the lumbar plexus L2 to L4. The plexus is formed anterior to the lumbar transverse processes. It is proximal attached by the psoas major (11). Furthermore, many anatomical variations of the lumbar plexus are described and prevalence of variations is about 20 % (12). The obturator nerve emerges from the medial boarder of the psoas major into the lower pelvis (13,14). It is passing inferior to the superior pubic ramus through the obturator foramen to the medial thigh, dividing into two branches, supplying the adductor muscles (5,15). The point of division for the nerve intro the anterior and posterior branches are highly variable. In 23% the point of division is intra-pelvic, 52 % in the obturator canal and in 25 % in the thigh (16).

The obturator nerve is in control for motor innervation of the adductor muscles of the lower extremity. The nerve supplies the muscle adductor longus, muscle adductor brevis, muscle gracile and partly the muscle pectineus (17). The roles of the muscles are adduction of the thigh and to promotion hip flexion. The gracile muscle supports the knee flexion and the obturator externus supports the lateral spin of the thigh. The active adduction of the thigh as a result tests the function of the nerve.

In about 20 % an accessory obturator nerve is present (18). It emerges from the lumbar spinal nerves L3 and L4 and is small of size. The accessory obturator parallels the medial border of the psoas, anterior to the obturator nerve. It passages with the obturator to the level of the pelvic brim. However instead of coursing through the obturator foramen, it inclines on the medial edge of the psoas muscle and crosses the anterior border of the pelvis. It crosses superior to the superior pubic ramus nearby the femoral vein (19). It supplies the pectineus and is distributed to the hip-joint. Sometimes, it communicates with the anterior branch of the obturator nerve and may make an important impact to the motor innervation of the adductor muscles.

The sensory innervation of the obturator nerve is variability as well. In many times the nerve is accountable for the innervation of the skin of the medial or posteromedial aspect of the thigh. A substantial overlay of cutaneous innervation occurs among the femoral, obturator and sciatic nerves (20,21).

1.3 Obturator nerve block in clinical settings

The obturator nerve block has several indications. Diagnostic and therapeutic procedures on the knee and thigh can be done by combining obturator nerve block with block of the femoral nerves, sciatic and femoral lateral cutaneous nerve (22,23). For hip fracture surgery the combination of obturator and lateral femoral cutaneous nerve blockade is highly effective against acute postoperative pain (24).

Hemi- or paraplegia is associated with adductor muscle spasm. Muscle spasticity is a common problem in patients suffering from central neurological disease. The obturator nerve block is used to relief this spasm and associated pain, and helps to groom and to

mobilize this patients (4,25,26). The muscle spasms can be (cost) effective reduced with the help of alcohol or phenol (27,28).

In some cases an obturator nerve block is useful in diagnosing certain pain conditions. For example, in case of chronic inguinal and back pain secondary to hip arthropathy, the obturator nerve block is used to determine the origin of the pain (29).

Patients who under transurethral resection of inferiors lateral bladder tumours, predict the need to block the adductor response (30). Surgery without obturator nerve block is potentially dangerous and increases the risk of severe complications such as vessel laceration, bladder wall perforation, incomplete tumour resection and obturator hematomas (31,32). A selective obturator nerve block is the safest and most effective precaution to this problem (33).

If a coagulopathy exists, the obturator nerve block should be avoided. Other contraindications are presence of inguinal lymphadenopathies, local infections or hematoma at the needle insertion place.

1.4 Local anaesthetic mechanism of action

The role of neural cells is to transmit information from one part of the body to another. The information is transmitted by electric action potentials along axons. Many axons are usually combined to a nerve. Every single axon is covered by a neural membrane; a phospholipid double diaphragm. In this membrane are different channels: Passive acting Na^+, K^+ and Cl^- and active Na^+/K^+ exchanger (34).

The active exchanger is responsible for maintaining the resting potential. In resting phase the Na^+/K^+ exchanger transports Na^+ ions form inside the axon to outside and K^+ from outside to inside. This processes consume energy in form of ATP by an enzyme-catalysed phosphoryl transfer reaction (35). ATP consists of three phosphate groups attached to the carbon location. A result of dephosphorylating of ATP by enzymes known as ATPases produces energy for the Na^+/K^+ exchanger (36).

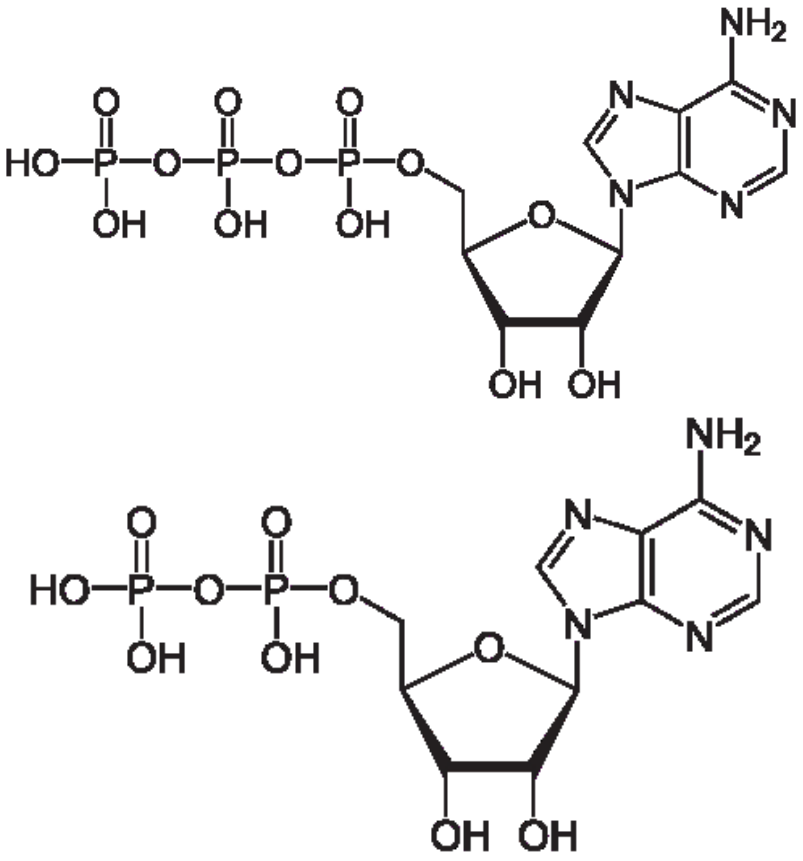

Figure 1: Skeletal formula of adenosine triphosphate (above) and adenosine diphosphate (below). A sugar backbone attached to a molecule of adenine and three phosphates in case of ATP and two phosphates in case of ADP. The phosphate groups are added in series to the 5# carbon of the sugar backbone, while the adenosine molecule attaches the 1# carbon.

The passive acting channel Na^+, K^+ and Cl^- are voltage-gated. For an action potential the Na^+ channel is primarily responsible. In the short-lasting event the membrane potential of the cell quickly increases and falls. The channel is closed when the membrane potential is nearby the resting potential of the cell, but quickly begins to open if the membrane potential is enlarged to an exactly well-defined threshold value. When the Na^+ channel opens, an inward movement of sodium ions produces an extra increase in the membrane potential. This causes more Na^+ channels to open and produces a bigger electrical current across the cell membrane. Shortly, the Na^+ channel rapidly inactivates because of the polarity of the plasma membrane. After that, potassium channels are activated returning the electrochemical gradient to the sleeping state (37,38).

All Local anaesthetics act by inhibiting this Na^+ channels. Consequently, the action potential cannot ascend and the signal conduction is interrupted. Local anaesthetics are bases and frequently formulated as the hydrochloride salt to render them water-soluble. The protonated (ionized) and un-protonated (unionized) forms are equal to the protonated base`s at the individual pKa[1], the molecule exist in equimolar amounts. Only the un-protonated base spreads readily across the nerve cell membranes (39). The receptor site of the local anaesthetics is located at the cytoplasmic portion of the sodium channel. In the cell, the local anaesthetic will be in equilibrium again. Now, the protonated form binds to the local anaesthetic binding site on the inside of the ion channel (40) and disables the conduction of sodium ions through the channel. So, the signal conducting is inhibited.

Two classes of local anaesthetics are used for regional anaesthesia: amino-amide and amino-ester. Amino-ester are prone to produce allergic reaction. They are metabolized by cholinesterase. Amino-amide are less prone for allergic reactions, but the metabolism is dependent on liver function.

Cocaine, procaine, benzocaine, piperocaine, chloroprocaine, and tetracain are examples for aminoester. Bupivacaine, levobupivacaine lidocaine, mepivacaine, prilocaine and ropivacaine are examples for aminoamide.

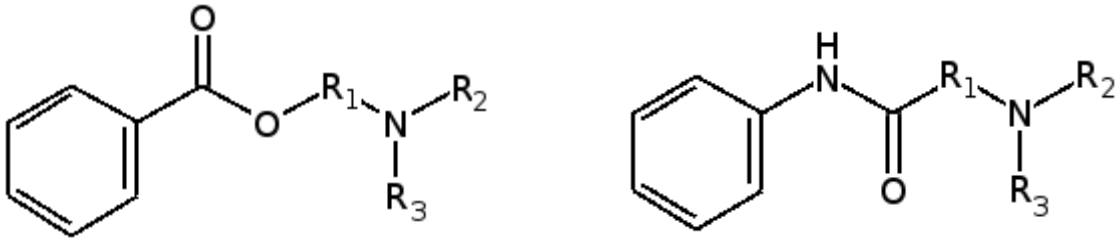

Figure 2: Skeletal formula of aminester (left) and aminoamide (right).

[1] An acid dissociation constant: A quantitative recording of the strength of an acid in solution. It is the steady state constant of chemical reaction noted as dissociation in context of acid-base reaction.

1.5 Complications of regional anaesthesia

1.5.1 Nerve injury

The risk for peripheral nerve injury during needling is rare (41). So, it is difficult to assess the incidence. Furthermore, the definition of injury is variable in studies (42). Most of the deficits are transient and lasting less than a month. Permanent nerve damage raged between 0.015 and 0.09 % in several studies (43,44).

Main reason for nerve injuries are likely intra-neural injections. To minimise the risk, injection should be stopped if patients feel a shooting pain or the pressure required for injection is high (45,45).

Pain, tingling and paraesthesia are primarily sensory symptoms of nerve injury. In severe cases a combination of motor and sensory deficits can occur. In many times the difference of surgical or regional anaesthesia induce nerve injury is difficult to evaluate.

1.5.2 Systemic toxicity of local anaesthetics

Systemic toxicity is related to huge plasma concentrations of local anaesthetics. Accidental injection of local anaesthetics into a blood vessel is the most common aetiology. This displays in the central nervous system as disorientation, tinnitus and seizures. Additionally, cardiovascular system toxicity can occur like hypotension, dysrhythmias and cardiac arrest. Central nervous system toxicity usually precedes the cardiovascular toxicity; therefore patients have sometimes cerebral signs without hemodynamic compromise (46). Only bupivacaine doesn't follow this sequence. The cardiac toxicity of bupivacaine may occur in the absence of central nervous system toxicity (47).

By needle aspiration before injection of local anaesthetics, the probability of systemic toxicity can be reduced, because the needle tip must not be located within a blood vessel. Furthermore, the doses of anaesthetics are highly relevant due to systemic resorption. Adding epinephrine to the solution can delay intravascular absorption (48).

The injection of local anaesthetics should be stopped immediately, if central system toxicity signs occur. Seizures should be treated with a minor amount of benzodiazepine

(e.g. midazolam). In case of severe cardiovascular toxicity, advanced cardiac life support should be provided. Dysrhythmia is difficult to control, especially if bupivacaine was used. The favoured treatment for this dysrhythmia is amiodarone (49).

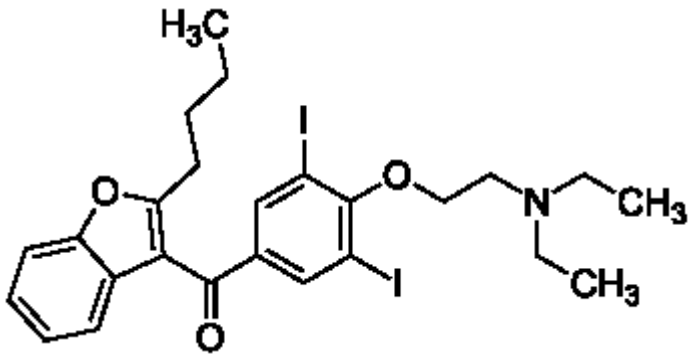

Figure 3: Skeletal formula of amiodarone (C25H29I2NO3). Systematic name (2-{4-[(2-butyl-1-benzofuran-3-yl)carbonyl]-2,6-diiodophenoxy}ethyl)diethylamine and CAS Registry Number 1951-25-3. The molecular mass is 681.31 g/mol.

However, dysrhythmias are often persistent. In severe cases an emergency cardiopulmonary bypass can buy some time until the drug dissociates from the patient's cardiac tissue (50).

A major component in resuscitation of local anaesthetic toxicity is the early administration of lipid emulsions (e.g. Intralipid®) (51). In 2006 first case reports documented the efficacy (52,53) and now the therapy has gained acceptance rapidly.

Figure 4: Picture of a 20 % Intralipid® 250 ml infusion glass bottle. This emulsion provides essential fatty acids, omega-6 fatty acid, linoleic acid, alpha-linolenic acid and omega-3 fatty acid.

This lipid rescue should be admitted at the first signs of severe systemic local anaesthetic toxicity. An intravenous bolus of 1.5 mL/kg body weight should be given over one minute, followed by an infusion of 0.25 mL/kg/min until successful achievement of circulatory stability. A second bolus may be administered, if the circulatory is still instable. The maximum cumulative dose of this lipid is 10 mL/kg (54).

The hypotension associated with the local anaesthetic toxicity should be treated with doses of epinephrine (see Figure 5):

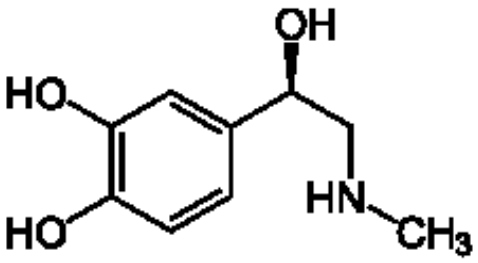

Figure 5: Skeletal formula of epinephrine (C9H13NO3). Systematic name (R)-4-[1-Hydroxy-2-(methylamino)ethyl]benzen-1,2-diol and CAS Registry Number 51-43-4. The molecular mass is 183.2 g/mol.

Vasopressin is not as good as epinephrine in treating cardiac arrest. Calcium channel blocker and beta blocker should be avoided during hypotension associated with local anaesthetic toxicity (54).

1.5.3 Hematoma

Peri-neural hematoma can occur by puncture of nearby vascular structures. Especially, patients with abnormal coagulation or antithrombotic therapies are at risk for larger hematomas. In case of a large hematoma, it can be controlled with direct pressure to the needling point side. In rare cases a surgical decompression may be required, especially in patients with higher risk of bleeding.

1.5.4 Infection

The risk of infection, due to single-shot regional anaesthesia is very low. The risk increases in patients with critical care unit admission, trauma, male sex, immune compromise and the absence of antibiotics. An aseptic procedure is crucial to avoid infections (55).

1.5.5 Allergic reactions to local anaesthetics

Local anaesthetics have been used to offer anaesthesia since the early beginning of anaesthesia. In 1884 the first local anaesthetic cocaine was discovered. All local anaesthetics can be administered by topical, infiltrative, nerve block epidural or spinal routes (56).

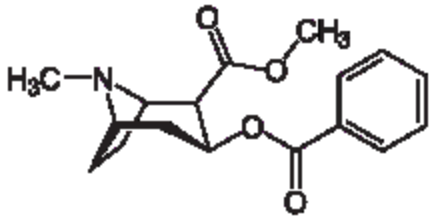

Figure 6: Skeletal formula of the fist local anaesthetic cocaine (C17H21NO4). Systematic name (R)-4-[1-Hydroxy-2-(methylamino)ethyl]benzen-1,2-diol and CAS Registry Number 50-36-2. The molecular mass is 303.4 g/mol.

Since the start of usage, allergic reaction has been described. Two types of allergic reaction were defined: First, allergic contact dermatitis and delayed swelling at the side of administration and second, urticarial and anaphylaxis.

Patients should be questioned about prior reactions to local anaesthetics used in medical settings and in over-the-counter products like patches against chronic pain, preparations for haemorrhoids, vaginal irritation, sunburn and more (57,58).

In case of systemic reactions during regional anaesthesia, physicians should review the medical procedure in detail. Possible exposure to other contact allergens can falsify the first suspected diagnosis of allergic reaction due to local anaesthetic, such as antibiotics administration before surgery.

A sufficient diagnosis of allergic reaction on local anaesthetics can be charged with a clinical history consistent with a delayed cutaneous reaction to a local anaesthetic, combined with a positive patch test result. Non-allergic reactions are far more common than real allergic reactions. For example anxiety-related reaction, vasovagal syncope and systemic toxic effects are pseudo-allergic reactions.

Local anaesthetics can cause contact dermatitis (type IV hypersensitivity) and in rare cases anaphylaxis (type I hypersensitivity). Anaphylaxis begins within one hour of drug administration and may lead to death. Epinephrine is the drug of choice for anaphylaxis (see Figure 5). The mediator release from mast cells will be decreased and it reverses obstruction to the airflow in the upper and lower respiratory tracts and reverses cardiovascular collapse (59). For adults, the recommended dose of epinephrine is 0.3 to 0.5 mg per single dose.

It should be injected intramuscularly into the mid-outer thigh (vastus lateralis muscle; Figure 7). The dose may be repeated at 10 minutes intervals (60,61). The evidence for H1 and H2 blockers and glucocorticoids are extrapolated from urticarial and asthma therapies and are often used for anaphylaxis as well.

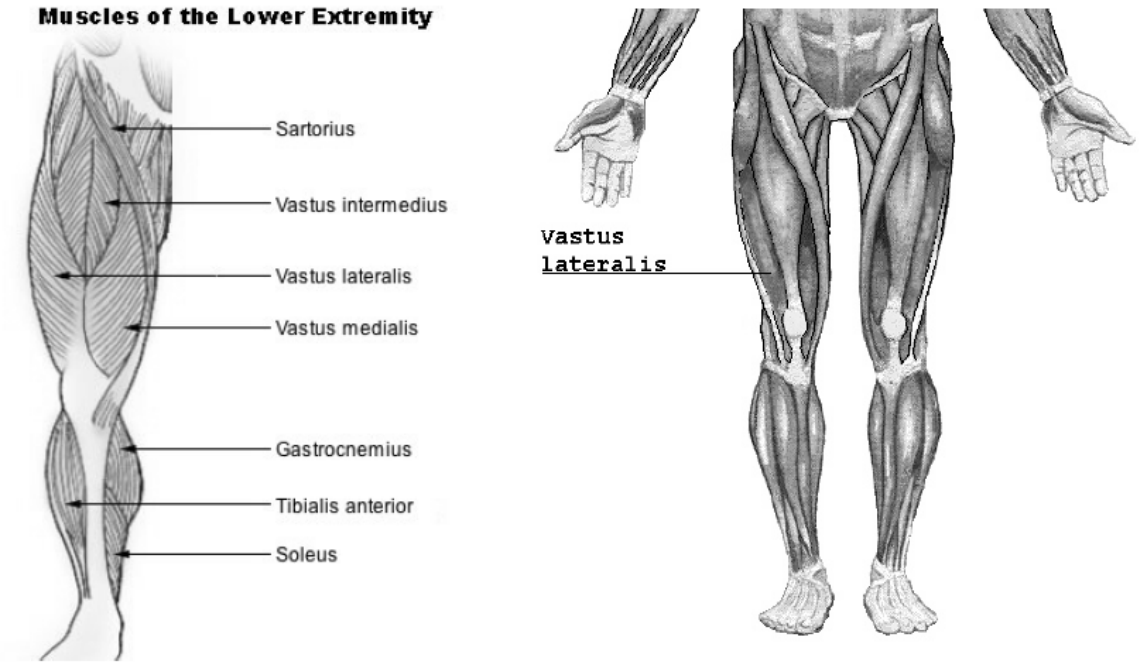

Figure 7: Drawings of the muscles of the lower extremity (62). Right: muscles of the right leg including muscular descriptions (rectus femoris have been removed). Left: Possible injection point for epinephrine.

Like described above, two groups of local anaesthetics based upon their chemical structure exists. Cross-reactivity among this groups are rare (63–65). Therefore, in case of allergic to a local anaesthetic in one group, it is reasonable to choose a drug of the other group (ester or amide).

1.5.6 Secondary injury

The reduced patient's sensation after nerve block in the blocked area causes risk of accidental tissue or nerve injury without patient's notice. Additionally, motor weakness in the lower extremity may lead to falls which leads to secondary injuries. So, clear instructions to patients and nurses in post-operative care are important to prevent those damages.

1.6 Contraindications for regional anaesthesia

Allergy to local anaesthetic and other agents with the same chemical classification (ester or amide) is a contraindication. Administration of a local anaesthetic of a different class is safe in most instances (56,65). In elective cases, it is best to have the patient evaluated by an allergist prior to the regional anaesthesia.

The maximum allowable anaesthetic dose must be considered prior to regional anaesthesia to avoid systemic toxicity. In some circumstances the risk for regional anaesthesia is higher than usual:

- Active infection at the site of injection
- Patients on antithrombotic drugs
- Patients with coagulopathy
- Pre-existing neural deficits in the distribution of the block

1.7 Inadequate or failed block

A failed block may be defined as inadequate analgesia/anaesthesia following regional anaesthesia. The precise incidence of failed block is unknown. Failed block may be caused by technical issues, drug dosing ore patient related factors. If the volume and/or the concentration of administered local anaesthetic is too low, pain relief will be incomplete. The precise dose to obtain a complete nerve block is yet unknown.

A failed block can also be caused by impatience (underestimating the latency of the local anaesthetic and not allowing sufficient time to pass before proclaiming the block as failed). Equipment related technical issues or operator issues may also result in failed block.

Other technical causes of failed block are related to patient's anatomy. As described above, many variabilities of the obturator nerve exists. Without using ultrasound or nerve stimulation, the variability of the obturator nerve can be undetected during regional anaesthesia.

Failure of a nerve block due to an inactive drug is very unlikely, as amid-linked drugs used for regional anaesthesia are very stable molecules.

1.8 Aim of this dissertation

The simplicity as well as the promising results described by Feigl et al. encouraged us to test the VOB for the first time in hospital routine. So, we conduct a clinical study at the University Hospital of Graz.

The aim of the prospective, randomized, double-blind, placebo controlled, pilot study was the assessment of the efficacy of the new block by measuring adductor muscle strength 15 minutes following completion of the block, required time to perform the block, patient's comfort and acceptance.

The zero hypothesis states that there is no difference in adductor strength change in the verum and the control group. The alternative hypothesis states that there is a difference in change of strength in both groups. Furthermore, this dissertation evaluates the clinical relevance of this change by measuring the success rate of the vertical obturator block in the

verum group. Secondary outcome is the time to perform the block, counts of bone contact during needling, patients comfort during the procedure and patient's acceptance of this new technique.

2 Materials and Methods

2.1 Ethics and international registration

On 22th April 2012, we submitted a standardized application to the local independent ethics committee at the Medical University Graz, including an Informed Consent Form and Case Report Form written in German (see Appendix). The committee is registered (Institutional Review Board number: IRC00002556 (66)) by the Office for Human Research Protections (OHRP) at the US Departments of Health and Human Services (DHHS (67,68)). On the 17th of May 2013 we received an approval by the committee. The vote is registered to 25-387 ex 12/13 at Medical University Graz, Institutional Review Board.

After an approval by the committee, we registered this study in a protocol registration and result system at ClinicalTrial. There, we defined and described the purpose of this study, the condition, the intervention, the primary outcome measure, the eligibility and specific additional information (see Appendix). This information was published at clinicaltrail.gov by the identifier NCT01875289 on the 10th of June 2013 (69). After wards, the enrolment of study patient started. At the end of patient's enrolment on the 20th of March 2014, we reported to the protocol registration and result system the completion of the study.

2.2 Study design

We designed a prospective, randomized, double-blind, parallel designed pilot trial to reach high methodological quality and minimal systematic error. The study was conducted at University Hospital of Graz, Austria, from June 2012 to March 2014. Patients were allocated at the ward of trauma surgery at least one day before scheduled surgery.

36 patients were primarily intended for sample size, including an estimated drop out of 20 %. A 2:1 randomization (verum/control group) was performed, to get more information on the efficacy of the vertical obturator nerve block. A computer generated non-restricted randomization list was produced by the Institute for Medical Informatics, Statistics and Documentation of the Medical University of Graz. Afterwards, this list was transferred to the institutional pharmacy of the University Hospital of Graz.

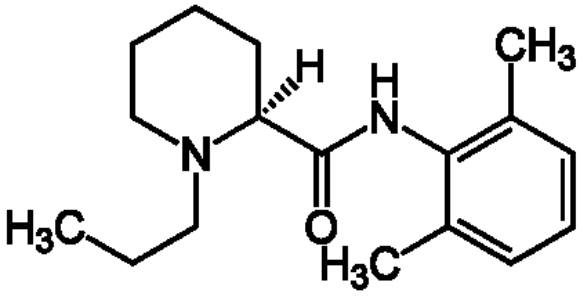

Figure 8: Skeletal formula of ropivacaine (C17H26N2O). Systematic name (S)-N-(2,6-dimethylphenyl)-1-propylpiperidine-2-carboxamide (IUPAC) and CAS Registry Number 84057-95-4. The molecular mass is 274.4 g/mol.

Based on the sealed randomization list, our institutional pharmacy produced blinded study medication: 5 ml standard syringe of 0.75 % ropivacaine (=37.5 mg) for the verum group and 5 ml standard syringe of 0.9% sodium chloride (NaCl) for the control group (Figure 9, Figure 10). Thereafter, the coded study medication was transferred to the investigators of the study at the operation theatre for trauma surgery at the University Hospital. According to the patients study ID, the blinded medication was assigned. According to the patients allocation time, the patients assigned to an ascending study ID (1, 2, 3…30)

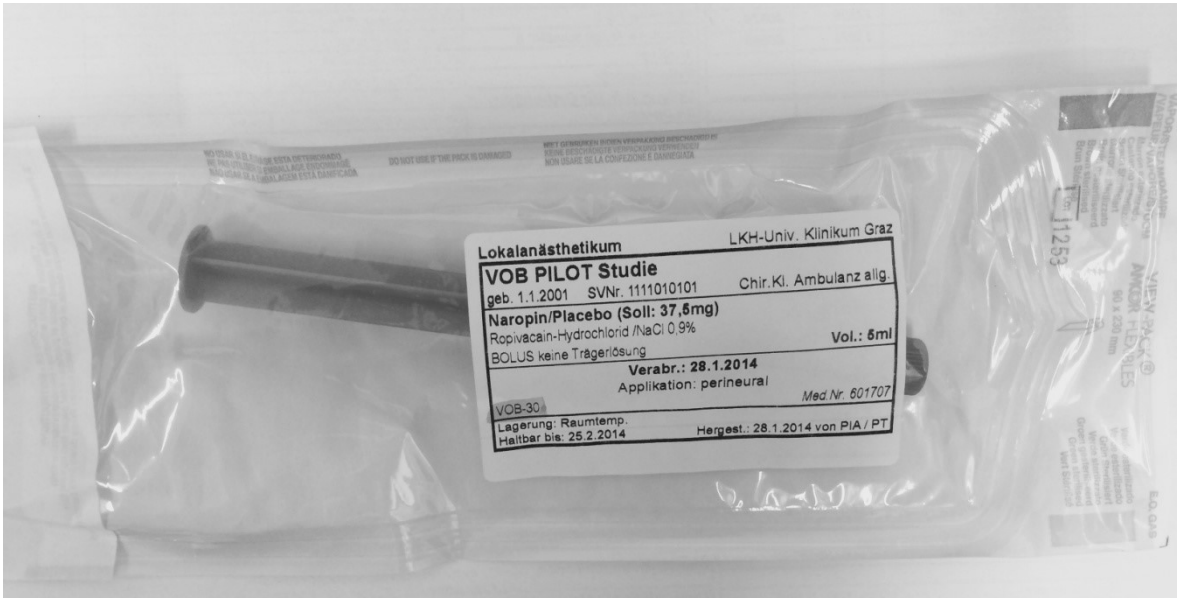

Figure 9: Picture of the study medication; produced and labelled by our institutional pharmacy, coded as VOB-30 for the 30th study patient. The label includes study name,

study ID, study hospital, storage information, study medication content (blinded: Naropin/placebo), date of expiry and patient ID. It is anti-septic produced and double packed in transparent plastic bag.

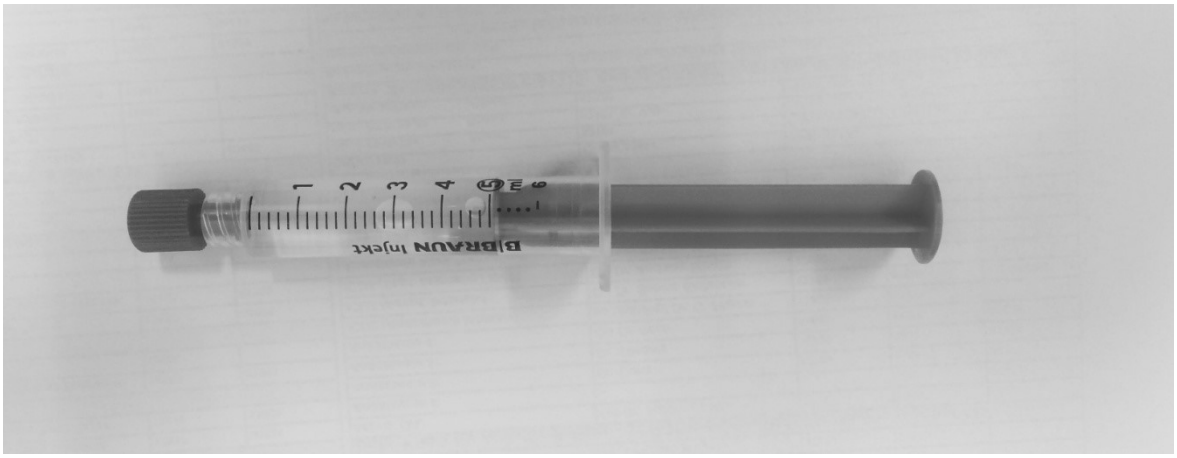

Figure 10: Picture of the unboxed study medication; a 5 ml standard syringe (Injekt® Solo, B. Braun Melsungen AG, Melsungen, Germany) made of Polypropylene/Polyethylene, according to ISO 7886-1 with 5 ml clear study medication, closed by a closing cone with Luer Lock fitting and ready to connect to the adaptable injection tube of the needle used in this study (see Figure 16).

The vertical obturator block and all measurements were performed after a routine premedication and before induction of general anaesthesia with or without regional anaesthesia (see Figure 13). For routine premedication midazolam 7.5 mg or 3.75 mg (see Figure 11) was orally administered depending on patient's age and comorbidities. In case of sleep apnoea in patient's history 150 µg clonidine (see Figure 12) was administered in preference to midazolam. No analgesics were administered during the study.

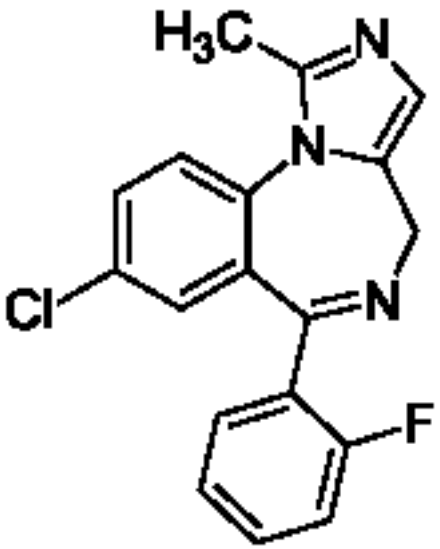

Figure 11: Skeletal formula of midazolam (C18H13ClFN3). Systematic name 8-Chlor-6-(2-fluorphenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepin (IUPAC) and CAS Registry Number 59467-70-8. The molecular mass is 325.77 g/mol.

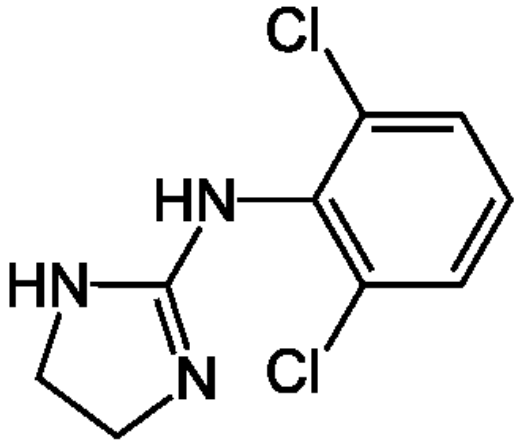

Figure 12: Skeletal formula of clonidine (C9H9Cl2N3). Systematic name N-(2,6-dichlorophenyl)-4,5-dihydro-1H-imidazol-2-amine (IUPAC) and CAS Registry Number 4205-90-70. The molecular mass is 230.10 g/mol.

After the collection of the complete study data, we reported the completion of the patients' assessment to the Institute for Medical Informatics, Statistics and Documentation of the Medical University of Graz and reported the end of patients' allocation to the protocol registration and result system at Clinical Trial. Subsequently, the randomization list was

released by our institutional pharmacy to the study team for un-blinding of groups and statistical analyses.

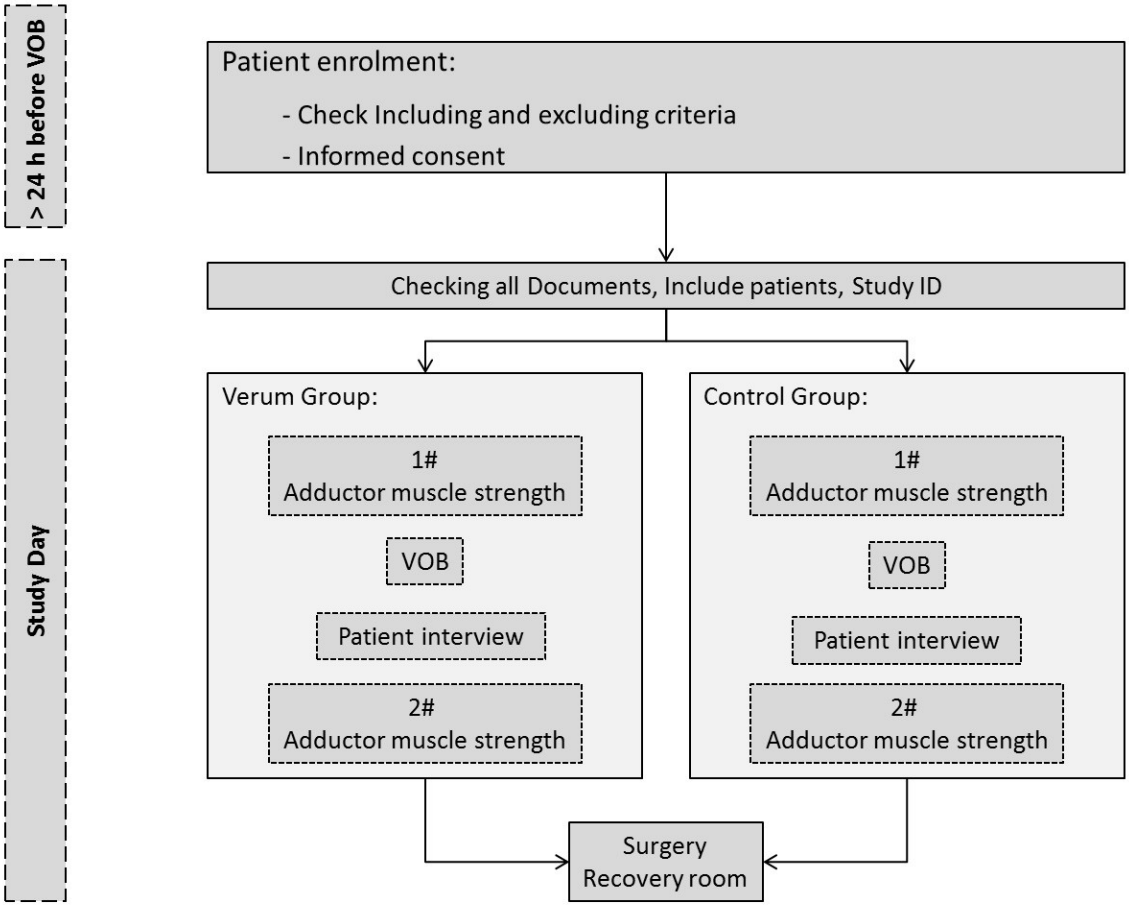

Figure 13: Study design description, including patient enrolment, randomization, allocation, testing and measurements before and on study day.

2.3 Funding

We did not receive any funding for this study. All cost for medication, staff and medical implement were provided by the clinical budget for patient care of the University Hospital of Graz. The Medical University of Graz provided the resources for the local independent ethics committee, the preparation costs for the manufacture of the blinded study

medication and the statistic processing (e.g. blinding, help for data interpretation). No cost for literature occurs, due to prior existed licenses for medical literature of the MUG.

2.4 Participating criteria

The allocation of patients was done at the ward of trauma surgery at the University Hospital of Graz during the routine anaesthetic visitation prior to surgery. Only patients scheduled for routine trauma surgery of knee region were asked to join the study. All subjects provided written informed consent before participating. Patients were scheduled for general anaesthesia in combination with regional anaesthesia (Vertical Obturator Nerve Block, plus possibly additional nerve blocks; femoral nerve block, ischiadic nerve block, cutaneous femoral lateral nerve block or saphenous nerve block).

Including criteria:

- ASA Score 1 to 3
- older than 18 years
- scheduled for routine trauma surgery of knee region

Exclusion criteria:

- neurologic disease (lowered cognitive power of judgment or intracranial diseases like Multiple Sclerosis, …)
- neuromuscular deficits of the lower extremities
- pregnancy
- signs of local or systemic infection
- patient`s weight < 45 kg
- patient`s weight > 100 kg

2.5 Definition of primary and secondary outcome

The adductor muscle strength was our primary outcome; measured before and 15 minutes after nerve block. The difference between the first and the second measurement implies an onset of the motor-neuron blockade. We predefined the success of the nerve block as a reduction of adductor muscle strength of more than 50 % relatively to the measurement before treatment. We also present the success rate on other muscle strength cut offs (40, 30 and 20 %). For statistical testing, we used the absolute decrease of adductor muscle strength in the verum and control group.

For the secondary findings, the patient was questioned about pain, discomfort due to the intimate block location, and possible regrets about participating in this study. The time from start to the end of the nerve block was noted.

2.6 Method of measurements

The adductor muscle strength was measured with a manual sphygmomanometer for adults (Figure 14): Patients were instructed to squeeze the sphygmomanometer cuff, already inflated to 40 mm Hg, between their extended knees. The maximal sustained pressure was taken as the baseline adductor strength before needling. Exact 15 minutes after the Vertical Obturator Nerve Block a second measurement of the adductor muscle strength was performed.

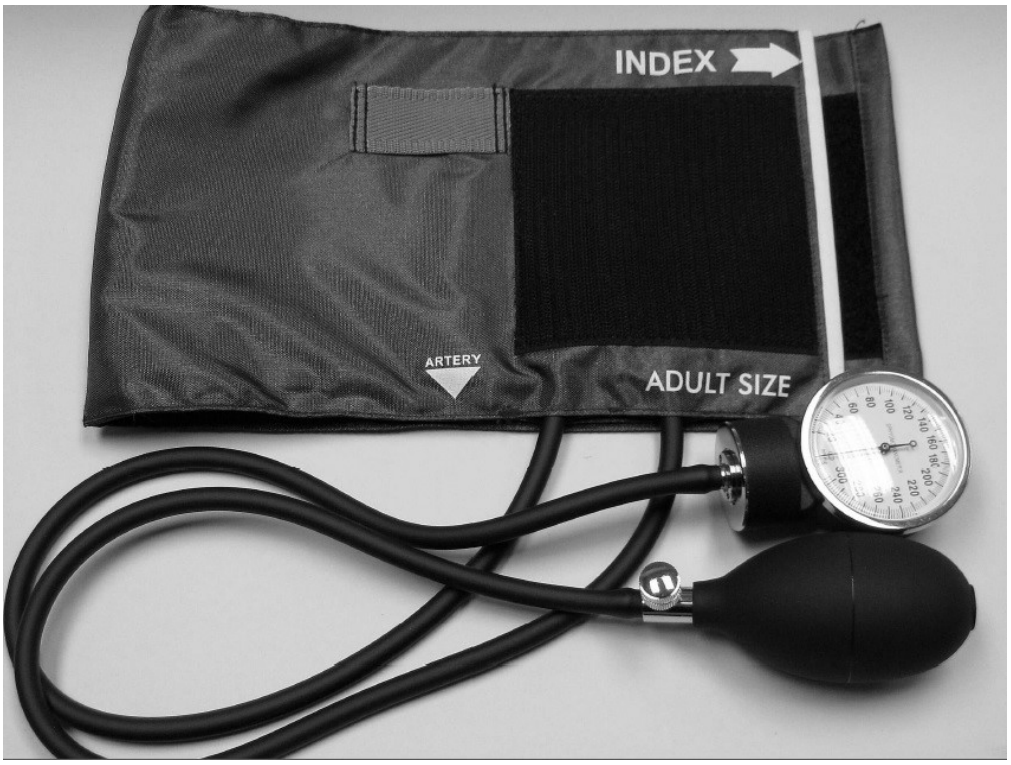

Figure 14: Picture of the manual sphygmomanometer used in this study. Before the adductor muscle strength testing, the cuff was manually insufflated by the investigator up to a pressure of 40 mm HG. The valve was firm locked during the measurements. The maximal sustained pressure was taken visual by reading the manometer indication needle.

Patient's pain intensity was assessed by the 11-point Numeric Rating Scale (70). The intensity of patient discomfort associated with the nerve block was assessed as published by Choquet et al. (6):

- 0 = "no or mild discomfort"
- 1 = "moderate discomfort"
- 2 = "important discomfort"

For possible regrets about patient´s participating, the patients were asked: "Do you regret to participate this stud? - Yes or No?"

The time from start to the end of the nerve block was defined and divided in two periods: Period one from the beginning of the procedure until the moment of needle insertion. This includes

- necessary shaving,
- disinfection,
- aseptic covering with blankets,
- needle and drug arrangement,
- palpation and identification of the puncture spot.

Period two was the needle-in-body time. Both periods together displays the total VOB time.

2.7 VOB performance

The obturator nerve block was performed according to the instructions given by Feigl et al. (10): A fingertip was placed lateral to the palpable pubic tubercle. A facet-tip needle (uniplex 25 G UP 3/80, Pajunk, Geisingen, Germany, Figure 15) was inserted directly laterally and adjacent to the distal part of the fingernail and advanced strictly perpendicular to the operating table (Figure 16).

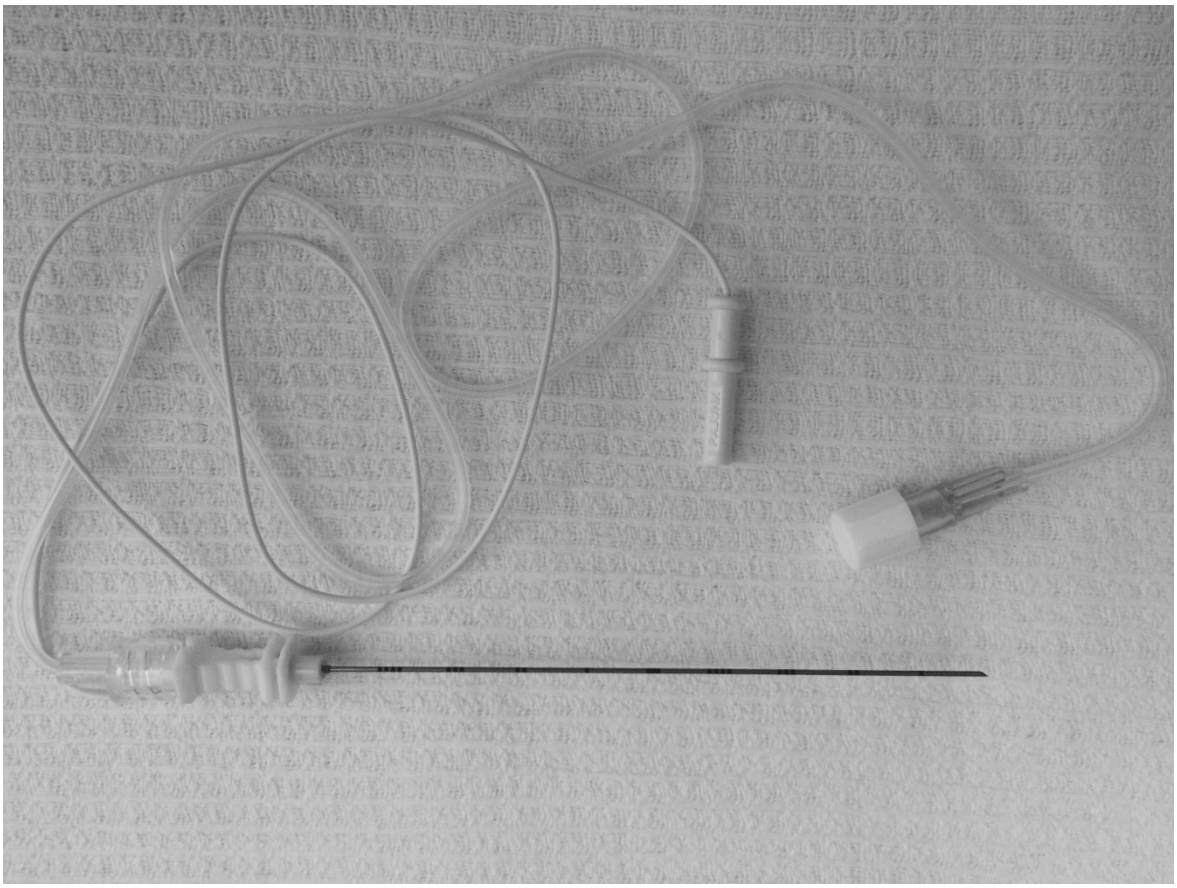

Figure 15: Picture of a uniplex 25 G Up 3/100 face tip needle with adaptable injection tube for aspiration and injection of the study medication. The cannula is provided with an ascending length indication in intervals of 1 cm for injection depth measurement. The cannula has a "cornerstone" surface (structured for ultrasound reflection for better identification of the needle during for Ultrasound) and has a connector for nerve stimulation (both not used in this study).

The calculated injection depth was between 2.5 and 6 cm depending on the weight of the patient according to Feigl at al. (10):

Weight of the patient	Calculated injection depth
< 45 kg	*
45 – 60 kg	2.5 – 3,5 cm
61 – 80 kg	3.5 – 4.5 cm
81 – 100 kg	4.5 – 6 cm
> 100 kg	*

Table 1: This table illustrates the injection depth [cm] of the needle based on patients weight [kg] in case of no bone contact according to the results of Feigl et al. * no depth available, exclusion criteria for participating in the study

In case of bone contact (superior pubic ramus), the needle was pulled back a short distance, the tip of the needle tilted slightly distally, and re-advanced till the bone was passed. In this case, the needle tip was inserted 1 cm deeper than the bone was encountered, according to the instruction given by Feigl et al. (10).

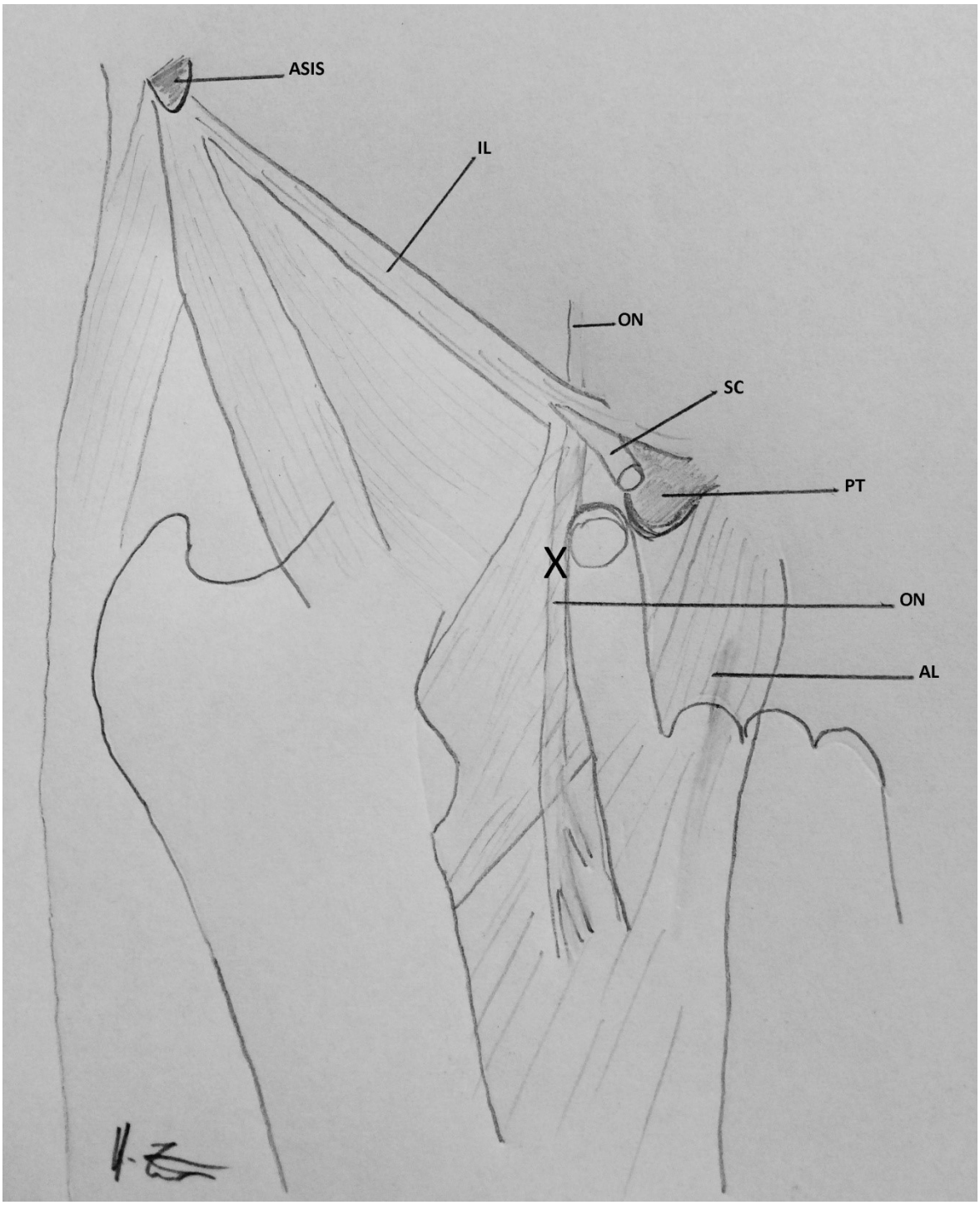

Figure 16: Drawing of the right femoral region with an anatomical overview: the inguinal ligament (IL) inserts at the pubic tubercle (PT) and the anterior superior iliac spine (ASIS). The finger is placed with its tip lateral to the PT. The needle is inserted at the 'X', passing the pectineus muscle to reach the trunk of the obturator nerve (ON); (AL) adductor longus and (SC) spermatic cord.

2.8 Management of local anaesthetic-induced toxicity and allergic reactions

In this study, there was a possibility of intravenous or intra-arterial injection of the local anaesthetic agent (ropivacaine). In this case, a high peak of ropivacaine would cause systemic toxicity. The toxicity could only occur in our verum group using ropivacaine, but not in the control group using NaCl. Systemic toxicity most often involves the cardiovascular system or the central nervous system. The toxicity often appears 1 to 5 minutes after the injection, but onset rage can be extended in rarely cases up to 60 minutes (71,72). So, because of the blinded design, we could not distinguish the study medication and the placebo. Therefore, in case of sins for systemic toxicity, an emergency un-blinding plan was arranged with the University's Institute for Medical Informatics, Statistics and Documentation of the MUG. Furthermore, we determined a standardized management according to current guidelines:

In case of signs for anaesthetic toxicity during this study, treatment was plant on the recommendations given by the American Society of the Regional Anaesthesia and Pain Medicine (ASRA). We decided to use the ASRA Checklist (73,74) for treatment of local anaesthetic systemic toxicity to provide a standardized fast and safe management in case of systemic anaesthetic toxicity of LA. An intravenous lipid emulsion as antidote was provided in the surgery area to ensure quick treatment (75,76).

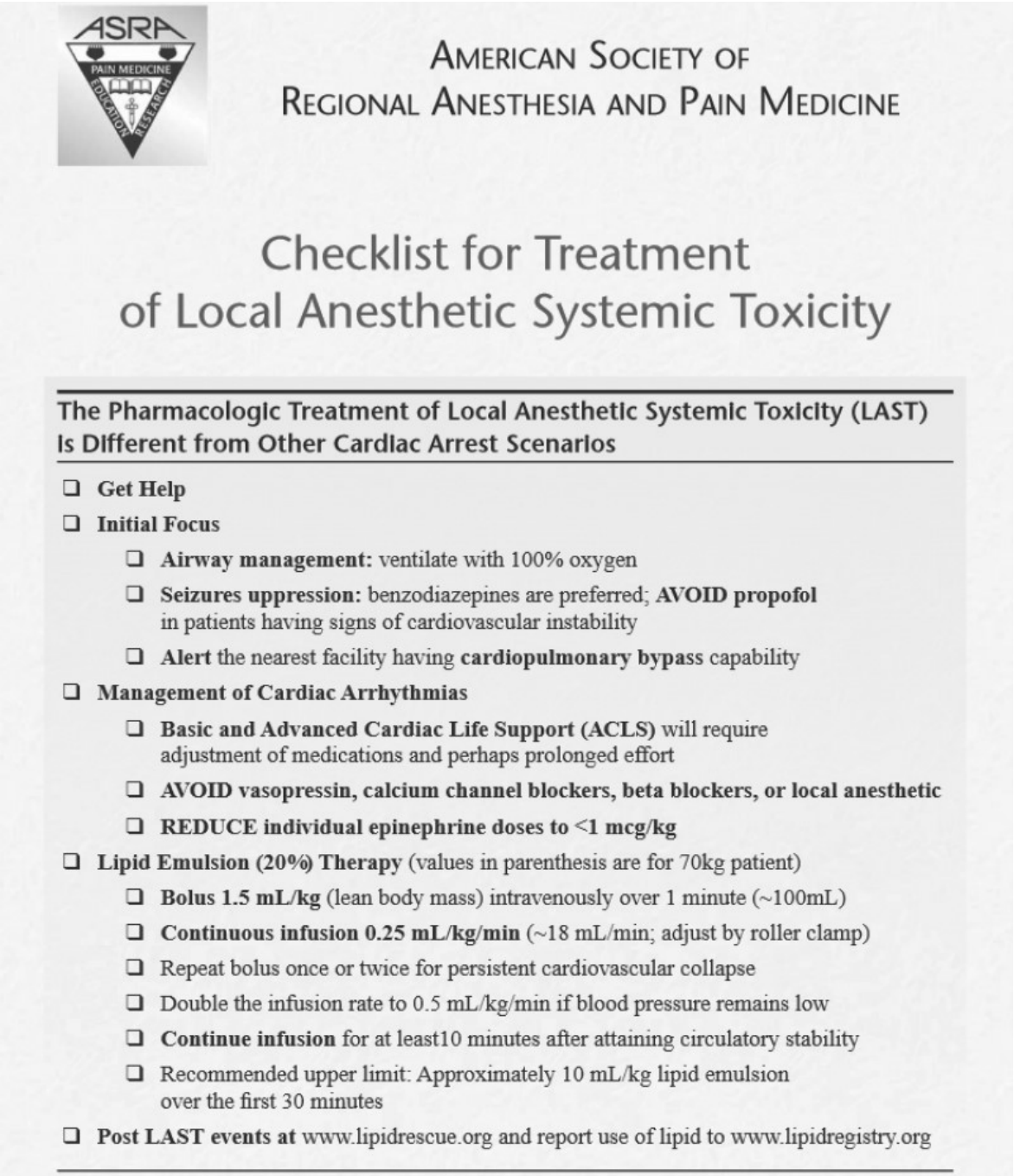

Figure 17: Picture of the ASRA Checklist (73,74) used in the study in case of local anaesthetic systemic toxicity to provide a standardized fast and safe management. This checklist was hanged in the operating theatre.

In case of allergic reactions, we plant to instantly interrupt the administration of the possible antigens immediately and respond with a symptom based treatment according to common known standardized managements (77,78).

2.9 Investigators, nurses and supervision

One of two investigators (#1 Dr. med. univ. Holger Simonis, MHBA; #2 Dr. med. univ. Bernhard Röschel) performed the study, dependent on a weekly schedule; both 3rd year residents of General Anaesthesiology, Emergency- and Intensive Care Medicine at the Medical University Graz. Both investigators were skilled in regional anaesthesia and capable to manage side effects and complications. During the nerve block and during the followed surgery, they were supervised by senior physicians in the operation theatre dependent on daily schedules for senior physicians.

Both investigators were supported by specialized nurses during the Vertical Obturator Nerve Block. The nurses assisted the doctors with preparing equipment for the nerve block, monitoring the patient's vital signs, local disinfection procedures and recording times during the study procedures.

The study development, registration into clinicaltrial.gov, patient allocation, progress, evaluation, statistical analyses and interpretation was monitored and supervised by the principal study investigator Prof. Dr. Andreas Sander-Kiesling.

2.10 Postoperative surveillance of patients

After surgery, the study investigators transferred the study patients into a standard recovery unit of our university hospital for postoperative surveillance. In this unit, patients were observed and monitored by specialized nurses. The nurses were well-briefed by the study team to detect late onset complications of the regional anaesthesia or signs for systemic toxicity of the local anaesthetic agent. In case of any complication or signs of systemic toxicity, the nurses had to contact the study team immediately.

Systemic toxicity signs were defined and as

- circum-oral and/or tongue numbness,
- metallic taste,
- disorientation,
- downiness,

- muscle twitching,
- convulsions,
- unconsciousness,
- coma,
- respiratory depression and
- arrest for central nervous toxicity.

Signs for cardiovascular manifestations were defined as

- signs of chest pain,
- shortness of breath,
- palpitations,
- light-headedness,
- diaphoresis,
- hypotension and
- syncopes.

After at least two hours of surveillance in the recovery room, all patients were transferred to the ward of trauma surgery for prolonged post-operative observation.

2.11 Statistics

In this study, $p < 0.05$ was considered significant. Because the data was not normally distributed, a Friedman-Test (79–81) for repeated measurements was used. Additionally, we rechecked the results by using a Mann-Whitney-U-Test (82) on the absolute difference in adductor muscle strength before and after treatment between groups. Changes in adductor muscle strength were tested by Wilcoxon-Tests (83). Correlations were tested by Kendall's tau Test (84,85) and Spearman's rho (86) test for nonparametric testing and Pearson Correlation Test (87) for parametric testing.

The descriptive statistics of the adductor muscle strength are presented by median and interquartile range. Further descriptive statistics of age, weight, intended injection depth, pain and time periods are presented as mean and standard deviation.

The statistical analyses were performed using NCSS 8 (NCSS, LLC. Kaysville, Utah, USA) for Friedman-Test (79) and SPSS Version 22 (IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY, USA) for all other statistics.

3 Results

3.1 Drop outs and missing data

During this study we had no drop outs for any reason. We stopped including patients into the study after 30 patients, because we attained the primarily intended sample size of n=30 (Fig. x). Including and excluding criteria were checked before allocation and a written informed consent was detained subsequently. According to the patients allocation time, the patients assigned to an ascending study ID (1, 2, 3…30).

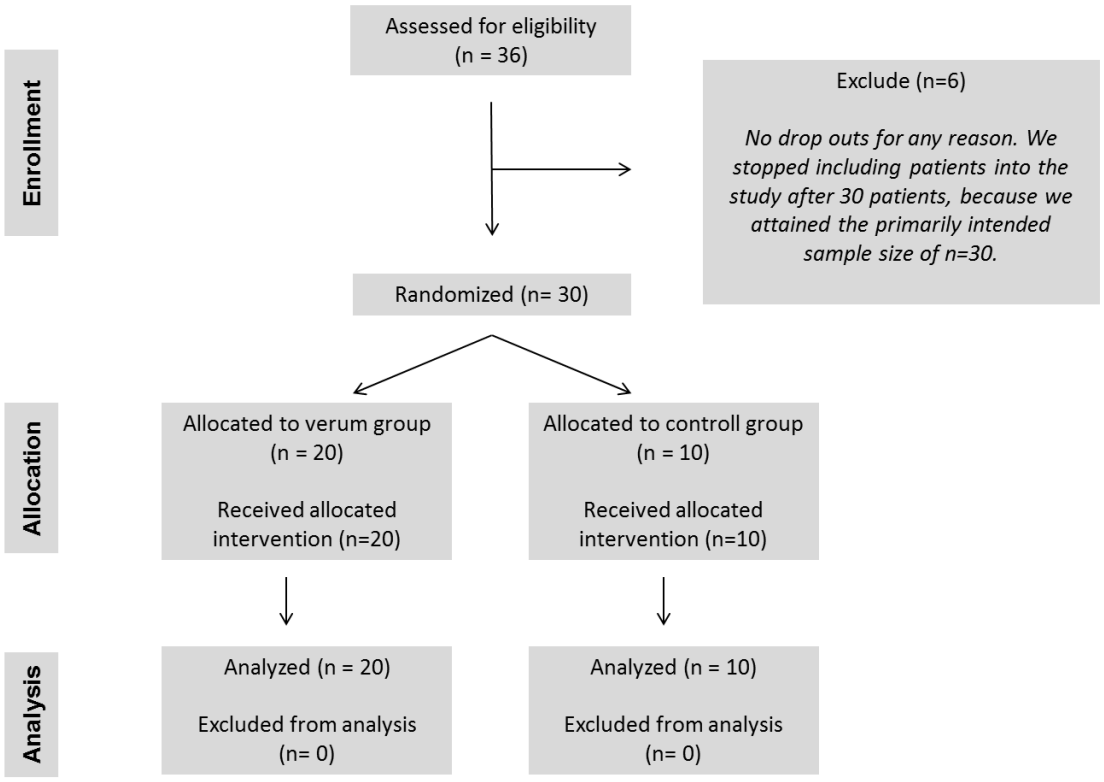

Figure 18: Flow of participants through each stage of the study trail (Enrolment, allocation, analysis) with numbers and explanation for excursions of patients.

After the allocation, the Study data was summarized. All patients were included in the study statistics. In 5 cases the data of time for preparation were missing and in one case the needle-in-body time was missing. All other data were complete.

3.2 Patients and group characteristics

3.2.1 Weight

The mean weight in all study patients was 81 kg with 9.9 kg standard deviation. Minimum weight was 59 kg and maximum weight was 100 kg: The patient's weight was almost normal distributed.

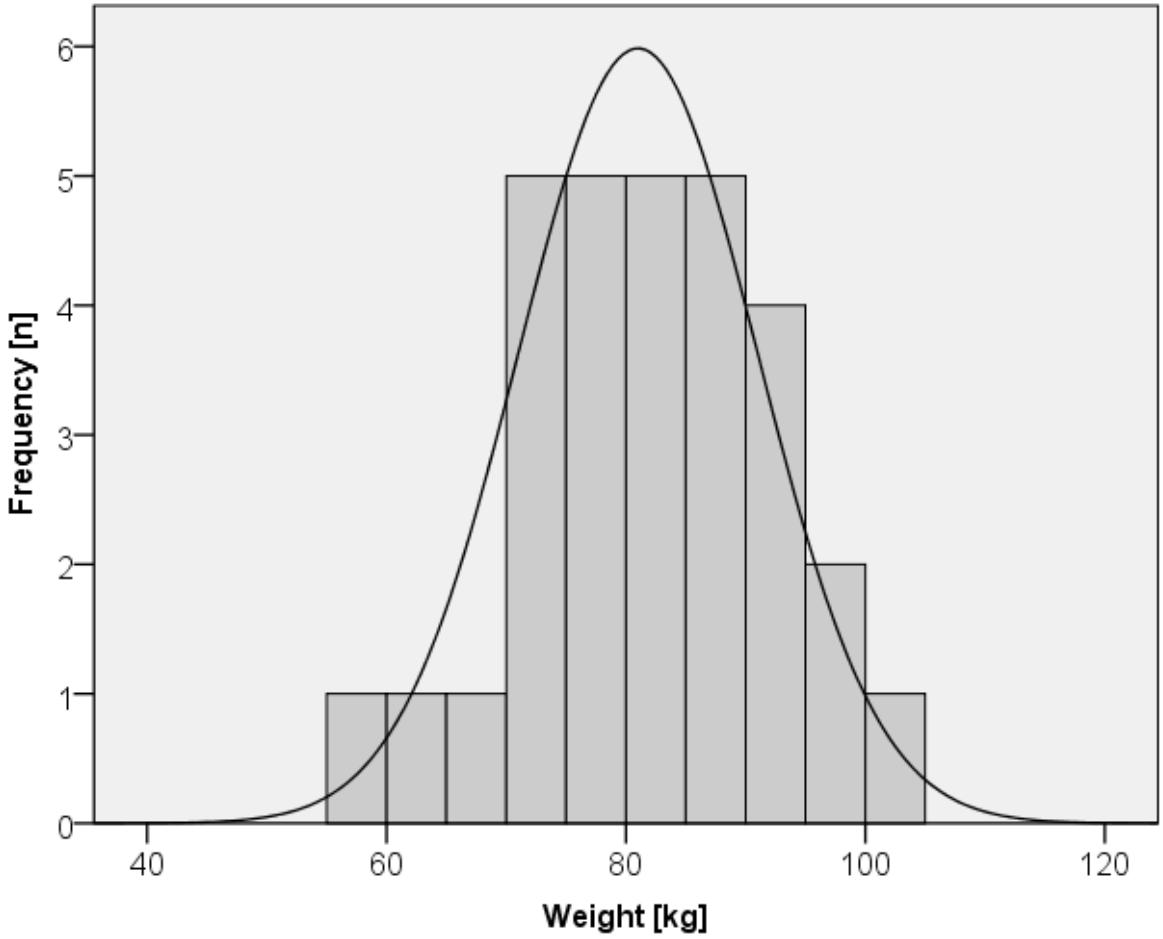

Figure 19: Histogram of study patient's weight in kg including normal curve. Interval broadness is 5 kg. Interquartile range was 16 kg. Skewness was -0.209 and kurtosis was 0.342.

3.2.2 Age

The mean age of study patients was 48.5 years with sandart deviation of 16.2 years. Minimum age was 19.9 years and maximum age was 83.6 years. The minimal possible age in this study was 18 years, due to the including citeria of this study.The age was roughly normal distributed as displayed in Figure 20:

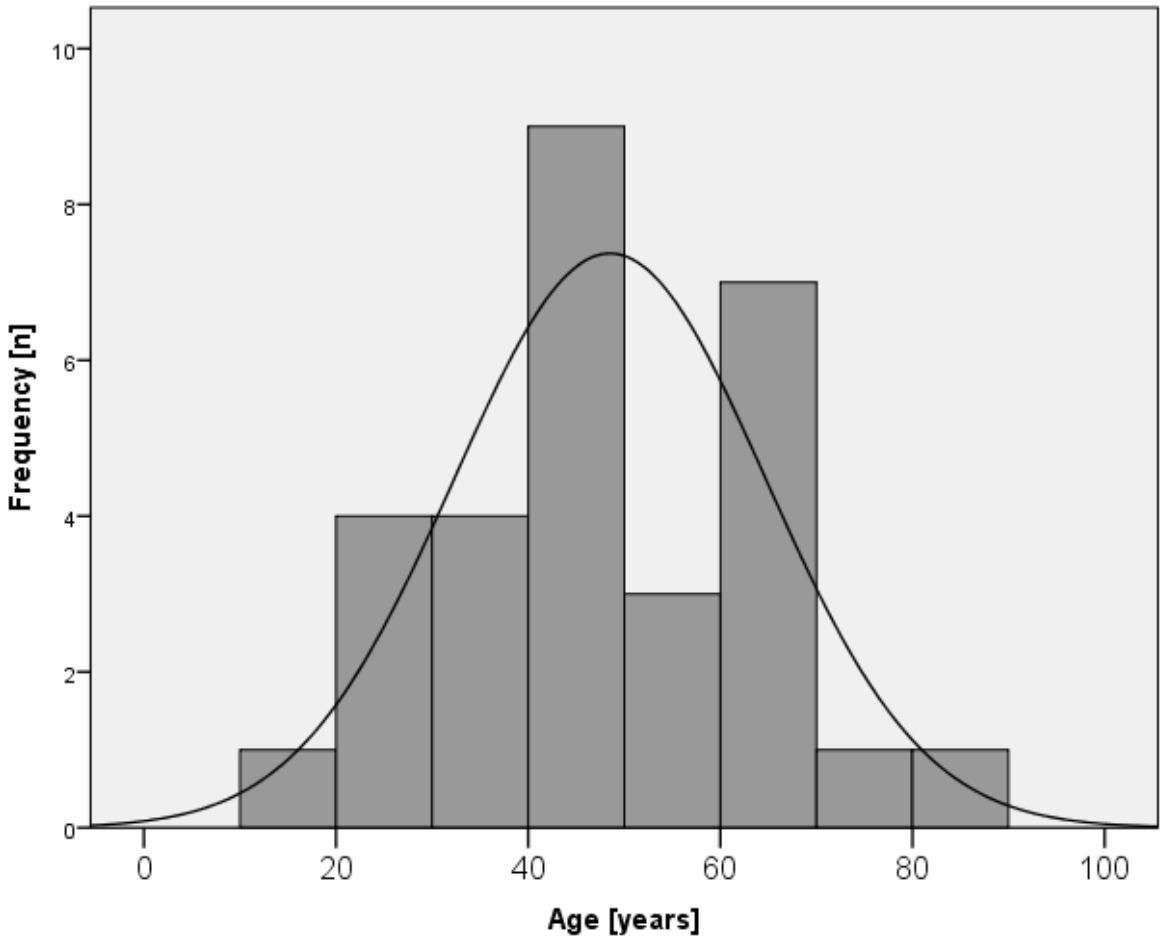

Figure 20: Histogram of study patient's age in years including normal curve. Interval broadness was 10 years. Interquartile range was 27.7 years. Skewness was 0.126 and kurtosis was -0.734.

3.2.3 Gender

Eight male and 22 female participated in the study: So, the patient's gender was not equally distributed. Figure 21 displays the gender:

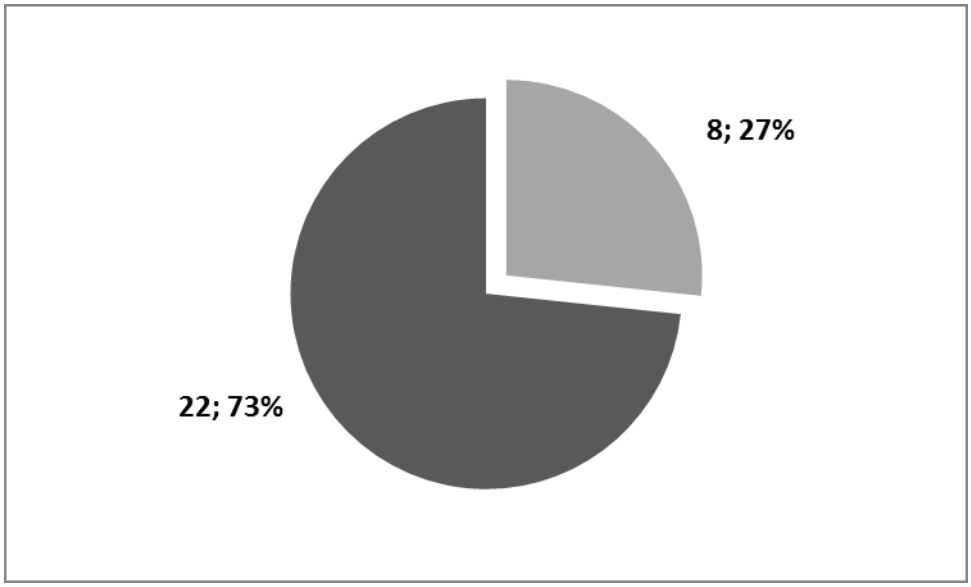

Figure 21: Circle diagram of patient's gender. Pale grey piece are male and dark piece are female. First number displays the count [n] and second number the relative amount [%].

3.2.4 Investigator distribution

Twenty patients received a VOB by investigator #1 and 10 patients received a VOB by investigator #2. Therefore, the investigator count was not equal. Figure 22 displays the investigator distribution in study patients:

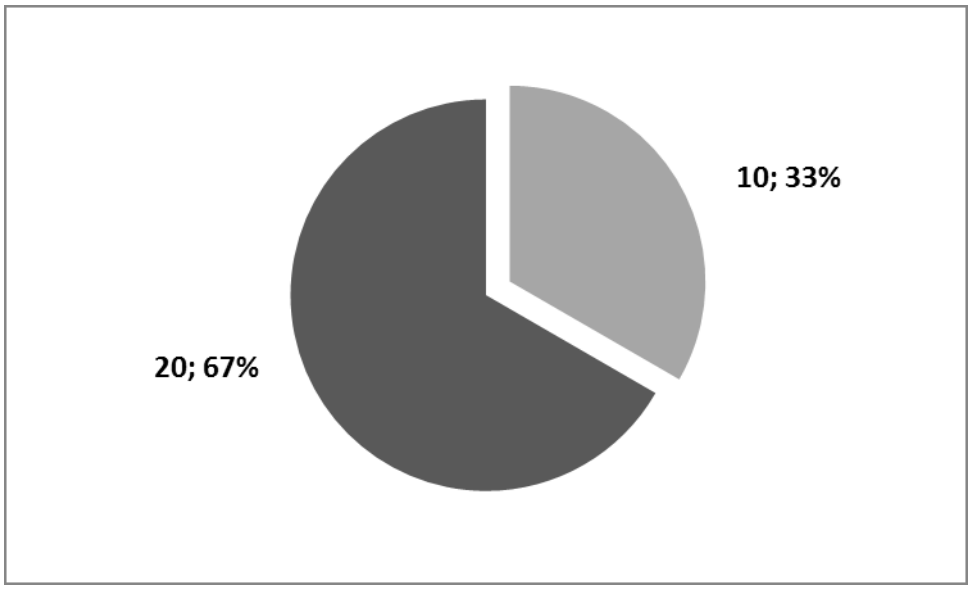

Figure 22: Circle diagram investor counts. Pale grey piece are patients who received a VOB by investigator #2 and dark piece represent patients who received a VOB by investigator #1. First number is the count [n] and second number is the relative amount [%].

3.2.5 Control vs verum group

In the control and verum group patients' data were comparable regarding investigator counts, age, bodyweight, intended injection depth and pain at an 11-pointed-NRS. Due to a 2:1 randomisation, 10 patients were in the control group and 20 patients in the verum group. Table 2 displays the patients characteristics in both groups.

However, the patients age was not equally distributed (p= 0.029): The mean age in the control group was 57.5 years (17.3 SD) and in verum group 44.0 (14.1 SD). The maximum age in control group was 83.6 years and 65.2 years in verum group. The minimum age in control group was 27.6 years and 19.9 years in the verum group (see Figure 23).

	control group	verum group
Patients, n	10	20
Investigator (#1/#2)	7/3	12/8
Sex (male/female)	3/7	5/15
Age, y	57.5 (17.3)*	44.0 (14.1)*
Weight, kg	82.2 (8.6)	80.4 (10.8)
Intended Injection Depth, cm	4.7 (0.6)	4.6 (0.7)
Pain, 11-point-NRS [0-10]	2.4 (1.3)	3.2 (1.9)

Table 2: This table displays the Patients characteristics in this pilot study. Age [years], Weight [kg], Intended injection depth [cm] and Pain [NRS 0-10] are reported as mean (standard deviation) for the control and verum group. Investigator counts for #1 and for #2, group size and sex were displayed as counts (n). * p= 0.029

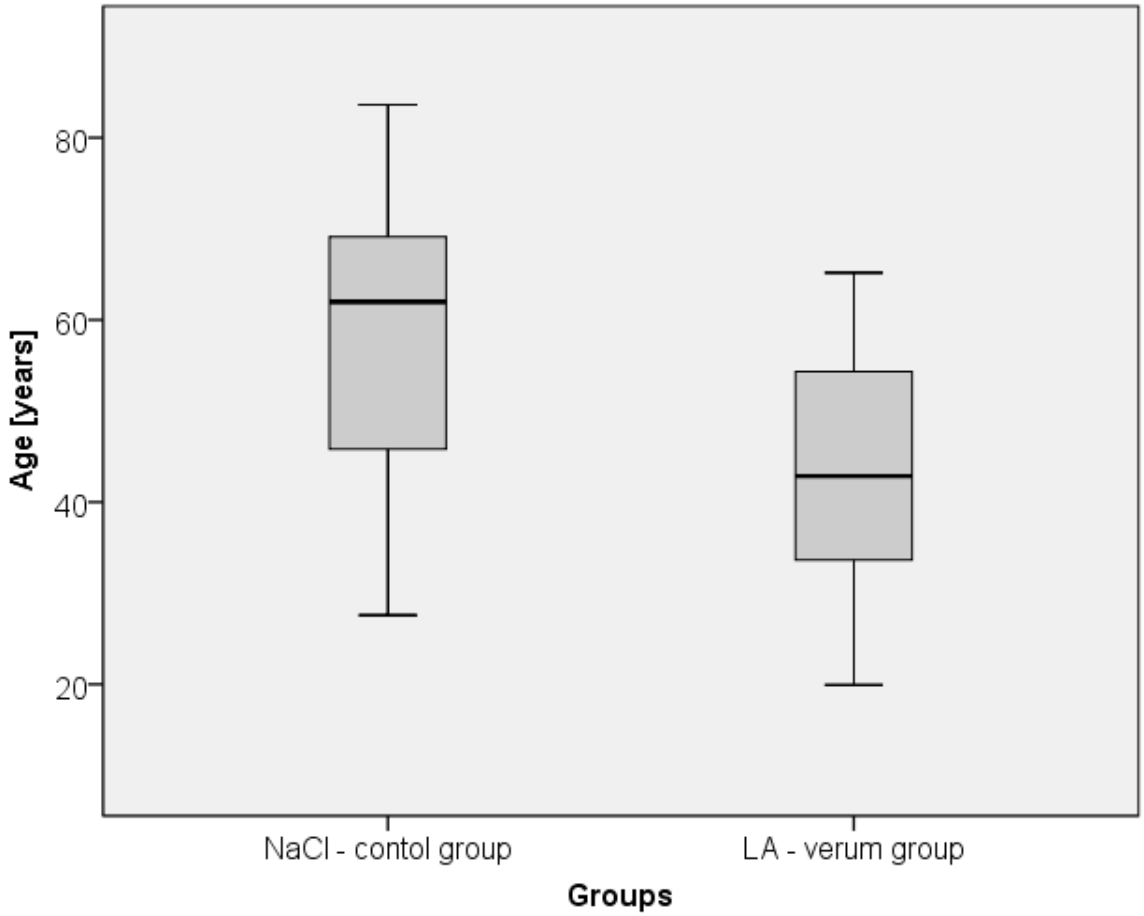

Figure 23: Boxplot of the patient age in the control group and the verum group in years. The interquartile range of control group was 25.6 years and 21.3 years in verum group.

3.3 Adductor muscle strength

The mean adductor muscle strength *before* nerve block was 135.4 mm Hg. Standard deviation was 35.9 mm Hg. The minimum strength was 70 mm Hg and the maximum was 190 mm Hg. Figure X displays the adductor muscle strength before nerve block:

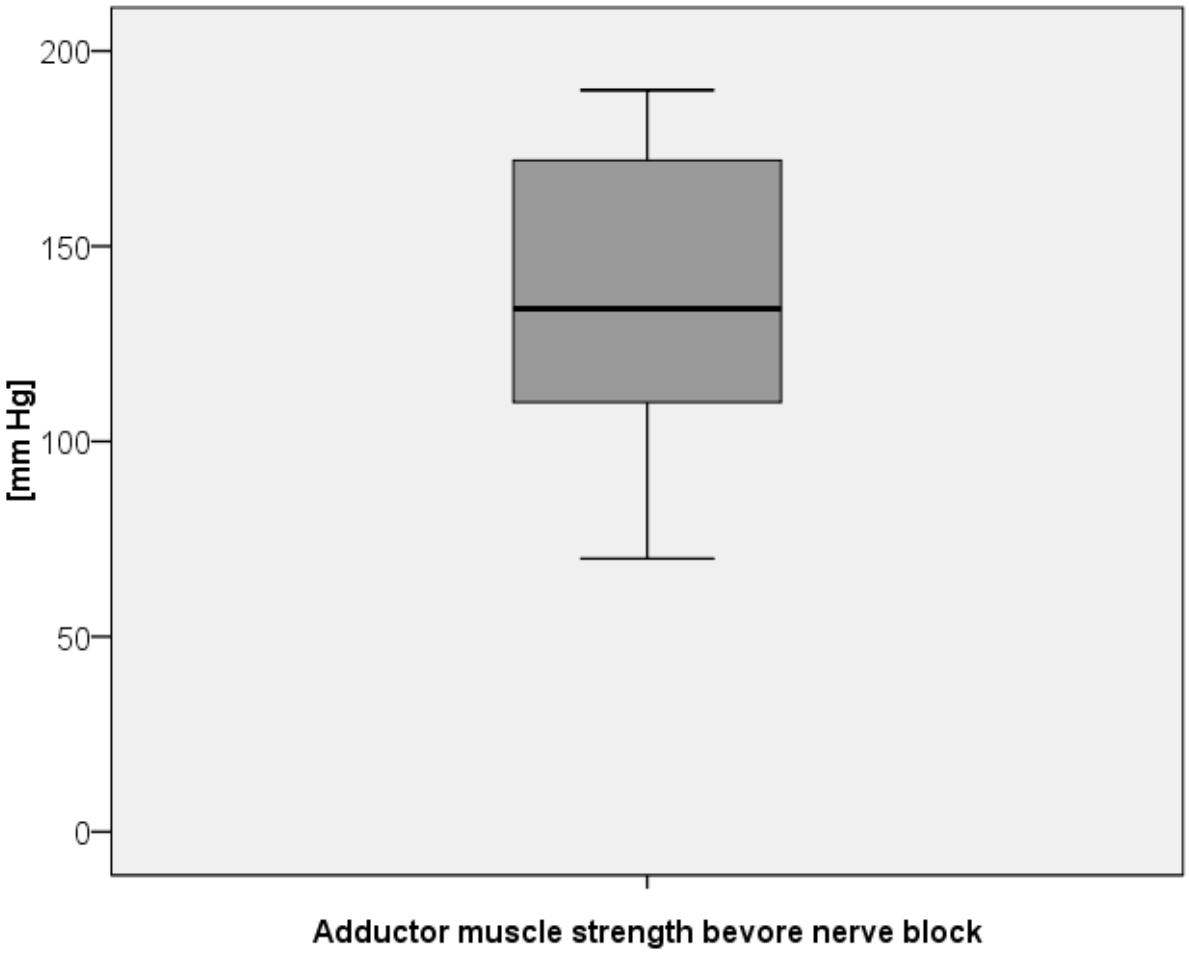

Figure 24: Boxplot of the adductor muscle strength measurement before VOB in mm HG. Median was 134.0 mm HG with an interquartile range of 63, skewness 0.006 and kurtosis -1.221.

The mean adductor muscle strength *after* nerve block was 116.9 mm Hg. Standard deviation was 33.1 mm Hg. The minimum strength was 60 mm Hg and the maximum was 180 mm Hg. Figure X displays the adductor muscle strength after nerve block:

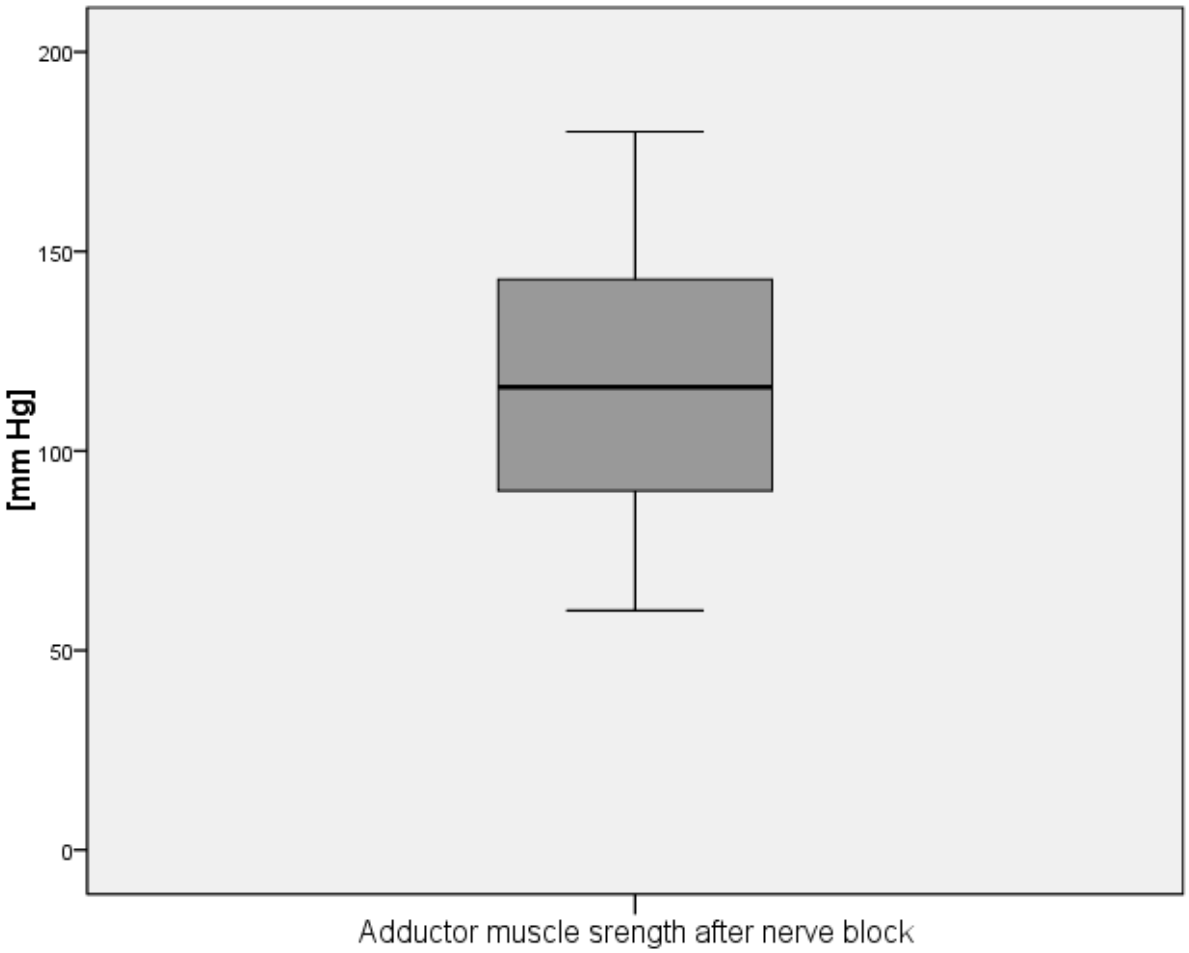

Figure 25: Boxplot of the adductor muscle strength measurement after VOB in mm HG. Median was 116.4 mm HG with an interquartile range of 53, skewness 0.191 and kurtosis -0.913.

3.3.1 Adductor muscle strenght and age

The correlation in a tow-tailed parametric Pearson Correlation Test was significant between adductor muscle strength before nerve block and age of patients (p= 0.011). Older patients had less adductor muscle strength before nerve block than younger. Figure X displays a negative correlation between adductor muscle strength and age:

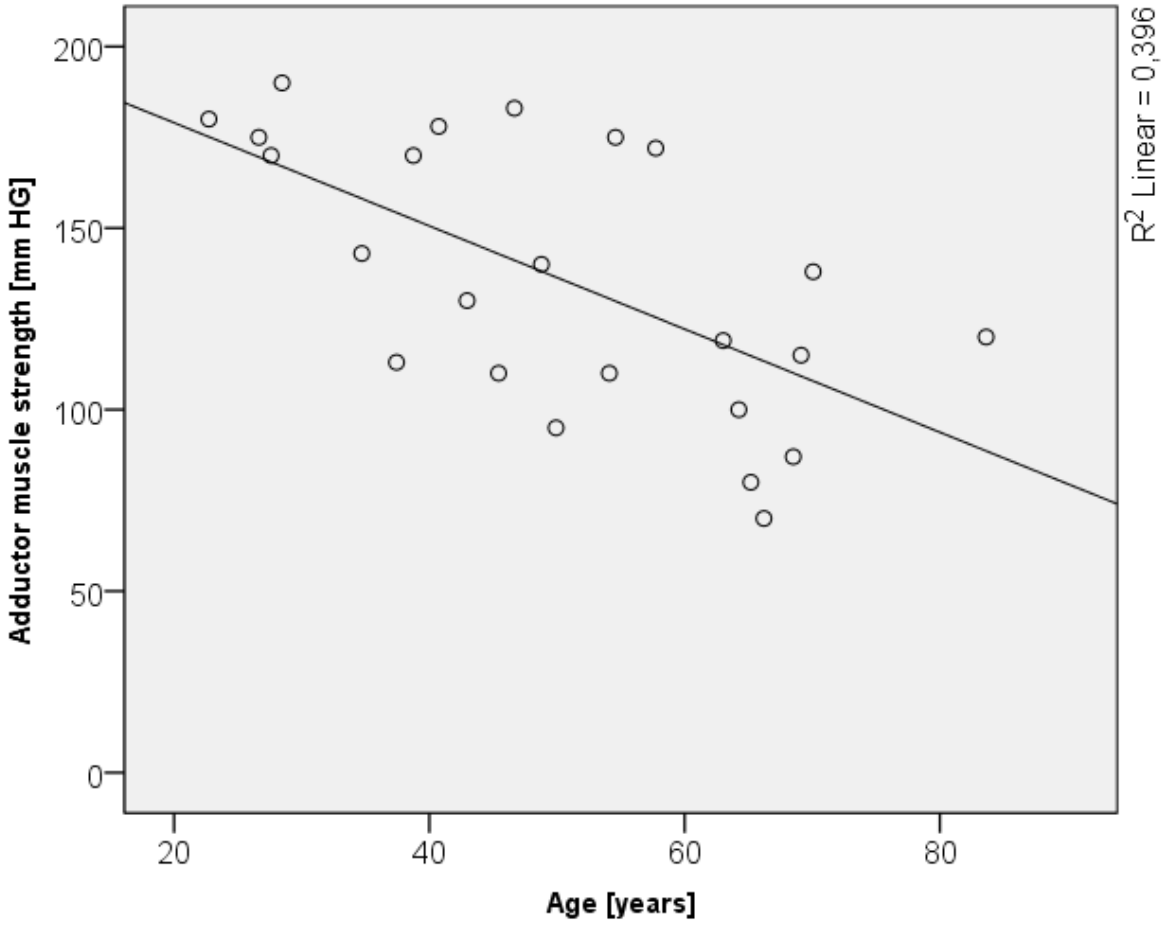

Figure 26: Scatter diagram of the adductor muscle strength in mm HG and the patients' age in years. The coefficient of determination (R squared) is displayed at the upper right side of the diagram.

3.3.2 Adductor muscle strength and weight

The correlation in a tow-tailed parametric Pearson Correlation Test was not significant between adductor muscle strength before nerve block and patient's weight (p= 0.536). Figure X displays independency between adductor muscle strength and age:

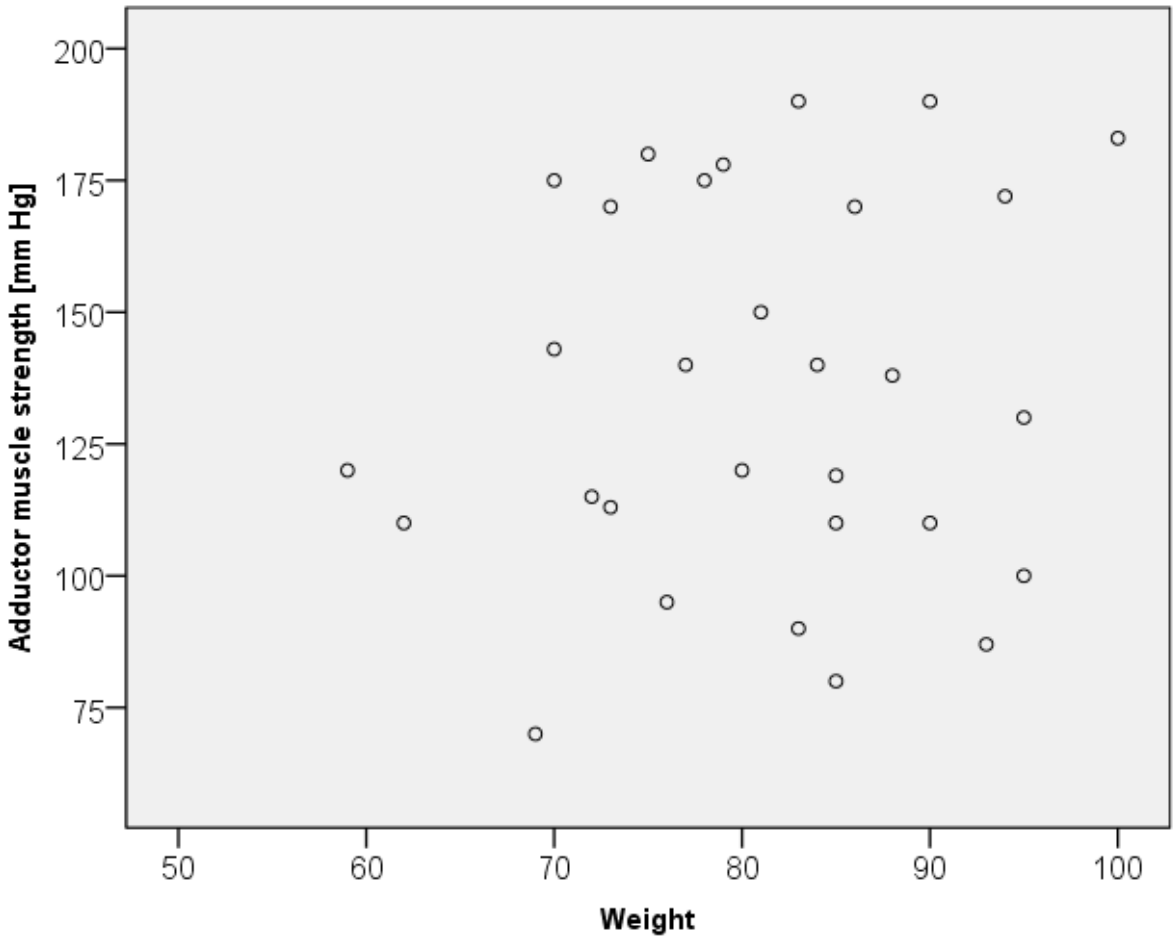

Figure 27: Scatter diagram of the adductor muscle strength before nerve block in mm HG and the patients' weight in kg.

3.3.3 Adductor muscle strength and gender

The mean adductor muscle strength in *male* before nerve block was 148.2 mm Hg. Standard deviation was 31.5 mm Hg. The minimum strength was 90 mm Hg and the maximum was 190 mm Hg.

The mean adductor muscle strength in f*emale* before nerve block was 100.3 mm Hg. Standard deviation was 21.4 mm Hg. The minimum strength was 70 mm Hg and the maximum was 130 mm Hg.

The difference between adductor muscle strength before nerve block and gender is significant ($p < 0.001$). Figure 28 displays the adductor muscle strength before nerve block in both genders:

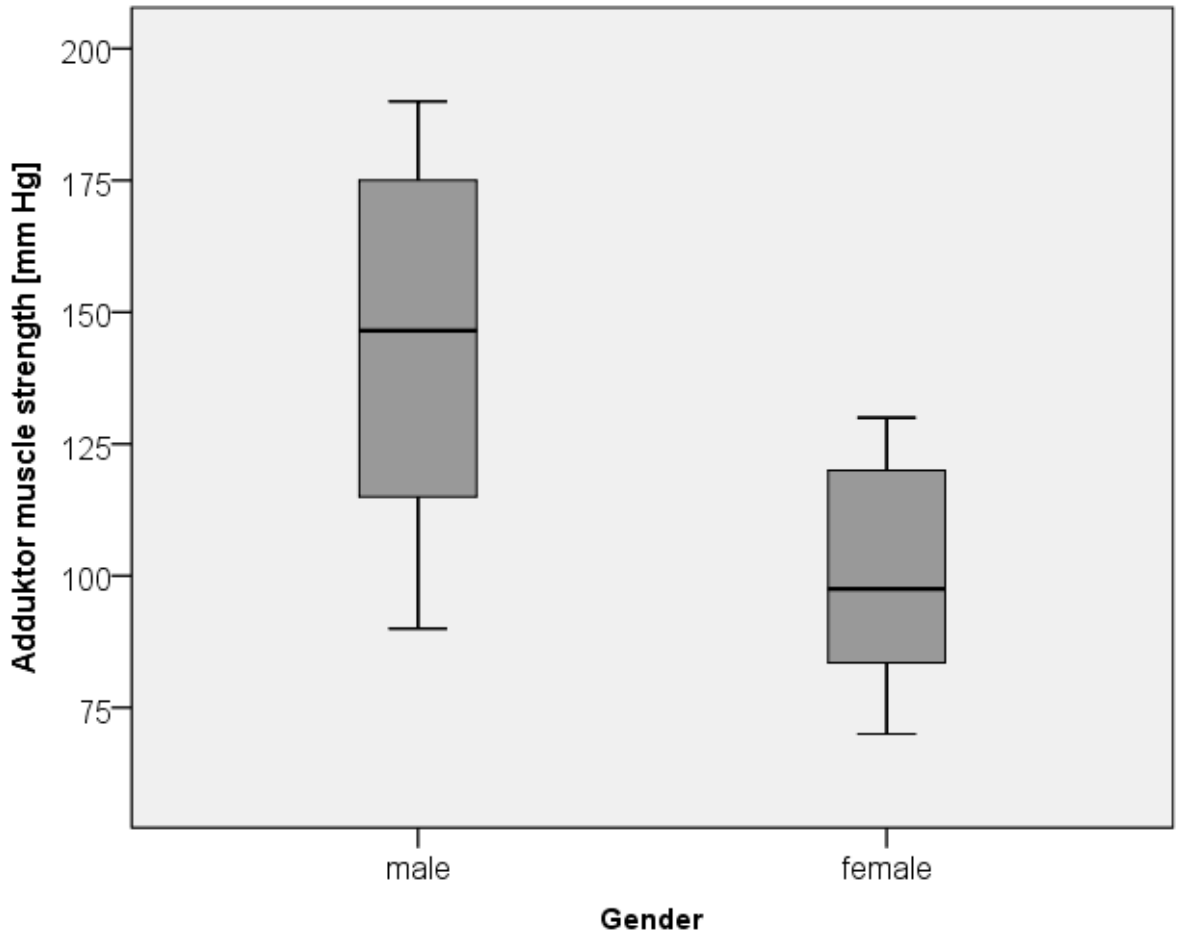

Figure 28: Boxplot of the adductor muscle strength measurement in male and female before VOB in mm HG. Median was 127.5 mm HG in male and 92.5 mm HG in female with an interquartile range of 52, skewness -2.224 and kurtosis -0.904 in male and interquartile range of 12, skewness -0.199 and kurtosis -2.523 in female.

3.3.4 Adductor muscle strength in groups

The adductor muscle strength in the control group before nerve block (129.0 median, interquartile range 64.0 [mm HG]) and in the verum group (135.0 median, interquartile range 65.0 [mm HG]) was not significant different. And the adductor muscle strength 15 minutes after the nerve block in the control group (136.5 median, interquartile range 58.0 [mm HG]) and the verum group (105.0 median, interquartile range 33.1 [mm HG]) was also not significant different.

A significant decrease of adductor muscle strength of 20.0 mm HG (median; interquartile range 29.5) was detected in the verum group (p=0.001), compared to no significant decrease of 1.5 mm HG (median; interquartile range 24.3) in the control group (Tab. 2).

The adductor strength change describes the subtraction of the strength after the nerve block and the strength before. In the control group the difference was 1.5 mm HG (median, interquartile range 24.3) and 20.0 mm HG (median, interquartile range 29.5) in the verum group. The difference of adductor muscle strength before and after the nerve block in both groups was not significant (p=0.074, Tab. 2).

	before nerve block [mm HG]	15 minutes after nerve block [mm HG]	Difference between both measurements before and after nerve block
control Group n=20	129.0 (64.0)	136.5 (58.0)	-1.5 (24.3)**
verum Group n=10	135.0 (65.0)*	105.0 (33.1)*	-20.0 (29.5)**

Table 3: This table presents the median Adductor Strength (interquartile range) before and 15 minutes after nerve block of both groups [mm HG]. Statistical significant changes are marked as * p= 0.001 and ** p= 0.074.

Descriptives

	Groups			Statistic	Std. Error
Adductor strength change (T2 - T1) [mm HG]	**NaCl - contol group**	Mean		-3,500	5,4370
		95% Confidence Interval for Mean	Lower Bound	-15,799	
			Upper Bound	8,799	
		5% Trimmed Mean		-3,333	
		Median		-1,500	
		Variance		295,611	
		Std. Deviation		17,1933	
		Minimum		-30,0	
		Maximum		20,0	
		Range		50,0	
		Interquartile Range		24,3	
		Skewness		-,241	,687
		Kurtosis		-,498	1,334
	LA - verum group	Mean		-26,050	7,8762
		95% Confidence Interval for Mean	Lower Bound	-42,535	
			Upper Bound	-9,565	
		5% Trimmed Mean		-23,667	
		Median		-20,000	
		Variance		1240,682	
		Std. Deviation		35,2233	
		Minimum		-105,0	
		Maximum		10,0	
		Range		115,0	
		Interquartile Range		29,5	
		Skewness		-1,602	,512
		Kurtosis		1,581	,992

Table 4: Descriptive data output of the adductor strength deviation between measurement time two and one in mm HG of the control and the verum group including mean, 95% confindence interval for mean, median, variance, std. deviation, minimum, maximum, range, interquartile range, skewness and kurtosis.

Figure 29 and Figure 30 displays the data of the adductor muscle strength before and 15 minutes after needling. The incline/decline of the straight lines in figure 1 describes the change of the adductor muscle strength:

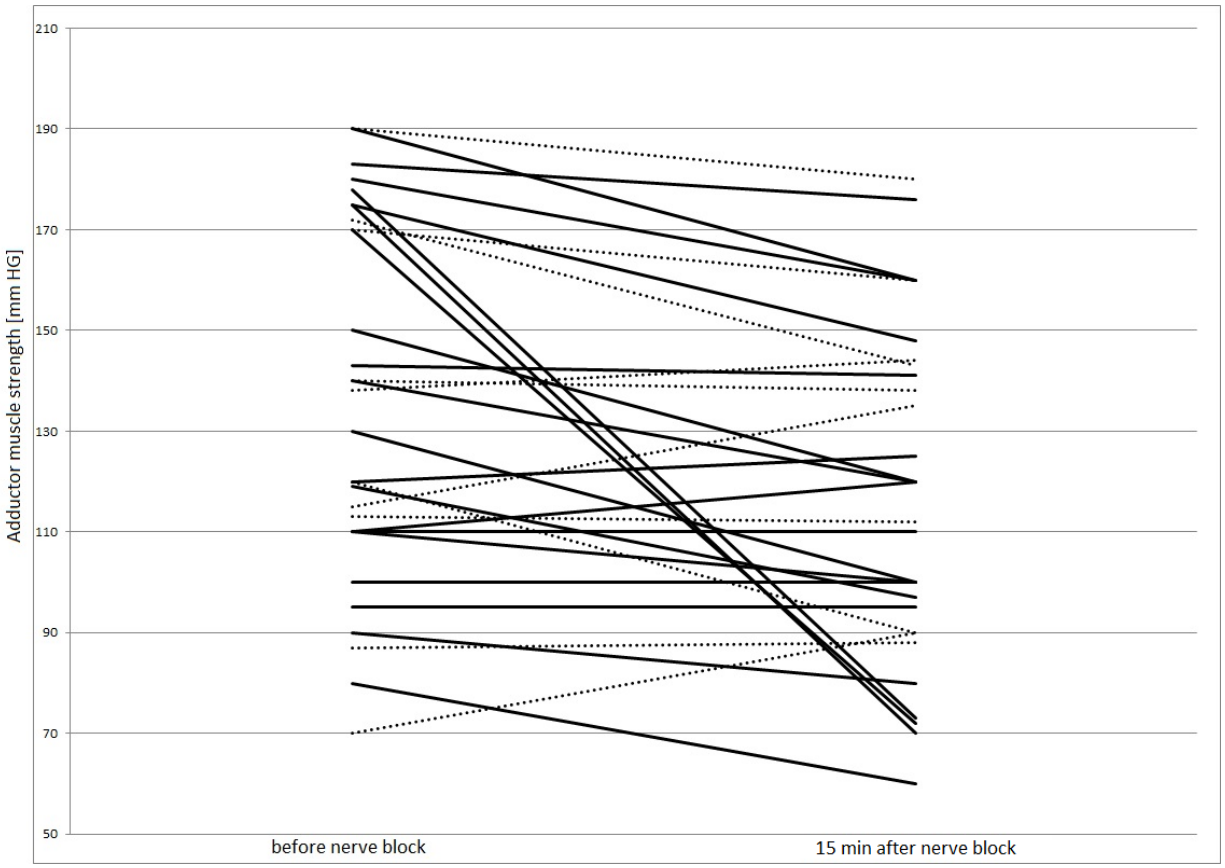

Figure 29: Maximal adductor muscle strength of study patients before and 15 minutes after nerve block. Every line displays one study patient and includes two measurements, dotted lines were control group patients and black lines were patients in the verum group. Adductor muscle strength was measured in mm HG. The slope of the lines illustrates the strength development before and after nerve block. Three black lines were notably steep (Study ID # 6, 11 and 14), all others were light steep.

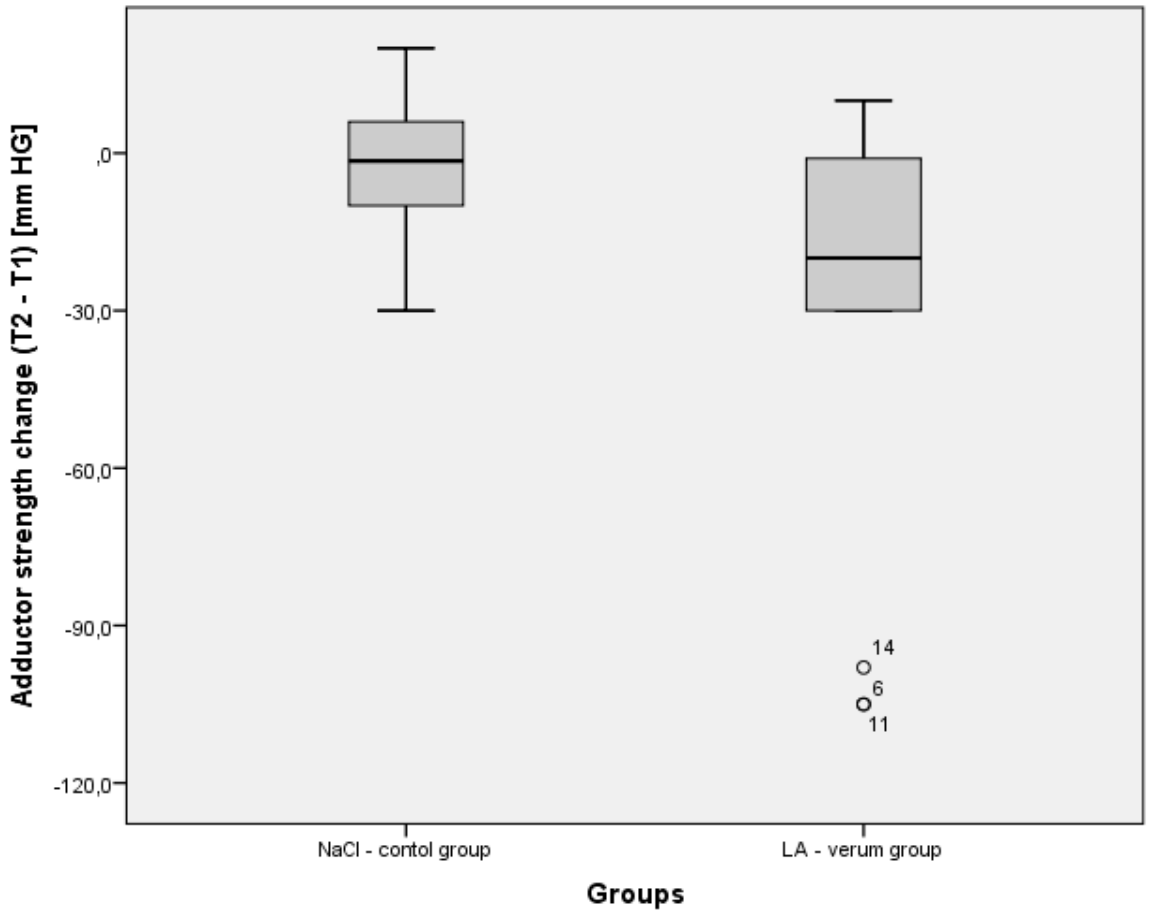

Figure 30: Boxplot of the absolute adductor muscle strength change between measurement time two (after VOB) and one (before VOB) for the control and verum group in mm HG (=adductor muscle strength after VOB – adductor muscle strength before VOB). In the verum group you see three outliers: Study ID # 6, 11 and 14.

3.3.5 Count of successful blocks

A successful obturator nerve block was observed in 3 patients in the verum group (Study ID # 6, 11 and 14), and in no patient in the control group, when a cut off of 30, 40, or 50 % decrease of adductor muscle strength was applied. The three successful obturator nerve blocks are displayed in Figure 29 and Figure 30 as three outliers.

However, 6 successful blocks where observed in the verum, and one in the control group, when a cut of at 20 % was chosen (Tab. 3, Fig. X).

Cut off [%]	success in verum group [n]	success in control group [n]
20	6	1
30	3	0
40	3	0
50	3	0

Table 5: The table displays the count of successful nerve blocks in the verum group and the control group, based on different cut offs (20%, 30%, 40% and 50%) for adductor muscle strength.

Based on a cut off at 30, 40, or 50 % decrease of adductor muscle strength, all successful nerve blocks were performed by the investigator #1; Dr. Simonis. Bases on a cut off at 20 %, 3 successful blocks were performed by investigator #1, and 3 by investigator #2.

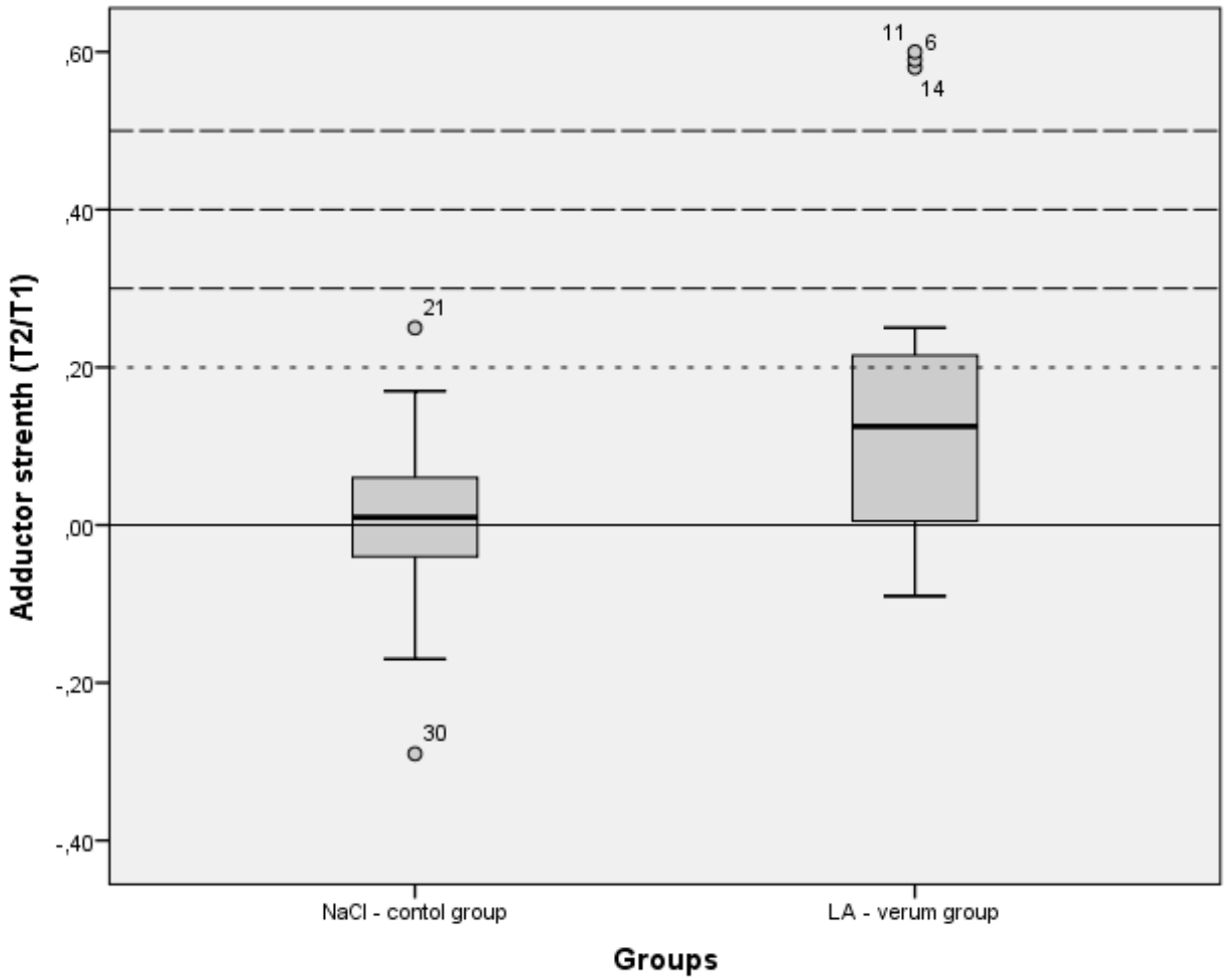

Figure 31: Boxplot of the percentage degrees of the adductor muscle strength after the obturator nerve block in the control and verum group. Depending on the chosen cut off for the definition of a successful nerve block, different counts of successful nerve blocks occur in groups. The dotted line presents the cut off at 20 % adductor muscle strength decrease and the dashed lines presents the cut of at 30, 40 and 50 %. In the control group you see two outliers: Study ID # 21 and #30. In the control group you see three outliers: Study ID #6, #11 and #14.

3.4 Patient's discomfort during needling

Asking about the intensity of discomfort, 22 patients report "no or mild discomfort", 7 "moderate discomfort" and one patient "important discomfort" associated with the nerve block (see Figure 32).

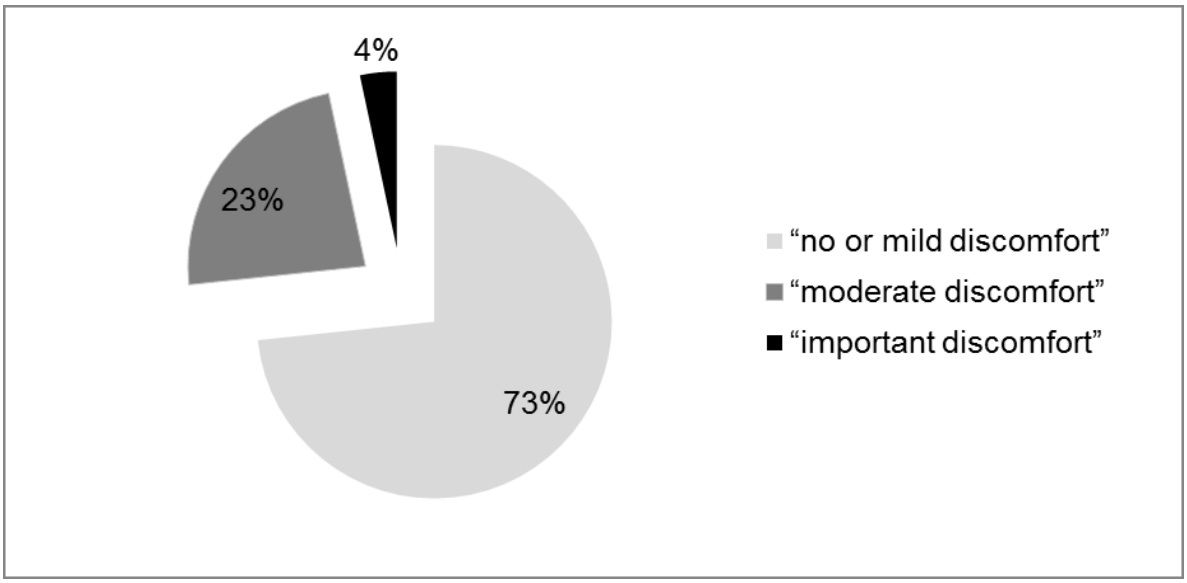

Figure 32: Circle diagram of patient´s discomfort during VOB. Patients could choose 3 different categories. Pale grey piece are patients with low, grey piece are patients with intermediate and the black piece are patients with high discomfort. This categories are displayed on a percentage basis. On the right side are the exact terms patients could choose.

3.5 Pain during needling

Pain was reported as NRS 2.9 ±1.73 (mean; SD). Two patients reported no pain [NRS 0], 22 patients reported mild pain [NRS 1 to 3], 6 patients reported moderate pain [NRS 4 to 6] one patient reported severe pain [NRS 7 to 10] (Fig. 3).

A two-tailed correlation analysis of the patients reported discomfort and the reported pain on the NRS was significant (p= 0.003).

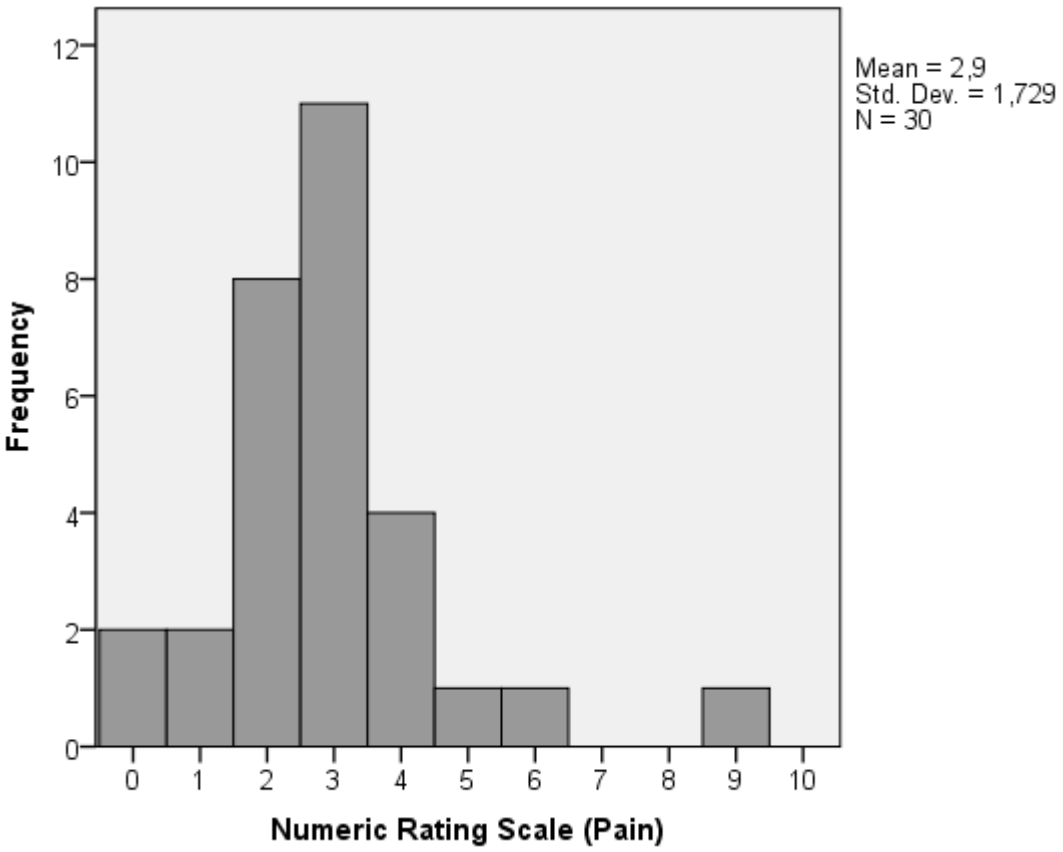

Figure 33: Bar diagram of patients' pain intensity during vertical obturator nerve block performance assessed by 11-point Numeric Rating Scale (abscissa). The absolute frequency is presented on the ordinate. Mean, standard division and patient's counts are presented beside the diagram.

No significant difference between patient´s pain and bone contact during needling was measured. Mean pain in the patient group with bone contact was 2.7 ±1.3 (mean; SD) and 3.0 ±1.8 (mean; SD) in the group without bone contact.

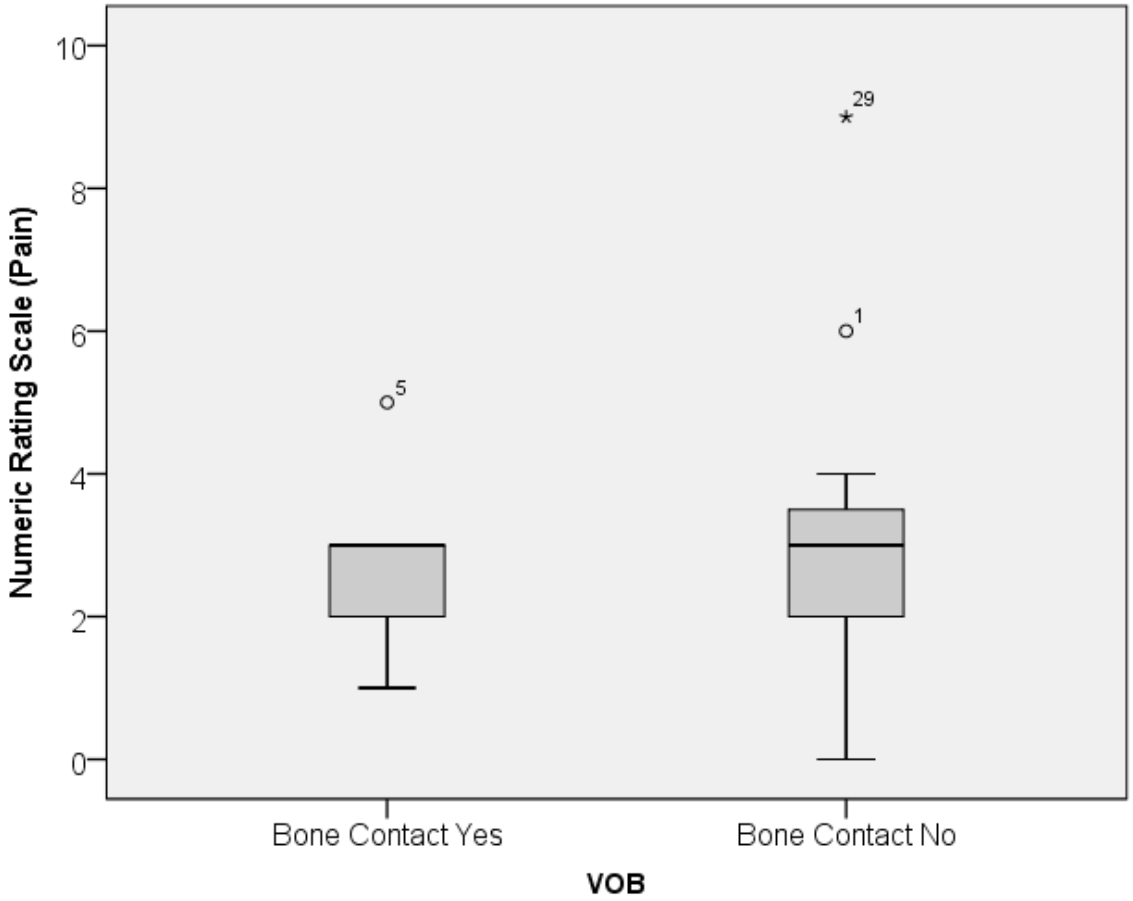

Figure 34: Boxplot of patient's pain on an 11-pointed Numeric Rating Scale of the group with bone contact during needling and of the group without bone contact. Two outliers Study ID # 1 and #5 and one extreme outlier Study ID 29.

The patient with severe pain was in the group without bone contact during needling. No significant different was detected in pain and the two investigators: Mean pain of investigator #1 was 3.0 NRS (SD 1.2) and mean pain of investigator #2 was 2.7 NRS (SD 2.5).

The mean pain in *male* during needling was 3.2 NRS. Standard deviation was 1.8 NRS. The minimum pain was 0 NRS and the maximum was 9 NRS. The mean pain in fe*male* during needling was 2.1 NRS. Standard deviation was 1.1 NRS. The minimum pain was 0 NRS and the maximum was 3 NRS.

The difference in gender and pain was not significant (p= 0.145). Figure 35 displays the distribution of pain and gender:

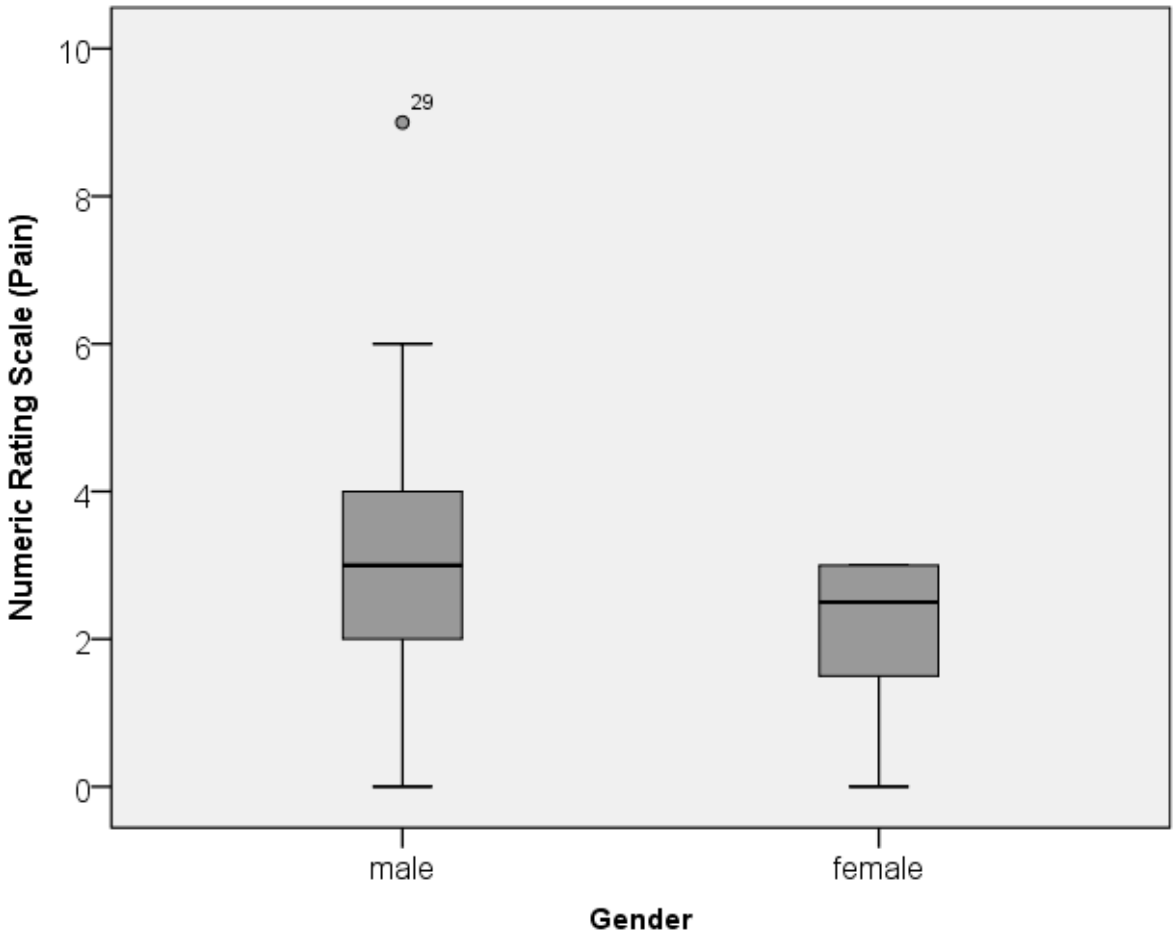

Figure 35: Boxplot of patient's pain on an 11-pointed Numeric Rating Scale of male and female during needling. One outlier was in the male group Study ID # 29.

A two-tailed correlation analysis of the patients' age and the reported pain on the NRS was not significant. There is no correlation between both:

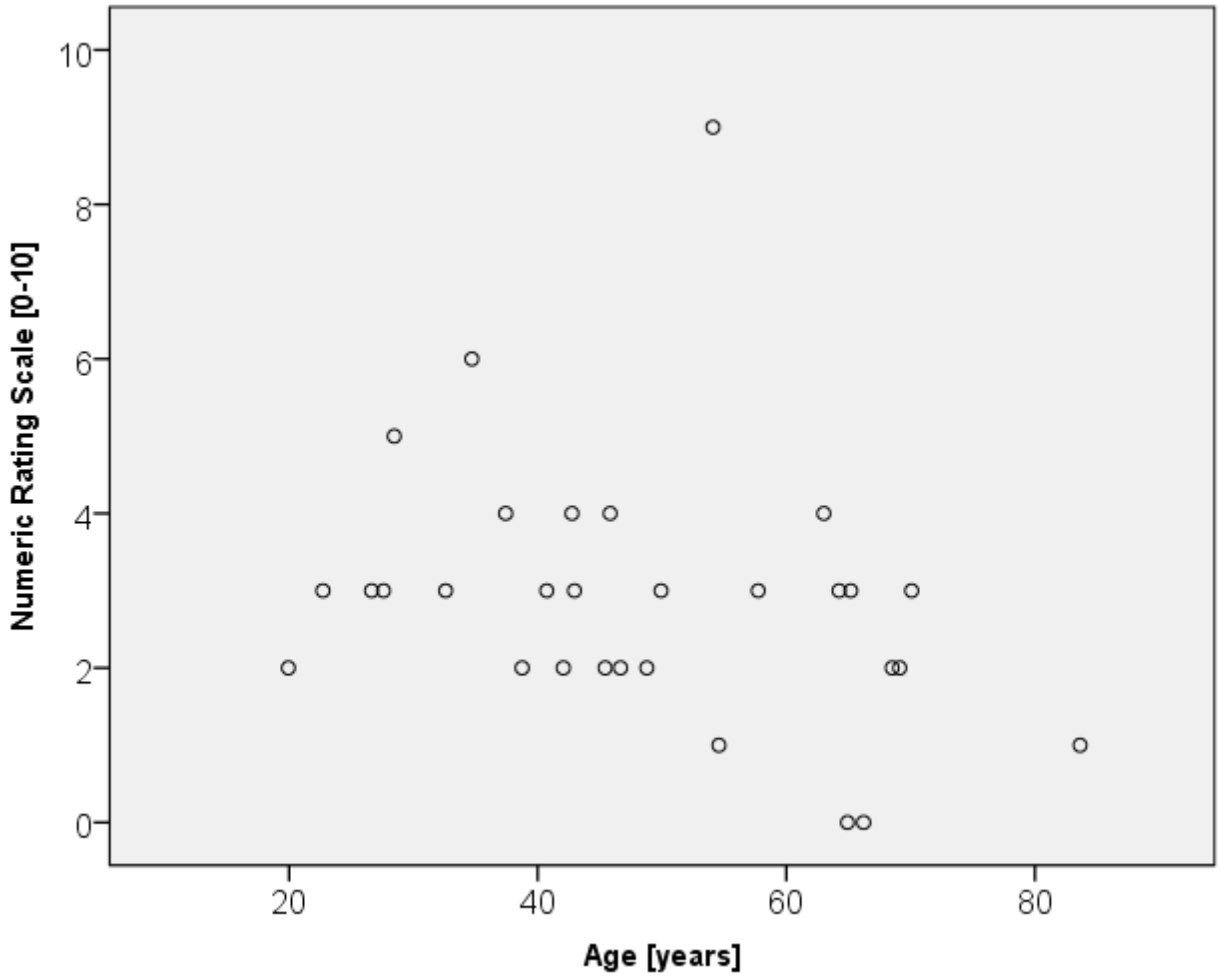

Figure 36: Scatter diagram of the numeric rating scale [0-10] on the ordinate and the patients' age in years on the abscissa.

3.6 Blood aspiration and patient's acceptability

Every patient (n=30) would be willing to agree to this nerve block in future and no blood was aspirated before injection of the study medication at any time of the study.

3.7 Time

3.7.1 Preparation time, needle-in-body time and total time

The preparation time before needling took 97.5 ±96.8 seconds (mean; SD). The needle-in-body time was 32.4 ±18.3 seconds (mean; SD). The whole nerve block took 129.8 ±100.7 seconds (mean; SD).

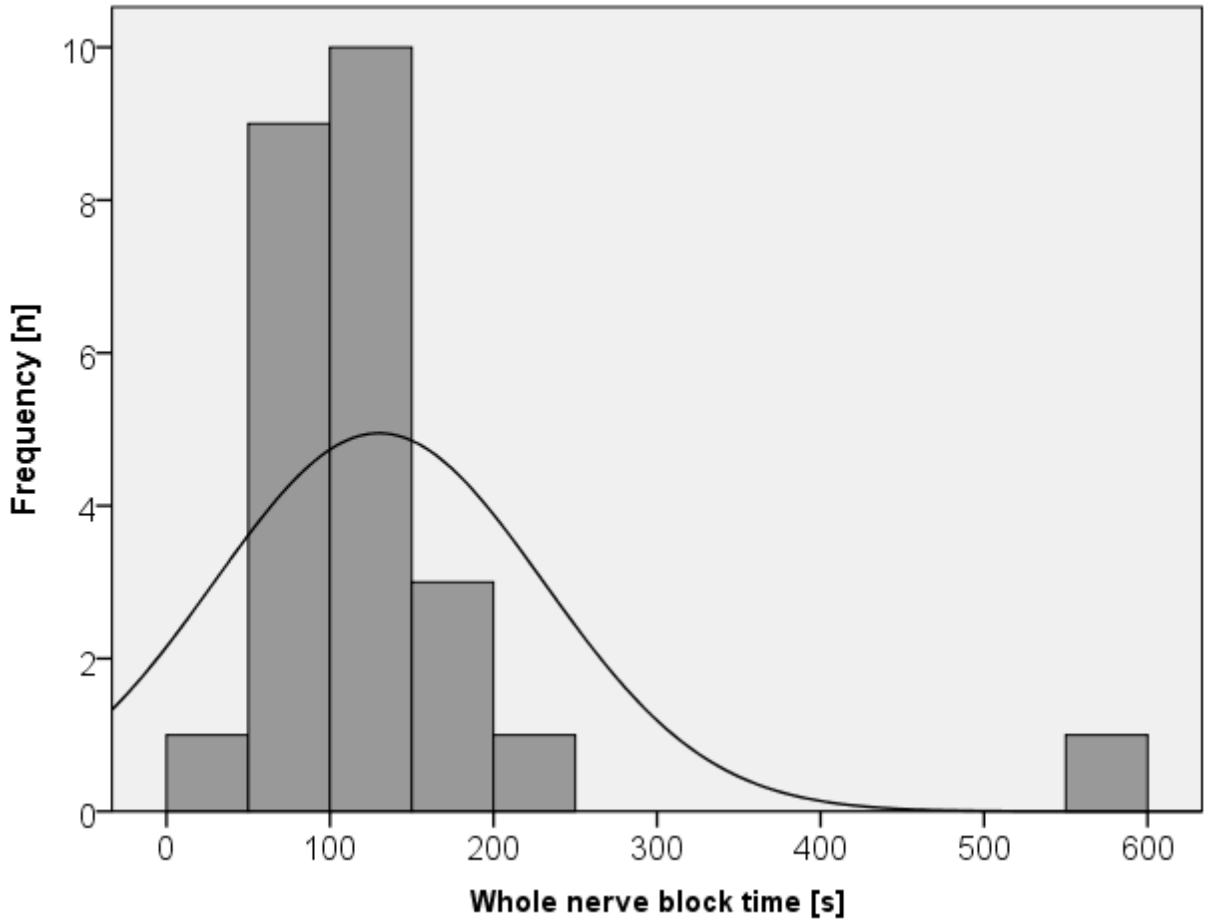

Figure 37: Histogram of the whole nerve block time in seconds including normal curve for each patient. The absolute frequency is presented on the ordinate. Interval broadness was 50 seconds. One time measurement is out of standard deviation and displayed on the right side of the histogram. Skewness is 3.363 and kurtosis is 13.741.

Figure 38 displays the relative time between the needle-in-body time and the time for preparation of the procedure:

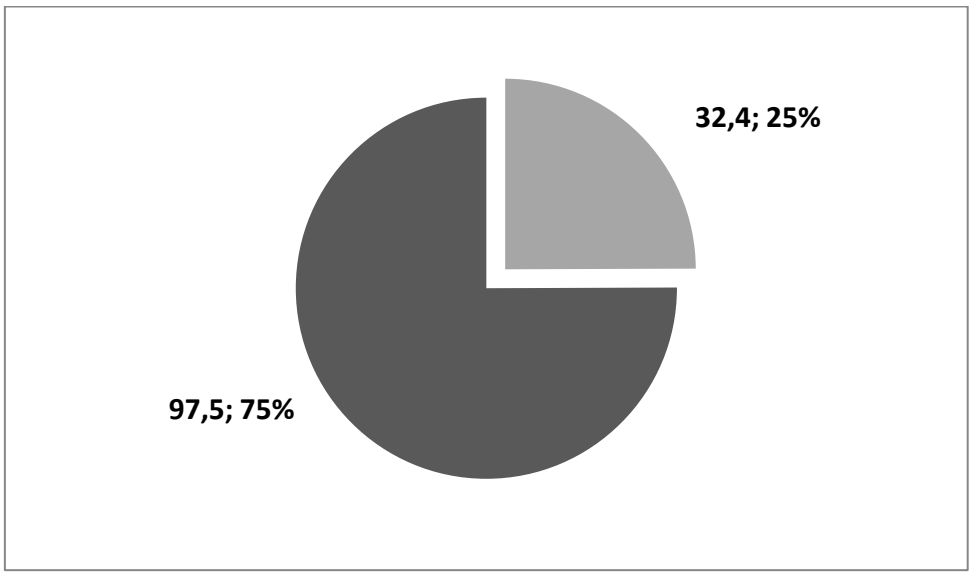

Figure 38: Relative time ratio of the preparation time (pale grey piece) and the needle-in-body time of the VOB (dark grey piece). First score displays the time for the procedure in seconds and the second the relative time [%]. The needle-in-body time took exact a fourth of the total VOB time.

3.7.2 Time and weight

The patients weight and the total time for the VOB is not significant correlated in nonparametric tests: In the Kendall's tau Test (p= 0.174) and in Spearman's rho Test (p= 0.170). In the parametic Pearson Correlation Test both are significant correlated (p= 0.024). Figure X displays the correlation in a scatter diagram. One outlier is responsible for the significant correlation by testing with Person Correlation Test. Without this outlier, the Person Correlation Test was also not significant (p= 0.359).

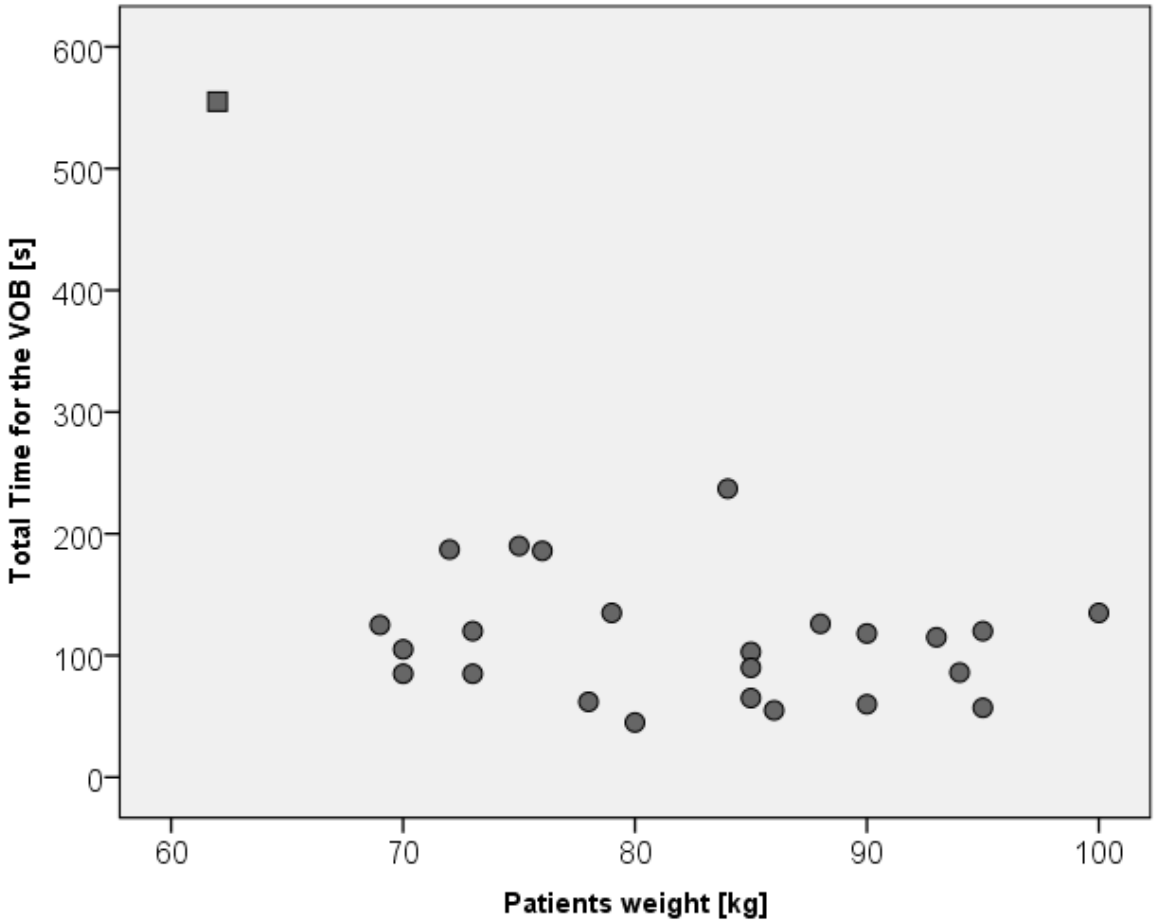

Figure 39: Scatter diagram of the total time for the VOB in seconds and patients weight in kilogram. One outlier is marked with a square; all others are marked with circles.

3.7.3 Time and investigator

The preparation time before needling took 113.3 ±105.5 seconds (mean; SD) in patients received a block by investigator #1 and 47.5 ± 30.9 (mean; SD) in patients received a block by investigator #2. The difference is significant (p= 0.024).

The needle-in-body time took 31.1 ±14.1 seconds (mean; SD) in patients received a block by investigator #1 and 73.0 ± 55.7 (mean; SD) in patients received a block by investigator #2. The difference is significant (p= 0.004).

The total time of the VOB took 144.3 ±111.0 seconds (mean; SD) in patients received a block by investigator #1 and 84.2 ± 33.1 (mean; SD) in patients received a block by investigator #2. The difference is not significant (p= 0.291). Figure X displays the total time and investigator:

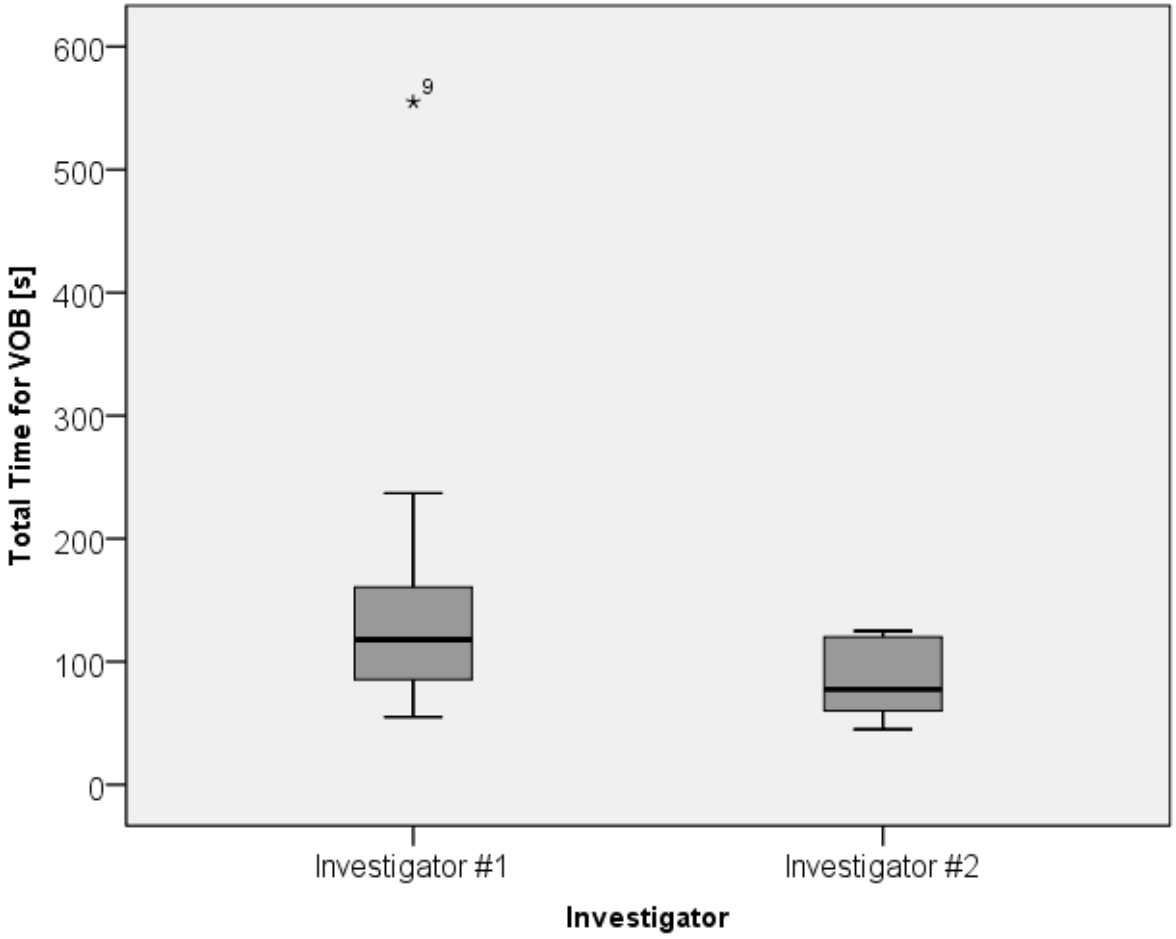

Figure 40: Boxplot of the total time for performing the VOB in seconds and both investigators. One outlier was in the investigator #1 group Study ID # 9.

3.7.4 Time and gender

The preparation time took 108.3 ±109.1 seconds (mean; SD) in male patients and 69.7 ±49.9 in female patients. The difference is not significant (p= 0.239).The needle-in-body

time took 43.3 ±35.3 seconds (mean; SD) in male patients and 51.3 ±50.4 in female patients. The difference is not significant (p= 0.636).

The total time was 139.4 ±114.9 seconds (mean; SD) in male patients and 105.4 ±47.3 in female patients. The difference is not significant (p= 0.306). Figure 41 displays the total time and gender:

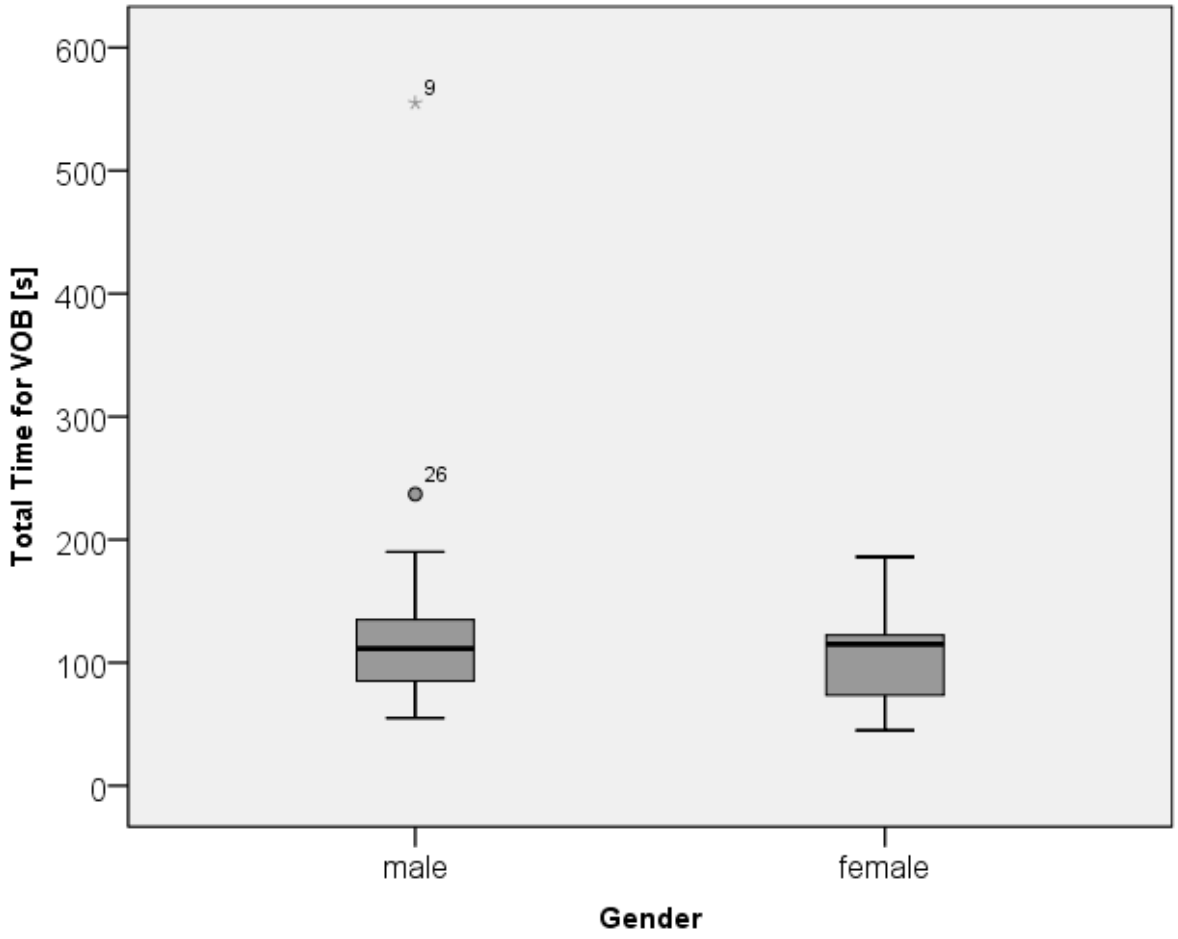

Figure 41: Boxplot of the total time for performing the VOB in seconds and gender. Two outliers were in males group Study ID # 9 and # 26.

3.8 Bone contact

During the VOB bone contact occurred in 30.4 % of cases. 25% in the contol group and 33.3% in the verum group. The difference in both is not significant by Chi-Quadrat Test.

			VOB		Total
			Bone Contact Yes	Bone Contact No	
Groups	NaCl - contol group	Count	2	8	10
		% of Total	6,7%	26,7%	33,3%
	LA - verum group	Count	5	15	20
		% of Total	16,7%	50,0%	66,7%
Total		Count	7	23	30
		% of Total	23,3%	76,7%	100,0%

Table 6: Cross tabulation of bone contact counts during the VOB for the verum and the control group including total counts and percentage.

3.8.1 Bone contact and needle-in-body time

In patients with bone contact during needling the mean needle-in-body time was 36.1 seconds (SD 20.1). In patients without bone contact during needling the mean needle-in-body time was 48.5 seconds (SD 43.6).

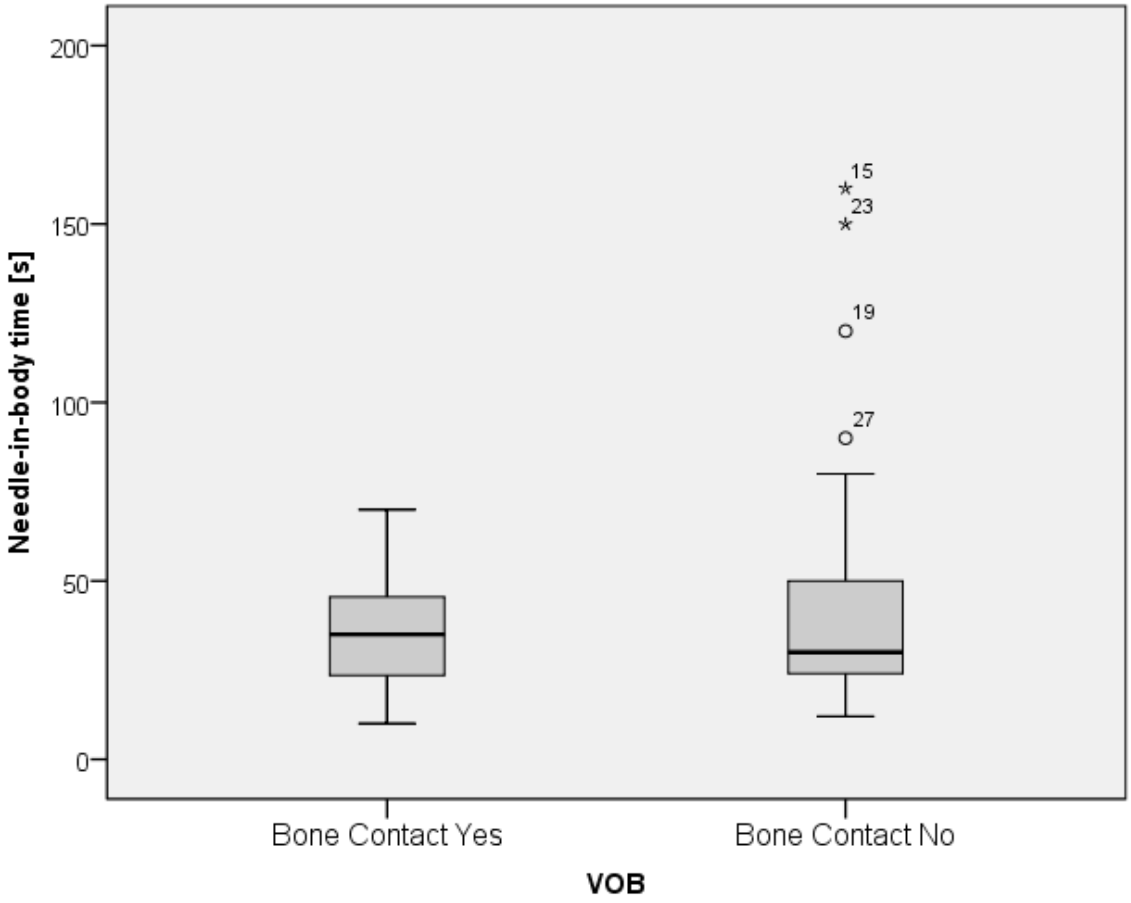

Figure 42: Boxplot of the needle-in-body time in the group with bone contact and the group without in seconds. In the group without bone contact you see two outliers: Study ID #19 and #27 and two extreme outliers Study ID #15 and #23.

The distribution of the needle-in-body time was not significant different in the cateories of bone contract (Yes/No).

3.8.2 Bone contact and injection depth

The mean calculated injection depth before needling in patients with bone contact was 4.6 cm (SD 0.7). In patients without bone contact during needling the mean calculated injection depth was 4.6 cm (SD 0.6).

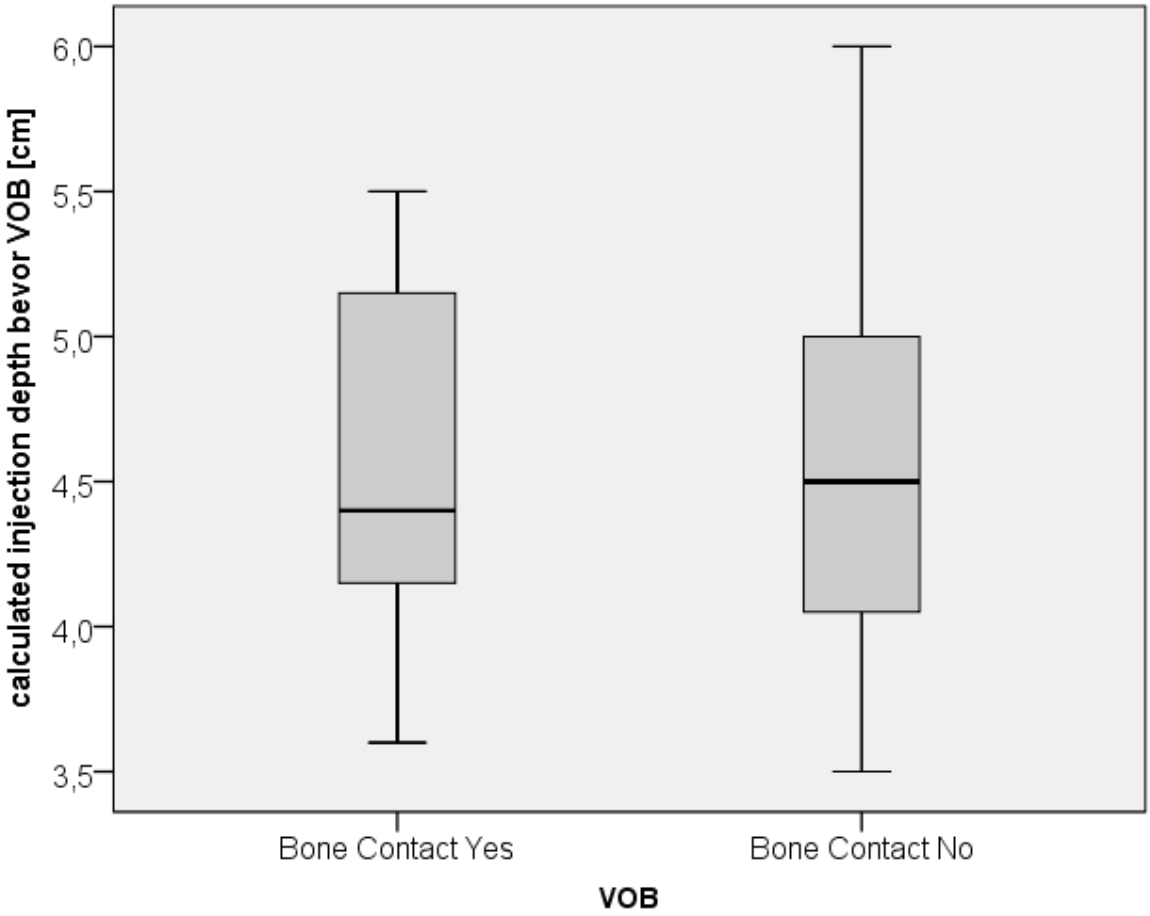

Figure 43: Boxplot of the calculated injection depth before needling in the group with bone contact and the group without.

No significant correlation between the calculated injection of the needle (depending on the weight of the patients) and the presence of bone contact was found (Figure 43) and no significant correlation between patient's weight and the presence of bone contact was found (Figure 44).

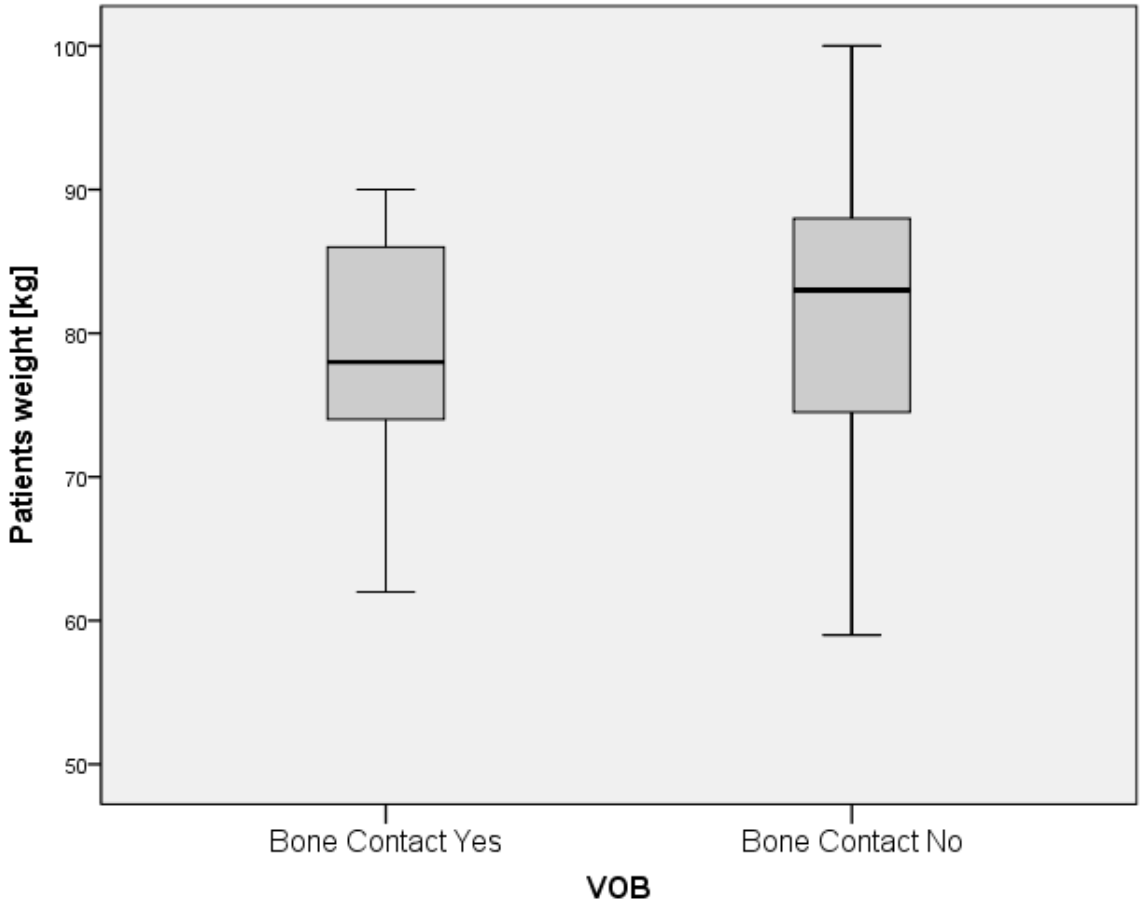

Figure 44: Boxplot of the patient´s weight in the group with bone contact and the group without in kg.

The mean body weight in patients with bone contact during needling was 78.6 kg (SD 9.7). In patients without bone contact during needling the mean body weight was 81.7 kg (SD 10.2). No significant correlation between age and bone contact was found.

3.8.3 Bone contact and investigators

A significant correlation between the counts of bone contact and the investigator was found (p= 0.021, Tab. X).

				Investigator #1	Investigator #2	Total
VOB	Bone Contact Yes		Count	7	0	7
			% of Total	23,3%	0,0%	23,3%
	Bone Contact No		Count	12	11	23
			% of Total	40,0%	36,7%	76,7%
Total			Count	19	11	30
			% of Total	63,3%	36,7%	100,0%

Table 7: Cross table of counts of bone contact during needling for investigator #1 and investigator #2 including total counts and percentage.

3.8.4 Bone contact and success of VOB

The following cross tables describe the bone contact during needling and the success of the block depending on the strict cut off of 50 % muscle decrease. The Table 8 describes this for all study patients and Table 9 describes this for all patients in the verum group:

				> 50 % strength decrease		Total
				no success	bloc success yes	
VOB	Bone Contact Yes		Count	5	2	7
			% of Total	16,7%	6,7%	23,3%
	Bone Contact No		Count	22	1	23
			% of Total	73,3%	3,3%	76,7%
Total			Count	27	3	30
			% of Total	90,0%	10,0%	100,0%

Table 8: Cross table of bone contacts and success of VOB counts (no/yes) including total counts and percentage of all patients in the study.

			> 50 % strength decrease		Total
			no success	bloc success yes	
VOB	Bone Contact Yes	Count	3	2	5
		% of Total	15,0%	10,0%	25,0%
	Bone Contact No	Count	14	1	15
		% of Total	70,0%	5,0%	75,0%
Total		Count	17	3	20
		% of Total	85,0%	15,0%	100,0%

Table 9: Cross table of bone contacts and success of VOB counts (no/yes) including total counts and percentage of patients in the verum group.

We did not find a significant correlation of bone contact and success in all study patients and in the verum group. In 40 % of all bone contacts in the verum group the vertical obturator block was a success (2 out of 5). Using different Chi-Square Tests this is not significant different to the success with no bone contact (15 %, 3 of 20):

- Pearson Chi-Square test p= 0.071
- Fisher's Exact Test p= 0.278
- Likelihood Ratio p= 0.092
- Linear-by- Linear Association p= 0.078

3.9 Local anaesthetic-induced toxicity and allergic reactions

In this study, no case of local anaesthetic toxicity (involving cardiovascular system or central nervous system) occurred during anaesthesia. No allergic reaction emerged during the study and the followed operation. All patients were admitted into the recovery room after surgery. No patient hat to be transferred into an intensive care unit. During the period

of the recovery room residence, no complications occurred. After that, all patients were transported to the ward of trauma surgery for prolonged post-operative observation.

So, no emergency un-blinding was done, no patient was cancelled for operation and no lipid emulsions for antidote was administered by the study team

4 Discussion

After the successful development of a new technique for the obturator nerve block on cadavers, it was consequential to test this block for the first time on living patients in clinical routine. The encouraging results on cadavers by Feigl et al. (10) and the simplicity of this block was convincing: No additional distance measurement or obligator change of the needle is necessary to perform the nerve block. No need for electrical nerve stimulation and no need of ultrasound for targeting the obturator nerve. This leads to very short procedure times.

Furthermore, older ONB techniques require two landmarks or needle turns inside patient´s body and block the obturator nerve often after the division of the obturator nerve. This new technique offers a most proximal nerve block of all existing ONBs. Therefore, the anterior and the posterior branch are blocked with certainty with the VOB. Additionally, one small branch of the ON innervates the medial hip joint and splits out of the obturator nerve very proximal. This branch can be blocked with this technique additionally, so this technique is superior to the others in case of hip surgery ore pain.

4.1 The mismatch between clinical and cadaver studies

Many important aspects are different between a study on cadavers and RCTs in clinical settings: The latex used by Feigl et al. had different physical qualities than the local anaesthetic in this pilot trial. In particular, the spread of both substances are different, and the tissues of both study collectives are divergent. Nevertheless, we decided to use the same volume of local anaesthetics as coloured latex was used in the cadaver study of Feigl. We seek to achieve the same success rates of the VOB like Feigl obtained in his cadaver study. On the other hand, it was reasonable to presume different success rates before conducting the study.

Furthermore, in cadaver studies it is not possible to make clams of patient's comfort during needling and you cannot access the risk of intra-vascular injection of local anaesthetics and risk of accidental vascular damage during needling because of the well-filled vessel in living patients discriminate to partly filled vessel in cadavers. Therefore, patient´s comfort

as well as the safety must be examined on living patients as well as the efficacy of the new technique. Additionally, feasible procedure times for this uncomplicated nerve block technique are only quantifiable in comparable hospital settings and not on anatomical theatres.

4.2 Evaluation of success

Like many other studies before (7,2,88,9,23), we measured the adductor muscle strength to evaluate the success of VOB. In this study only 3 out of 20 VOBs have been successful, based on a very strict chosen cut off at 50% decrease of adductor muscle strength leant on the cut off by Sinha (8). Furthermore, we have found a mix of different cut offs in other ONB studies, therefore we also presented success rates with different cut offs in our results.

In the anatomical investigation of Feigl et al. a spread of coloured latex around the obturator nerve was evinced in 95.5 %. However, aware of the divergence between clinical studies and cadaver studies, we expected high success rate in this clinical pilot trial. Unfortunately, we did not see comparable results.

4.2.1 Reasons for low success

We consider two reasons for the low success: First, we used a quite small volume (5 ml) of local anaesthetics. We used the exact volume (of coloured latex) Feigl used in his *anatomical* study to perform an equal procedure setting. Nevertheless, many other *clinical* ONB studies used 10 to 25 ml of local anaesthetic for their ONBs (6,8,23,89).

Secondly, we tested the success of the VOB by measuring the adductor muscle strength 15 minutes after nerve block. The measuring was chosen very early, due to time restriction of this study before surgery. The study team was forced to fit the study setting into a routine trauma surgery operation schedule. Because of the lack of financial support for this study, resources like time collaborators were limited. Thus, the onset of the motor blockade using

0.75 % ropivacaine might take more than 15 minutes (90,91). An additional measurement 30 minutes after nerve block was desirable but not possible.

As a consequence, we would likely see more successful blocks by using higher volumes of LA and delayed testing of the adductor muscle strength.

4.2.2 Success and bone contact

We did not find a correlation between counts of bone contact and success of the vertical obturator nerve block. In 40 % of all bone contacts in the verum group the vertical obturator block was a success and only 15 % of patients without a bone contact had a successful nerve block. By using different tests, none of them found a significant difference. Because, the absolute numbers were small (Table 9: 2 out of 5 in bone contact group; 3 oft of 20 in no bone contact group), testing these small numbers is inaccurate.

So, we need higher numbers to make secure states about the coherence of success of the VOB and bone contact. Nerveless, a bone contact may increase the chance for a success of the vertical obturator nerve block.

4.2.3 Varieties in the results between investigators

All successful nerve blocks (n=3) were performed by the investigator #1 and zero VOBs has been successful performed by investigator #2. Because of the small numbers and because investigator #2 performed only 37 % of all VOBs, the difference is not statistical quantifiable.

Considering the counts of bone contact a significant difference between investigators was found. All bone contacts emerged by investigator #1. This is surprising; because the performance of the VOB is very accurate described and both investigators were constrained to perform the block exact according to description of Feigl.

Additionally, we found a significant difference between the preparation time and the needle-in-body time between both investigators. In both times the investigator #2 was faster than investigator #1. This may refer to the higher bone contact rate.

However, we found some significant differences between the results depending on the investigators. So, the VOB procedure might be slightly different of both investigators. This may explain the different results, but it also evokes questions about consistency of the VOB performance.

According to the description of Feigl, the needle was inserted next to the investigators fingertip. The fingertip was placed next to the tubercle pubis. So, the broadness of the investigator´s fingertip affects the point of insertion. But after these findings, we measured the broadness of both investigator fingertips and we did not find a difference in the fingertips. As a consequence, this inaccuracy for block performance defined by Feigl did not affect our results.

4.3 Patients characteristics and bias

Eight male and 22 female participated in the study. So, patient's gender was not equally distributed in this study. However, in study groups (verum and control group) the gender was equally distributed, so the gender should not bias the primary outcome of this study. On the other hand the gender distribution can affect the secondary outcome variables like patient´s discomfort, absolute adductor muscle strength and pain. Due to different anatomy of the human pelvis in men and women, different bone contact rates may occur in equal gender patient populations.

Furthermore, male study patients may have different discomfort levels, because the spermatic cord is very close to the insert needle point and an accidental contact with during needling might occur (see Figure 16).

4.3.1 Group's characteristics

By considering our patients characteristics in groups (verum/control group), most of the patients properties are equally distributed in study groups (see Table 2). However, patients' age was not equally. Because of the strictly blinded randomization without any restriction, unequal distributions can occur. The mean patient´s age between control and verum group discriminates by 14 years (see Figure 23). This could bias our adductor muscle strength results, because strength is often invers related with age.

In this study we found a significant correlation between adductor muscle strength and age (Figure 26), as consequence this can bias the results. We found median adductor muscle strength in the control group of 129 mm HG and 135 mm HG in the verum group, but these differences are not significant (see Table 3).

Furthermore, patients' age can bias the intensity of discomfort patients associate with the nerve block and its intimate needling spot near their sexual organs. Younger patients are often more concerned about their personal integrity than older patients.

All patients received standard premedication before needling. We used midazolam in our study. The effect of this drug is highly dependent on patients' age (92). Therefore, an unequally distributed age in both study groups may bias many of our measurements due to the diverse effects of the premedication.

In conclusion we have to mind these to interpret the results of this study. The primary outcome variable in this study was the decrease in muscle strength before and after nerve block. We used a percentage reduction between measurement two and one for the definition of a successful nerve block to reduce the effects described above. These calculations should not bias much, because of their relative nature. In contrast, the different between both groups were calculated on the absolute reduction of adductor muscle strength in mm HG. So, these findings should be treated with caution.

4.4 Bone contact and needle-in-body time

In 23.3 % of the study cases bone contact occurred (Table 6). Like described above, all contacts occurred by investigator #1 (Table 7). In case of bone contact, a needle turn was necessary and may delay the application of the study medication. Surprisingly, the distribution of bone contact had no significant effect on the needle-in-body time. Furthermore, two extreme outliers are in the group of patients without bone contact. So, bone contact may not lead to longer needle-in-body time.

Unsurprisingly, no significant difference in the bone contact and study group occurred. The block technique is the same in both groups, so the contact rate had to be equally.

4.5 Evaluation of the VOB performance time

The whole VOB took about 2 minutes to perform. This is very fast comparing other regional anaesthesia techniques (93,94). Most of the total block time is necessary for preparations, only a quarter of the total time is used for needling. The time for preparation is equally to other nerve block techniques, because disinfection and preparation of drugs are necessary in all kinds of regional anaesthesia. The shortness of the needle-in-body time displays the simplicity of the VOB. Usage of ultrasound devices or electrical nerve stimulation for regional anaesthesia prolongs the needle-in-body time.

Patients discomfort during regional anaesthesia is probably related to the needle-in-body time in regional anaesthesia. The 32 seconds of needle-in-body time in this study may result in high patient acceptance for this technique in the study.

Surprisingly, the patients' weight did not correlate with the total VOB time. Regional anaesthesia can be difficult in overweight patients (95,96), but we did not find a distinct significant correlation between both in this study. However, we did not include patients with more than 100 kg body weight, so this could bias these results.

In case of obesity, location of the tubercle pubis may be difficult. This could affect the preparation time, which includes the localism of this anatomical landmark. The needle-in-body time should not differ in patient with obesity.

4.6 Thoughts about the choosing study medication

4.6.1 The placebo

We used 0.9 % concentrated sodium chloride (NaCl) solution for the control group medication. The commonly uses saline is quite isotonic, translucent and has no anaesthetic effect on local nerves. In case of intravascular injection, this saline does not harm the patient because of its isotonic nature and no allergic reaction can occur. Many controlled studies use this saline for control group medication and so did we. Furthermore, this solution is easy available in every pharmacy and it is very cheap.

4.6.2 Local anaesthetic

In this study we used 5 ml of 0.75 % ropivacaine (= 37.5 mg ropivacaine). This drug belongs to the amino amide local anaesthetic group. Amino amide anaesthetics are prone to produce less allergic reaction than esters (56,97,98). Furthermore, animal toxicological studies have shown a lower propensity for cardiac toxicity than other local anaesthetics (99,100).

The metabolism of ropivacaine depends on the liver function of the patients (101). In case of hepatic failure severe hypoalbuminemia can occur and that can lead to systemic toxicity of local anaesthetics (102). Nevertheless, hepatic failure was not a excluding criteria in this study. We decided to scrap this, because we only use a single shot of local anaesthetic in a small dosage of 37.5 mg and did not continuous peripheral nerve catheter infusions (103).

Ropivacaine is a long-acting local anaesthetic (104). In our clinic we used ropivacaine to achieve a long time of sensory anaesthesia for the patients, so they can benefit from a long time of analgesia after surgery. In our clinic most of the regional anaesthesia is performed with ropivacaine for this reason, so it was consequential to use this anaesthetic in this study to provide a faithful clinical study setting.

We used a high concentration of ropivacaine (0.75 %; 7.5 mg/ml) to achieve a full motor blockade and to accomplish a shot onset time (105). A full motor blockade was necessary

to evaluate the success of the nerve block by adductor muscle strength measurements and a short onset time was important because we had a limited timeframe for measurements after the nerve block, due to a strict surgery schedule.

Ropivacaine solutions are translucent as well as 0.9% sodium chloride, so the study team could not distinguish the verum and the control study medication. This provided a double blinded study setting.

4.7 Limited study resources

4.7.1 Time

This study was not founded. So, the study investigators had to integrate the whole patient enrolment and data collecting into the daily patient care. No additional employees were available for this study. Furthermore, we had to pay attention to the restrict surgery schedule.

The patient enrolment took place during the medical education of the patients at least one day before anaesthesia and surgery. Nerve block, measurements and questioning of the patient took place before induction of general anaesthesia and surgery start. Therefore, the measurement of the muscle adductor strength was chosen very early after the VOB (15 minutes after VOB) to prevent a limited time delay on the operation schedule.

4.7.2 Nurses and physician

Due to financial restrictions, no study nurse was available for this study. Dependent on a weekly schedule, several nurses specialized in anaesthesia and intensive care supported the study team during the patient enrolment. Before VOB performance and measurements, the study physicians had to explain the procedure to the nurses, if they are for the first time assisting by the VOB. Therefore, study procedure was slowly and the physician had to double check important steps during needling. This delay amplified our needs for fast study performance and measurements during patient enrolment and possibly delayed the time for the nerve block arrangements before needling.

For this study, two physicians were willing to perform the VOB during their daily duties, dependent on a weekly schedule; both 3rd year residents of General Anaesthesiology, Emergency- and Intensive Care Medicine. They were supervised by senior physicians during needling and induction of general anaesthesia. Due to the restrict count of physicians, we could compensate the lack of a study nurse and could provide a similar and fast study processing.

4.7.3 Post-operative surveillance

No additional measurement of the muscle adductor strength or pain measurements was done after surgery. Because of the limited personal resources of this study, we decided to take out the postoperative study surveillance. For the main study hypothesis, post-operative study surveillance was dispensable. So, no additional measurement of the muscle adductor strength or pain measurements was done after surgery.

Nevertheless, all patients were transported into a specialized post-operative care unit after surgery. The local employees were instructed to report any VOB related adverse events to the study team. Besides, no additional study data was elective recorded form the post-operative surveillance.

4.7.4 Sensory testing

Sensory testing was not performed due to the variability in its sensory distribution (20,21) and its difficulty to objectify and to quantify. Furthermore, we had limited time for the testing before surgery and limited money for sensory testing equipment. So unfortunately, we cannot provide any data of the sensory blockade after a VOB in this study. Like described before, we assumed a sensory block if the motoric block was functional (= decrease of adductor muscle strength more than 50 %)

4.8 Claims about safety

4.8.1 Nerve injuries and bleeding

The incidence of severe complications during regional anaesthesia is low and varies from 0 to 5 % (106). Nerve injuries and major bleeding can occur during regional anaesthesia, but the incidence is very low. During this study, we did not detect any bleeding or nerve injuries after VOB. Nevertheless, it is not possible to make claims of safety with this pilot trail with 30 patients. To estimate the safety of this nerve block technique, futures studies with thousands of patients are necessary to detect and evaluate rare complications.

However, the results of this pilot trial are valuable: The absence of complications during this study will help to obtain approval for future VOB studies by discussions with Institutional Ethics Committees.

4.8.2 Intravascular injection and systemic absorption

Systemic toxicity can occur after accidental intravascular injection during regional anaesthesia (107). Additionally, fast systemic absorption of big quantities of local anaesthetics can produce high plasma levels and systemic toxicity (108,109). Absorption of local anaesthetic varies in different parts of the body (107,110). Currently, no data exists about absorption in the VOB region.

The cumulative dosage of local anaesthetic is highly relevant to avoid dangerous plasma level (107). During this study, no signs of local anaesthetic toxicity had been observed after needling, during the surgery and later on in the recovery unit. We used only very small dosage (37.5 mg ropivacaine) for VOB, so it was unlikely to detect signs of systemic toxicity.

In our study, no blood was aspirated before injection of study medication during the VOB. The aspiration test does not rule out an intravascular injection with certainty (111–113). Due to the low incidence of intravascular injection and the small count of patients in the verum group (n=20), the incidence for intravascular injection for the VOB is not

appreciable with this pilot trial. Again, future studies with more patients are necessary to estimate the risk of local anaesthetic toxicity.

4.8.3 Allergic reactions

No allergic reaction emerged during the nerve block and the followed operation. All kinds of substances can emerge allergic reactions during general anaesthesia and surgery. Allergic reactions during regional anaesthesia are very rare, especially for the amino-amid local anaesthetics like ropivacaine (114). So, it was very unlikely to see one in this small study group (n=30).

4.9 Conventional obturator nerve block techniques

Comparing to other ONB techniques, this block appears to be fast, save and easy to perform. The time of preparing and the needle-in-body time was shorter comparing to other studies blocking the ON (9,115,116). The whole time to perform the VOB took about 2 minutes.

No blood was aspirated before injection of the study medication, so an intra-vascular injection was unlikely. The approach first described by Labat consists of three consecutive movements of the needle till the top of the needle is placed over the top of the obturator foramen, where the nerve is located before dividing into its two terminal branches.

With the Feigl technique, no additional measurements or obligatory needle turns are needed for the VOB. Other studies reported high discomfort due to pain using a para-pubic tubercle approach (4,6). In our study, the intensity of discomfort was low: Every patient would be willing to agree to this nerve block in future, pain was reported as NRS 2.9; only one patient complained about “important discomfort”.

Comparing to the recently often used ultrasound directed inter-adductor approach for an ONB, the VOB is notably more proximately. Consecutive, the ON is not divided into the 2 branches and the sensory innervation of the hip by the OB will be blocked additionally

(117,118). So, in case of hip surgery a most proximal block of the ON appears to be superior.

4.10 Procedure time and Needle-in-body time

For scheduled knee replacement surgery a femoral nerve block, sciatic nerve block and an ONB is often used in combination with general anaesthesia. Under these conditions, there is limited time for performing three nerve blocks in daily routine. So, the outstanding fast VOB technique helps to save time.

Additionally, the needle-in-body time is the most suffering part for patients in regional anaesthesia. The VOB has a short needle-in-body time (see Figure 37). This may lead to low pain intensity, as well as to the low discomfort levels in our study.

Depending on the investigators, the time for preparations and needle-in-body time discriminate significant. In both times the investigator #2 was faster than investigator #1 (see Figure 39). This result represent impressive the individual procedure times of physicians for regional anaesthesia. For better understanding of this significant difference in our study, further studies with more than two investigators are necessary. Additionally, this result impairs the comparison qualities of the times in this study with other ONB times.

4.11 Ultrasound and nerve stimulation for a obturator nerve blocks

4.11.1 Peripheral electrical nerve stimulation

For this study, we did not use peripheral electrical nerve stimulation. By using electrical nerve stimulation, nerve location can be tested (119,120). The use of nerve stimulation appears to be safe (121). In this pilot study, we wanted to perform the VOB as closely as possible to the method described by Feigl et al.: In case of using electrical nerve stimulation for the VOB, we had to change in the direction of the needle or the depth for

drug injection depending on the current needed for nerve stimulation; both not designated by Feigl et al.

For future studies electrical nerve stimulation might be helpful to increase the success rate of the VOB (122). However, the additional usage of this tool can be associated with more complications like bleeding or nerve injury based on more needle turns during needling. Especially the higher risk of bleeding must be considered:

The very proximal puncture point for VOB makes it more difficult to detect bleeding, because there is more room for blood than in distal muscle-nerve-fascia. Furthermore, in case of bleeding the blood might drain through the inguinal canal into the pelvic (123). This could result in undetected bleeding and in large blood losses because less internal compression arises. Additionally, treatment of bleeding is more difficult in this region. External compression might be more difficult. Because of the pilot setting and its fist time of testing the VOB on living patients, we wanted to minimize the risk of bleeding. Particularly, treatment of bleeding is more challenging in this body region.

In contrast, bleeding by using the inter-adductor approach for ONB is likely easier to manage and therefore using electrical nerve stimulation might be more suitable for this block technique.

4.11.2 Ultrasound targeting VOB

Over the past four decades, ultrasound guided regional anaesthetic and analgesic techniques have grown considerably (124). Peripheral nerve catheters and single-injections are valuable options for controlling peri-operative and post-operative pain (125). The ultrasound technique has potential advantages like real-time visualization of anatomical structures, the shaft and tip of the needle and the spread of the local anaesthetic (126). Ultrasound-guided regional anaesthesia may decrease the risk of peripheral injuries and decreases the risk of local anaesthetic systemic toxicity. Shorter procedure time, block onset time and an increase of block success rates can be seen (127).

Particularly, the real-time visualization of vessel during needling can help to decrease the risk of vessel damage. Like described above, bleeding in this part of the body is potential

hazardous. Therefore, ultrasound assistance during needling and using the VOB technique may enhance the safety of this procedure.

Nevertheless, Feigl et al. did not use the ultrasound for the VOB. Regional anaesthesia without electrical never stimulation and without ultrasound support is less complex, cheaper and universally available.

4.12 Conclusion

This dissertation attempts to translate anatomical findings from a cadaver study to a viable alternative technique for the obturator nerve block in hospital routine: The VOB is viable on living patients. It is simple, painless and fast. This technique offers a most proximal block of the obturator nerve with all its advantages. Nevertheless, we could not reproduce the high success rates in clinical practice compared to the cadavers presented by Feigl. From 20 blocks, only three were positive according to our criteria. The low success is partly caused by the low volume of LA used in our study, and by our short time frame until muscle adductor strength was measured.

The necessity to improve this nerve block technique is most obvious, especially if this technique is compared to already existing obturator nerve blocks. Thus, for future studies we consider to use electro-stimulation plus/minus ultrasound targeting, higher volumes and nerve block efficacy assessments later after nerve block.

5 References

1. Labat G, Mayo WJ. Regional anesthesia : its technic and clinical application. Philadelphia and London : W. B. Saunders company; 1922. 526 p.

2. Parks CR, Kennedy WF. Obturator nerve block: a simplified approach. Anesthesiology. 1967 Aug;28(4):775–8.

3. Pinnock CA, Fischer HBJ, Jones RP: Perepheral Nerve Blockade. New York, Churchill Livingstone, 1996.

4. Wassef MR. Interadductor approach to obturator nerve blockade for spastic conditions of adductor thigh muscles. Reg Anesth. 1993 Feb;18(1):13–7.

5. Soong J, Schafhalter-Zoppoth I, Gray AT. Sonographic imaging of the obturator nerve for regional block. Reg Anesth Pain Med. 2007 Apr;32(2):146–51.

6. Choquet O, Capdevila X, Bennourine K, Feugeas J-L, Bringuier-Branchereau S, Manelli J-C. A new inguinal approach for the obturator nerve block: anatomical and randomized clinical studies. Anesthesiology. 2005 Dec;103(6):1238–45.

7. Helayel PE, da Conceição DB, Pavei P, Knaesel JA, de Oliveira Filho GR. Ultrasound-guided obturator nerve block: a preliminary report of a case series. Reg Anesth Pain Med. 2007 Jun;32(3):221–6.

8. Sinha SK, Abrams JH, Houle TT, Weller RS. Ultrasound-guided obturator nerve block: an interfascial injection approach without nerve stimulation. Reg Anesth Pain Med. 2009 Jun;34(3):261–4.

9. Manassero A, Bossolasco M, Ugues S, Palmisano S, De Bonis U, Coletta G. Ultrasound-guided obturator nerve block: interfascial injection versus a neurostimulation-assisted technique. Reg Anesth Pain Med. 2012 Feb;37(1):67–71.

10. Feigl GC, Ulz H, Pixner T, Dolcet C, Likar R, Sandner-Kiesling A. Anatomical investigation of a new vertical obturator nerve block technique. Ann Anat. 2013 Jan;195(1):82–7.

11. Urbanowicz Z. Connections between the lumbar and the sacral plexus in man. Folia Morphol (Warsz). 1981;40(3):271–9.

12. Anloague PA, Huijbregts P. Anatomical variations of the lumbar plexus: a descriptive anatomy study with proposed clinical implications. J Man Manip Ther. 2009;17(4):e107–14.

13. Kirchmair L, Lirk P, Colvin J, Mitterschiffthaler G, Moriggl B. Lumbar plexus and psoas major muscle: not always as expected. Reg Anesth Pain Med. 2008 Apr;33(2):109–14.

14. Kendir S, Akkaya T, Comert A, Sayin M, Tatlisumak E, Elhan A, et al. The location of the obturator nerve: a three-dimensional description of the obturator canal. Surg Radiol Anat. 2008 Aug;30(6):495–501.

15. Moore KL, Agur AMR, Dalley AF. Clinically Oriented Anatomy. 7th revised international ed edition. Lippincott Williams and Wilkins; 2013. 1168 p.

16. Anagnostopoulou S, Kostopanagiotou G, Paraskeuopoulos T, Chantzi C, Lolis E, Saranteas T. Anatomic variations of the obturator nerve in the inguinal region: implications in conventional and ultrasound regional anesthesia techniques. Reg Anesth Pain Med. 2009 Feb;34(1):33–9.

17. Anderhuber F, Pera F, Waldeyer A, editors. Waldeyer - Anatomie Des Menschen: Lehrbuch Und Atlas in Einem Band. 19 Rev Upd edition. Berlin: Walter de Gruyter; 2012. 1176 p.

18. Yasar S, Kaya S, Temiz C, Tehli O, Kural C, Izci Y. Morphological structure and variations of lumbar plexus in human fetuses. Clin Anat. 2014 Apr;27(3):383–8.

19. Akkaya T, Comert A, Kendir S, Acar HI, Gumus H, Tekdemir I, et al. Detailed anatomy of accessory obturator nerve blockade. Minerva Anestesiol. 2008 Apr;74(4):119–22.

20. Bouaziz H, Vial F, Jochum D, Macalou D, Heck M, Meuret P, et al. An evaluation of the cutaneous distribution after obturator nerve block. Anesth Analg. 2002 Feb;94(2):445–9, table of contents.

21. Enneking FK, Chan V, Greger J, Hadzić A, Lang SA, Horlocker TT. Lower-extremity peripheral nerve blockade: essentials of our current understanding. Reg Anesth Pain Med. 2005 Feb;30(1):4–35.

22. Sakura S, Hara K, Ota J, Tadenuma S. Ultrasound-guided peripheral nerve blocks for anterior cruciate ligament reconstruction: effect of obturator nerve block during and after surgery. J Anesth. 2010 Jun;24(3):411–7.

23. Macalou D, Trueck S, Meuret P, Heck M, Vial F, Ouologuem S, et al. Postoperative analgesia after total knee replacement: the effect of an obturator nerve block added to the femoral 3-in-1 nerve block. Anesth Analg. 2004 Jul;99(1):251–4.

24. Rashiq S, Vandermeer B, Abou-Setta AM, Beaupre LA, Jones CA, Dryden DM. Efficacy of supplemental peripheral nerve blockade for hip fracture surgery: multiple treatment comparison. Can J Anaesth. 2013 Mar;60(3):230–43.

25. Kim PS, Ferrante FM. Cryoanalgesia: a novel treatment for hip adductor spasticity and obturator neuralgia. Anesthesiology. 1998 Aug;89(2):534–6.

26. Viel EJ, Perennou D, Ripart J, Pélissier J, Eledjam JJ. Neurolytic blockade of the obturator nerve for intractable spasticity of adductor thigh muscles. Eur J Pain. 2002;6(2):97–104.

27. Viel E, Pelissier J, Pellas F, Boulay C, Eledjam J-J. [Alcohol neurolytic blocks for pain and muscle spasticity]. Neurochirurgie. 2003 May;49(2-3 Pt 2):256–62.

28. Kirazli Y, On AY, Kismali B, Aksit R. Comparison of phenol block and botulinus toxin type A in the treatment of spastic foot after stroke: a randomized, double-blind trial. Am J Phys Med Rehabil. 1998 Dec;77(6):510–5.

29. Hong Y, O'Grady T, Lopresti D, Carlsson C. Diagnostic obturator nerve block for inguinal and back pain: a recovered opinion. Pain. 1996 Oct;67(2-3):507–9.

30. Mihara T, Itoh H, Hashimoto K, Goto T. Trans-resectoscope stimulation predicts the need to block adductor response during bladder tumor resection. Anesth Analg. 2013 Sep;117(3):740–4.

31. Akata T, Murakami J, Yoshinaga A. Life-threatening haemorrhage following obturator artery injury during transurethral bladder surgery: a sequel of an unsuccessful obturator nerve block. Acta Anaesthesiol Scand. 1999 Aug;43(7):784–8.

32. Shulman MS, Vellayappan U, Monaghan TG, Coukos WJ, Krenis LJ. Simultaneous bilateral obturator nerve stimulation during transurethral electrovaporization of the prostate. J Clin Anesth. 1998 Sep;10(6):518–21.

33. Deliveliotis C, Alexopoulou K, Picramenos D, Econornacos G, Goulandris N, Kostakopoulos A. The contribution of the obturator nerve block in the transurethral resection of bladder tumors. Acta Urol Belg. 1995 Sep;63(3):51–4.

34. PhD JEH. Guyton and Hall Textbook of Medical Physiology, 13e. 13 edition. Philadelphia, PA: Saunders; 2010. 1168 p.

35. Knowles JR. Enzyme-catalyzed phosphoryl transfer reactions. Annu Rev Biochem. 1980;49:877–919.

36. Silverthorn DU. Human Physiology: An Integrated Approach. 6 edition. Boston: Pearson; 2012. 992 p.

37. Diss JKJ, Fraser SP, Djamgoz MBA. Voltage-gated Na+ channels: multiplicity of expression, plasticity, functional implications and pathophysiological aspects. Eur Biophys J. 2004 May;33(3):180–93.

38. Docherty RJ, Farmer CE. The pharmacology of voltage-gated sodium channels in sensory neurones. Handb Exp Pharmacol. 2009;(194):519–61.

39. Strichartz GR. The inhibition of sodium currents in myelinated nerve by quaternary derivatives of lidocaine. J Gen Physiol. 1973 Jul;62(1):37–57.

40. Strichartz G. Molecular mechanisms of nerve block by local anesthetics. Anesthesiology. 1976 Oct;45(4):421–41.

41. Watts SA, Sharma DJ. Long-term neurological complications associated with surgery and peripheral nerve blockade: outcomes after 1065 consecutive blocks. Anaesth Intensive Care. 2007 Feb;35(1):24–31.

42. Fredrickson MJ, Kilfoyle DH. Neurological complication analysis of 1000 ultrasound guided peripheral nerve blocks for elective orthopaedic surgery: a prospective study. Anaesthesia. 2009 Aug;64(8):836–44.

43. Auroy Y, Benhamou D, Bargues L, Ecoffey C, Falissard B, Mercier FJ, et al. Major complications of regional anesthesia in France: The SOS Regional Anesthesia Hotline Service. Anesthesiology. 2002 Nov;97(5):1274–80.

44. Sites BD, Taenzer AH, Herrick MD, Gilloon C, Antonakakis J, Richins J, et al. Incidence of local anesthetic systemic toxicity and postoperative neurologic symptoms associated with 12,668 ultrasound-guided nerve blocks: an analysis from a prospective clinical registry. Reg Anesth Pain Med. 2012 Oct;37(5):478–82.

45. Hara K, Sakura S, Yokokawa N, Tadenuma S. Incidence and effects of unintentional intraneural injection during ultrasound-guided subgluteal sciatic nerve block. Reg Anesth Pain Med. 2012 Jun;37(3):289–93.

46. MS RDMM, FRCA LIEMP, FACC LAFM, MD JPW-K, MPH NHCMM, MD WLY. Miller's Anesthesia, 2-Volume Set, 8e. 8 edition. Philadelphia, PA: Saunders; 2014. 3576 p.

47. Scott DB, Lee A, Fagan D, Bowler GM, Bloomfield P, Lundh R. Acute toxicity of ropivacaine compared with that of bupivacaine. Anesth Analg. 1989 Nov;69(5):563–9.

48. Liu S, Carpenter RL, Chiu AA, McGill TJ, Mantell SA. Epinephrine prolongs duration of subcutaneous infiltration of local anesthesia in a dose-related manner. Correlation with magnitude of vasoconstriction. Reg Anesth. 1995 Oct;20(5):378–84.

49. Weinberg GL. Current concepts in resuscitation of patients with local anesthetic cardiac toxicity. Reg Anesth Pain Med. 2002 Dec;27(6):568–75.

50. Soltesz EG, van Pelt F, Byrne JG. Emergent cardiopulmonary bypass for bupivacaine cardiotoxicity. J Cardiothorac Vasc Anesth. 2003 Jun;17(3):357–8.

51. Picard J, Ward SC, Zumpe R, Meek T, Barlow J, Harrop-Griffiths W. Guidelines and the adoption of "lipid rescue" therapy for local anaesthetic toxicity. Anaesthesia. 2009 Feb;64(2):122–5.

52. Rosenblatt MA, Abel M, Fischer GW, Itzkovich CJ, Eisenkraft JB. Successful use of a 20% lipid emulsion to resuscitate a patient after a presumed bupivacaine-related cardiac arrest. Anesthesiology. 2006 Jul;105(1):217–8.

53. Litz RJ, Popp M, Stehr SN, Koch T. Successful resuscitation of a patient with ropivacaine-induced asystole after axillary plexus block using lipid infusion. Anaesthesia. 2006 Aug;61(8):800–1.

54. Weinberg GL. Treatment of local anesthetic systemic toxicity (LAST). Reg Anesth Pain Med. 2010 Apr;35(2):188–93.

55. Neuburger M, Büttner J, Blumenthal S, Breitbarth J, Borgeat A. Inflammation and infection complications of 2285 perineural catheters: a prospective study. Acta Anaesthesiol Scand. 2007 Jan;51(1):108–14.

56. Eggleston ST, Lush LW. Understanding allergic reactions to local anesthetics. Ann Pharmacother. 1996 Aug;30(7-8):851–7.

57. Connolly M, Mehta A, Sansom JE, Dunnill MGS. Allergic contact dermatitis from tetracaine in the beauty industry. Contact Derm. 2004 Aug;51(2):95–6.

58. Villarreal LC, de Frutos FJO, Del Prado Sánchez Caminero M, Sebastián FV. Perineal allergic contact dermatitis due to tetracaine in a urological lubricant. Contact Derm. 2004 Dec;51(5-6):321–2.

59. Vadas P, Perelman B. Effect of epinephrine on platelet-activating factor-stimulated human vascular smooth muscle cells. J Allergy Clin Immunol. 2012 May;129(5):1329–33.

60. Brown SGA, Mullins RJ, Gold MS. Anaphylaxis: diagnosis and management. Med J Aust. 2006 Sep 4;185(5):283–9.

61. Kemp SF, Lockey RF, Simons FER, World Allergy Organization ad hoc Committee on Epinephrine in Anaphylaxis. Epinephrine: the drug of choice for anaphylaxis. A statement of the World Allergy Organization. Allergy. 2008 Aug;63(8):1061–70.

62. Vastus lateralis muscle [Internet]. Wikipedia, the free encyclopedia. 2015 [cited 2015 Jun 22]. Available from: https://en.wikipedia.org/w/index.php?title=Vastus_lateralis_muscle&oldid=665728664

63. Bircher AJ, Messmer SL, Surber C, Rufli T. Delayed-type hypersensitivity to subcutaneous lidocaine with tolerance to articaine: confirmation by in vivo and in vitro tests. Contact Derm. 1996 Jun;34(6):387–9.

64. Curley RK, Macfarlane AW, King CM. Contact sensitivity to the amide anesthetics lidocaine, prilocaine, and mepivacaine. Case report and review of the literature. Arch Dermatol. 1986 Aug;122(8):924–6.

65. Klein CE, Gall H. Type IV allergy to amide-type local anesthetics. Contact Derm. 1991 Jul;25(1):45–8.

66. Ethikkommission der Medizinischen Universität Graz [Internet]. [cited 2015 Mar 4]. Available from: http://www.medunigraz.at/ethikkommission/Graz/

67. (OHRP) O for HRP. Office for Human Research Protections (OHRP) [Internet]. [cited 2015 Mar 4]. Available from: http://www.hhs.gov/ohrp/

68. HHS. United States Department of Health and Human Services [Internet]. [cited 2015 Mar 4]. Available from: http://www.hhs.gov/

69. Home - ClinicalTrials.gov [Internet]. [cited 2015 Mar 4]. Available from: https://clinicaltrials.gov/

70. Farrar JT, Young Jr. JP, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. PAIN. 2001 Nov;94(2):149–58.

71. Zink W, Graf BM. [Toxicology of local anesthetics. Clinical, therapeutic and pathological mechanisms]. Anaesthesist. 2003 Dec;52(12):1102–23.

72. Naguib M, Magboul MM, Samarkandi AH, Attia M. Adverse effects and drug interactions associated with local and regional anaesthesia. Drug Saf. 1998 Apr;18(4):221–50.

73. Anesthesia AS of R, science PMA the, Anesthesia P of R, Avenue pain medicine 239 F, Pittsburgh S 1714. Checklist for Treatment of Local Anesthetic Systemic Toxicity [Internet]. [cited 2015 Mar 5]. Available from: https://www.asra.com/advisory-guidelines/article/3/checklist-for-treatment-of-local-anesthetic-systemic-toxicity

74. Neal JM, Mulroy MF, Weinberg GL, American Society of Regional Anesthesia and Pain Medicine. American Society of Regional Anesthesia and Pain Medicine checklist for managing local anesthetic systemic toxicity: 2012 version. Reg Anesth Pain Med. 2012 Feb;37(1):16–8.

75. Cave G, Harvey M, Graudins A. Intravenous lipid emulsion as antidote: a summary of published human experience. Emerg Med Australas. 2011 Apr;23(2):123–41.

76. Corman SL, Skledar SJ. Use of lipid emulsion to reverse local anesthetic-induced toxicity. Ann Pharmacother. 2007 Nov;41(11):1873–7.

77. Mertes PM, Aimone-Gastin I, Guéant-Rodriguez RM, Mouton-Faivre C, Audibert G, O'Brien J, et al. Hypersensitivity reactions to neuromuscular blocking agents. Curr Pharm Des. 2008;14(27):2809–25.

78. Mertes PM, Laxenaire MC. Allergy and anaphylaxis in anaesthesia. Minerva Anestesiol. 2004 May;70(5):285–91.

79. Friedman M. The Use of Ranks to Avoid the Assumption of Normality Implicit in the Analysis of Variance. Journal of the American Statistical Association. 1937 Dec 1;32(200):675–701.

80. Friedman M. A Correction: The Use of Ranks to Avoid the Assumption of Normality Implicit in the Analysis of Variance. Journal of the American Statistical Association. 1939 Mar 1;34(205):109.

81. Friedman M. A Comparison of Alternative Tests of Significance for the Problem of m Rankings. The Annals of Mathematical Statistics. 1940 Mar 1;11(1):86–92.

82. Mann HB, Whitney DR. On a test of whether one of two random variables is stochastically larger than the other. Ann Math Stat. 1947;18:50–60.

83. Wilcoxon F. Individual Comparisons by Ranking Methods. Biometrics Bulletin. 1945 Dec 1;1(6):80–3.

84. Mirkin B. Core Concepts in Data Analysis: Summarization, Correlation and Visualization: Summarization, Correlation and Visualization. Springer Science & Business Media; 2011. 402 p.

85. Kendall M, Stuart A, Ord JK. Kendall's Advanced Theory of Statistics, Vol. 2: Classical Inference and Relationship, 5th Edition. 5 edition. New York: Oxford University Press; 1991. 736 p.

86. Spearman C. The Proof and Measurement of Association between Two Things. The American Journal of Psychology. 1904 Jan 1;15(1):72–101.

87. Lockyer SN. Nature. Macmillan Journals Limited; 1877. 724 p.

88. Lang SA, Yip RW, Chang PC, Gerard MA. The femoral 3-in-1 block revisited. J Clin Anesth. 1993 Aug;5(4):292–6.

89. McNamee DA, Parks L, Milligan KR. Post-operative analgesia following total knee replacement: an evaluation of the addition of an obturator nerve block to combined femoral and sciatic nerve block. Acta Anaesthesiol Scand. 2002 Jan;46(1):95–9.

90. Marhofer P, Oismüller C, Faryniak B, Sitzwohl C, Mayer N, Kapral S. Three-in-one blocks with ropivacaine: evaluation of sensory onset time and quality of sensory block. Anesth Analg. 2000 Jan;90(1):125–8.

91. Cuvillon P, Nouvellon E, Ripart J, Boyer J-C, Dehour L, Mahamat A, et al. A comparison of the pharmacodynamics and pharmacokinetics of bupivacaine, ropivacaine (with epinephrine) and their equal volume mixtures with lidocaine used for femoral and sciatic nerve blocks: a double-blind randomized study. Anesth Analg. 2009 Feb;108(2):641–9.

92. Childers RE, Williams JL, Sonnenberg A. Practice patterns of sedation for colonoscopy. Gastrointest Endosc. 2015 Apr 4;

93. Chin KJ, Handoll HH. Single, double or multiple-injection techniques for axillary brachial plexus block for hand, wrist or forearm surgery in adults. Cochrane Database Syst Rev. 2011;(7):CD003842.

94. Liu SS, Ngeow JE, Yadeau JT. Ultrasound-guided regional anesthesia and analgesia: a qualitative systematic review. Reg Anesth Pain Med. 2009 Feb;34(1):47–59.

95. Adam C, Standl T. [Regional anaesthesia in obese patients: what's different?]. Anasthesiol Intensivmed Notfallmed Schmerzther. 2012 Nov;47(11-12):676–81.

96. Brodsky JB, Mariano ER. Regional anaesthesia in the obese patient: lost landmarks and evolving ultrasound guidance. Best Pract Res Clin Anaesthesiol. 2011 Mar;25(1):61–72.

97. Fuzier R, Lapeyre-Mestre M, Mertes P-M, Nicolas J-F, Benoit Y, Didier A, et al. Immediate- and delayed-type allergic reactions to amide local anesthetics: clinical features and skin testing. Pharmacoepidemiol Drug Saf. 2009 Jul;18(7):595–601.

98. Gall H, Kaufmann R, Kalveram CM. Adverse reactions to local anesthetics: analysis of 197 cases. J Allergy Clin Immunol. 1996 Apr;97(4):933–7.

99. Groban L. Central nervous system and cardiac effects from long-acting amide local anesthetic toxicity in the intact animal model. Reg Anesth Pain Med. 2003 Feb;28(1):3–11.

100. Copeland SE, Ladd LA, Gu X-Q, Mather LE. The effects of general anesthesia on the central nervous and cardiovascular system toxicity of local anesthetics. Anesth Analg. 2008 May;106(5):1429–39, table of contents.

101. Jokinen MJ. The pharmacokinetics of ropivacaine in hepatic and renal insufficiency. Best Pract Res Clin Anaesthesiol. 2005 Jun;19(2):269–74.

102. Calenda E, Baste JM, Hajjej R, Danielou E, Peillon C. Toxic plasma concentration of ropivacaine after a paravertebral block in a patient suffering from severe hypoalbuminemia. J Clin Anesth. 2014 Mar;26(2):149–51.

103. Bleckner L, Solla C, Fileta BB, Howard R, Morales CE, Buckenmaier CC. Serum free ropivacaine concentrations among patients receiving continuous peripheral nerve block catheters: is it safe for long-term infusions? Anesth Analg. 2014 Jan;118(1):225–9.

104. Wulf H, Worthmann F, Behnke H, Böhle AS. Pharmacokinetics and pharmacodynamics of ropivacaine 2 mg/mL, 5 mg/mL, or 7.5 mg/mL after ilioinguinal blockade for inguinal hernia repair in adults. Anesth Analg. 1999 Dec;89(6):1471–4.

105. Markham A, Faulds D. Ropivacaine. A review of its pharmacology and therapeutic use in regional anaesthesia. Drugs. 1996 Sep;52(3):429–49.

106. Martínez Navas A, DE LA Tabla González RO. Ultrasound-guided technique allowed early detection of intravascular injection during an infraclavicular brachial plexus block. Acta Anaesthesiol Scand. 2009 Aug;53(7):968–70.

107. Müller M, Litz RJ, Hüler M, Albrecht DM. Grand mal convulsion and plasma concentrations after intravascular injection of ropivacaine for axillary brachial plexus blockade. Br J Anaesth. 2001 Nov;87(5):784–7.

108. Mardirosoff C, Dumont L. Convulsions after the administration of high dose ropivacaine following an interscalenic block. Can J Anaesth. 2000 Dec;47(12):1263.

109. Kimura Y, Kamada Y, Kimura A, Orimo K. Ropivacaine-induced toxicity with overdose suspected after axillary brachial plexus block. J Anesth. 2007;21(3):413–6.

110. Satsumae T, Tanaka M, Saito S, Inomata S. Convulsions after ropivacaine 300 mg for brachial plexus block. Br J Anaesth. 2008 Dec;101(6):860–2.

111. Dolan J, McKinlay S. Early detection of intravascular injection during ultrasound-guided axillary brachial plexus block. Reg Anesth Pain Med. 2009 Apr;34(2):182.

112. Forero CM, Gomez Lora CP, Bayegan D. Undetected intravascular injection during an ultrasound-guided axillary block. Can J Anaesth. 2013 Mar;60(3):329–30.

113. VadeBoncouer TR, Weinberg GL, Oswald S, Angelov F. Early detection of intravascular injection during ultrasound-guided supraclavicular brachial plexus block. Reg Anesth Pain Med. 2008 Jun;33(3):278–9.

114. Dullenkopf A, Borgeat A. [Local anesthetics. Differences and similarities in the "-cains"]. Anaesthesist. 2003 Apr;52(4):329–40.

115. Sinha SK, Abrams JH, Houle TT, Weller RS. Ultrasound-guided obturator nerve block: an interfascial injection approach without nerve stimulation. Reg Anesth Pain Med. 2009 Jun;34(3):261–4.

116. Thallaj A, Rabah D. Efficacy of ultrasound-guided obturator nerve block in transurethral surgery. Saudi J Anaesth. 2011 Jan;5(1):42–4.

117. Birnbaum K, Prescher A, Hessler S, Heller KD. The sensory innervation of the hip joint--an anatomical study. Surg Radiol Anat. 1997;19(6):371–5.

118. Helayel PE, da Conceição DB, Pavei P, Knaesel JA, de Oliveira Filho GR. Ultrasound-guided obturator nerve block: a preliminary report of a case series. Reg Anesth Pain Med. 2007 Jun;32(3):221–6.

119. Ford DJ, Pither C, Raj PP. Comparison of insulated and uninsulated needles for locating peripheral nerves with a peripheral nerve stimulator. Anesth Analg. 1984 Oct;63(10):925–8.

120. Johnson CR, Barr RC, Klein SM. A computer model of electrical stimulation of peripheral nerves in regional anesthesia. Anesthesiology. 2007 Feb;106(2):323–30.

121. Neuburger M, Schwemmer U, Volk T, Gogarten W, Kessler P, Steinfeldt T. [Localization of peripheral nerves. Success and safety with electrical nerve stimulation]. Anaesthesist. 2014 May;63(5):422–8.

122. Lam K, Wong D, Tam CK, Wah SH, Myint MWWJ, Yu TKK, et al. Ultrasound and electrical stimulator-guided obturator nerve block with phenol in the treatment of hip adductor spasticity in long-term care patients: a randomized, triple blind, placebo controlled study. J Am Med Dir Assoc. 2015 Mar;16(3):238–46.

123. Bhosale PR, Patnana M, Viswanathan C, Szklaruk J. The inguinal canal: anatomy and imaging features of common and uncommon masses. Radiographics. 2008 Jun;28(3):819–35; quiz 913.

124. Mariano ER, Marshall ZJ, Urman RD, Kaye AD. Ultrasound and its evolution in perioperative regional anesthesia and analgesia. Best Pract Res Clin Anaesthesiol. 2014 Mar;28(1):29–39.

125. Merritt CK, Mariano ER, Kaye AD, Lissauer J, Mancuso K, Prabhakar A, et al. Peripheral nerve catheters and local anesthetic infiltration in perioperative analgesia. Best Pract Res Clin Anaesthesiol. 2014 Mar;28(1):41–57.

126. Dhir S, Ganapathy S. Use of ultrasound guidance and contrast enhancement: a study of continuous infraclavicular brachial plexus approach. Acta Anaesthesiol Scand. 2008 Mar;52(3):338–42.

127. Salinas FV, Hanson NA. Evidence-based medicine for ultrasound-guided regional anesthesia. Anesthesiol Clin. 2014 Dec;32(4):771–87.

6 Appendix

6.1 Case Report Form 1.1

[German]

Efficacy of a modified obturator nerve block technique by using only a single morphological landmark: A double-blinded randomised pilot study

Arzt: _____ Datum: ___:___:_____

Pateintennummer/ID: ___

Name: .....

„Patientenetikette“

Informed Consent unterzeichnet/ in der Studienmappe abgelegt? Ja: ☐ Nein: ☐

Aufkleber

„Studienmedikation“

Gewicht des Patienten: ____ kg

Geplante Stichtiefe: ____ cm

Patientengewicht	→	Stichtiefe
kleiner 45 kg	→	Ausschluss des Patienten
45-60 kg	→	2,5-3,5 cm
61-80 kg	→	3,5-4,5 cm
81-100 kg	→	4,5-6 cm
größer 100 kg	→	Ausschluss des Patienten

Einschlusskriterien	Ja	Nein	**Ausschlusskriterien**	Ja	Nein
ASA I-III	☐	☐	Ablehnung durch den Patienten, keine Kooperation des Patienten (z.b. Morbus Alzheimer, neurolog. Erkrankungen ..)	☐	☐
Der Patient ist im Rahmen seiner bevorstehenden Operation für eine Blockade des N. obturatorius vorgesehen und eine **Kombinierte Anästhesie** (Regionales Verfahren + allgemeine Anästhesie) ist geplant	☐	☐	Alle Kontraindikationen für Regionalanästhesien (z.B. **Infektion** im Bereich der Einstichstelle, **Allergie** auf das Lokalanästhetikum etc.)	☐	☐
der Patient ist mindestens 18 Jahre alt	☐	☐	Schwangerschaft möglich	☐	☐
Körpergewicht des Patienten **zwischen 45 kg und 100 kg**	☐	☐	die Testung der Adduktoren Kraft ist beeinträchtigt (Max. **Adduktorenkraft < 120 mmHG**, im Zweifel vorher Testen)	☐	☐
Anästhesiologische Aufklärung vorhanden	☐	☐	**Schwangerschaft** möglich	☐	☐

1:

Max. Adduktorenkraft vor Blockade:

(3 Versuche → Maximalwert) ____ mm HG

Zeitpunkte:

Beginn Desinfektion/Anatomische Orientierung Uhrzeit: ___ :___:___ (Std/Min/Sek)

Zeitpunkt Beginn der Punktion Uhrzeit: ___ :___:___ (Std/Min/Sek)

Zeitpunkt Ende der Punktion Uhrzeit: ___ :___:___ (Std/Min/Sek)

Knochenkontakt: Ja: ☐ Nein: ☐

Aspiration von Blut: Ja: ☐ Nein: ☐

Abbruch der Blockade: Ja: ☐ Nein: ☐

→ Wenn Abbruch „Ja“ Begründung: _____

_____

Max. Adduktorenkraft 15 min. nach Blockade:

(3 Versuche → Maximalwert) ____ mm HG

Maximales Schmerzempfinden des Patienten? (NRS 0-10) ____ NRS

Unbehagen des Pat.: ☐ kein bis geringes Unbehagen

☐ mittleres Unbehagen/ Unannehmlichkeit

☐ Sehr großes Unbehagen

Dokumentation der Antwort: „Würden Sie unter ähnlichen Umständen wieder ihre Zustimmung für diesen Block geben?“ Ja: ☐ Nein: ☐

Nebenwirkungen/Komplikationen (Freitext):

_____

6.2 Informed Consent From 1.0

[German]

PatientInneneninformation[2] und Einwilligungserklärung zur Teilnahme an der klinischen Pilotstudie

„Wirksamkeit einer modifizierten Nadelstichmethode um den Nervus Obturatorius auszuschalten[3]“

Sehr geehrte Teilnehmerin, sehr geehrter Teilnehmer!

Wir laden Sie ein an der oben genannten klinischen Studie teilzunehmen. Die Aufklärung darüber erfolgt in einem ausführlichen ärztlichen Gespräch.

Ihre Teilnahme an dieser klinischen Prüfung erfolgt freiwillig. Sie können jederzeit ohne Angabe von Gründen aus der Studie ausscheiden. Die Ablehnung der Teilnahme oder ein vorzeitiges Ausscheiden aus dieser Studie hat keine nachteiligen Folgen für Ihre medizinische Betreuung.

Klinische Studien sind notwendig, um verlässliche neue medizinische Forschungsergebnisse zu gewinnen. Unverzichtbare Voraussetzung für die Durchführung einer klinischen Studie ist jedoch, daß Sie Ihr Einverständnis zur Teilnahme an dieser klinischen Studie schriftlich erklären. Bitte lesen Sie den folgenden Text als Ergänzung zum Informationsgespräch mit Ihrem Arzt sorgfältig durch und zögern Sie nicht Fragen zu stellen.

Bitte unterschreiben Sie die Einwilligungserklärung nur

---

[2] Wegen der besseren Lesbarkeit wird im weiteren Text zum Teil auf die gleichzeitige Verwendung weiblicher und männlicher Personenbegriffe verzichtet. Gemeint und angesprochen sind – sofern zutreffend – immer beide Geschlechter.

[3] Die Blockade des Nerven Obturatorius ist eine etablierte Methode zur Schmerzbehandlung im Bereich der Hüfte, Oberschenkel und des Knies. Hierbei wird der Nerv mit einem Lokalanästhetikum umspritzt. Die modifizierte Methode verwendet einen anatomischen Orientierungspunkt, jedoch kein Nervenstimulations- oder Ultraschallgerät.

- wenn Sie Art und Ablauf der klinischen Studie vollständig verstanden haben,
- wenn Sie bereit sind, der Teilnahme zuzustimmen und
- wenn Sie sich über Ihre Rechte als Teilnehmer an dieser klinischen Studie im klaren sind.

Zu dieser klinischen Studie, sowie zur Patienteninformation und Einwilligungserklärung wurde von der zuständigen Ethikkommission eine befürwortende Stellungnahme abgegeben.

1. Was ist der Zweck der klinischen Studie?

Der Zweck dieser klinischen Studie ist es, eine modifizierte Technik für die Blockade eines Nervens zur Schmerzbehandlung im Bereich der Hüfte, Oberschenkel und Knie auf Wirksamkeit zu testen.

2. Wie läuft die klinische Studie ab?

Diese klinische Studie wird an der Universitätsklinik für Anästhesiologie durchgeführt, und es werden insgesamt ungefähr 30 Personen daran teilnehmen.

Ihre Teilnahme an dieser klinischen Studie wird voraussichtlich 1 Stunde dauern.

Folgende Maßnahmen werden ausschließlich aus Studiengründen durchgeführt:

Bei dieser klinischen Studie wird vor der eigentlichen Behandlung eine genaue Beurteilung der Kraft Ihrer Adduktoren[4] im Oberschenkel gemessen. Danach erfolgt die Nervenblockade, die – je nach Zufallszuordnung – entweder mit Lokalanästhetikum oder mit Kochsalzlösung durchgeführt wird. Die eingesetzte Technik beinhaltet eine modifizierte Stichrichtung. Nach 15 Minuten wird ihre Adduktorenkraft noch einmal gemessen und Sie werden über Ihr Schmerzempfinden und Unbehagen befragt.

3. Worin liegt der Nutzen einer Teilnahme an der klinischen Studie?

Es ist möglich, dass Sie durch Ihre Teilnahme an dieser klinischen Studie keinen direkten Nutzen für Ihre Gesundheit ziehen. Durch die modifizierte Technik ist es allerdings zu erwarten, dass der schmerzlindernde Effekt der Nervenblockade ohne

[4] Muskeln der Adduktorenloge des Oberschenkels ziehen das abgespreizte Bein zurück in die Ausgangslage

Nervenstimulations-und Ultraschallgerät erreicht werden kann und diese Stichmethode weniger schmerzhaft ist und kürzer dauert als die Standardverfahren.

4. Gibt es Risiken, Beschwerden und Begleiterscheinungen?

Es gibt keine Hinweise, dass die durchgeführte Behandlung mit höheren Risiken einhergeht als das Routineverfahren. Möglich Komplikationen sind demnach dieselben (Nervenschäden, Lähmungen, Blutergüsse, Infektionen, Schmerzen beim Einstich)

5. Was ist zu tun beim Auftreten von Symptomen, Begleiterscheinungen und/oder Verletzungen?

Sollten im Verlauf der klinischen Studie irgendwelche Symptome, Begleiterscheinungen oder Verletzungen auftreten, müssen Sie diese Ihrem Arzt mitteilen, bei schwerwiegenden Begleiterscheinungen umgehend, ggf. telefonisch (Telefonnummern, etc. siehe unten).

6. Wann wird die klinische Studie vorzeitig beendet?

Sie können jederzeit auch ohne Angabe von Gründen, Ihre Teilnahmebereitschaft widerrufen und aus der klinischen Studie ausscheiden ohne dass Ihnen dadurch irgendwelche Nachteile für Ihre weitere medizinische Betreuung entstehen.

Ihr Prüfarzt wird Sie über alle neuen Erkenntnisse, die in Bezug auf diese klinische Studie bekannt werden, und für Sie wesentlich werden könnten, umgehend informieren. Auf dieser Basis können Sie dann Ihre Entscheidung zur **weiteren** Teilnahme an dieser klinischen Studie neu überdenken.

Es ist aber auch möglich, dass Ihr Prüfarzt entscheidet, Ihre Teilnahme an der klinischen Studie vorzeitig zu beenden, ohne vorher Ihr Einverständnis einzuholen. Die Gründe hierfür können sein:

a) Sie können den Erfordernissen der Klinischen Studie nicht entsprechen;
b) Ihr behandelnder Arzt hat den Eindruck, dass eine weitere Teilnahme an der klinischen Studie nicht in Ihrem Interesse ist;

7. In welcher Weise werden die im Rahmen dieser klinischen Studie gesammelten Daten verwendet?

Sofern gesetzlich nicht etwas anderes vorgesehen ist, haben nur die Prüfer und deren Mitarbeiter Zugang zu den vertraulichen Daten, in denen Sie namentlich genannt werden. Diese Personen unterliegen der Schweigepflicht.

Die Weitergabe der Daten erfolgt ausschließlich zu statistischen Zwecken und Sie werden ausnahmslos darin nicht namentlich genannt. Auch in etwaigen Veröffentlichungen der Daten dieser klinischen Studie werden Sie nicht namentlich genannt.

8. Entstehen für die Teilnehmer Kosten? Gibt es einen Kostenersatz oder eine Vergütung?

Durch Ihre Teilnahme an dieser klinischen Studie entstehen für Sie keine zusätzlichen Kosten. Sie erhalten keine Form von Vergütung oder Kostenersatz.

9. Möglichkeit zur Diskussion weiterer Fragen

Für weitere Fragen im Zusammenhang mit dieser klinischen Studie stehen Ihnen Ihr Prüfarzt und seine Mitarbeiter gern zur Verfügung. Auch Fragen, die Ihre Rechte als Patient und Teilnehmer an dieser klinischen Studie betreffen, werden Ihnen gerne beantwortet.

Name der Kontaktperson: Ass. Dr. med. univ. Holger Simonis

Ständig erreichbar unter: 0316-385-80921

Name der Kontaktperson: Ao. Univ. –Prof. Dr. med. Univ. Andreas Sandner-Kiesling

Ständig erreichbar unter: 0316-385-81858

Name der Kontaktperson: OA Dr. med. univ. Helmut Bauernfeind

Ständig erreichbar unter: 0316-385-84661

Name der Kontaktperson: Ass. Dr. med. univ. Bernhard Röschel

Ständig erreichbar unter: 0316-385-81114

Name der Kontaktperson: Ass. Dr. med. univ. Barbara Hallmann

Ständig erreichbar unter: 0316-385-14909

10. Einwilligungserklärung

Name des Patienten in Druckbuchstaben: .....

.....

Geb.Datum: .....

Ich erkläre mich bereit, an der klinischen Studie „Wirksamkeit einer modifizierten Nadelstichmethode um den Nervus Obturatorius auszuschalten“ teilzunehmen.

Ich bin von Herrn/Frau *(Dr.med.)* ……...ausführlich und verständlich über Ablauf , mögliche Belastungen und Risiken, sowie über Wesen, Bedeutung und Tragweite der klinischen Studie, sich für mich daraus ergebenden Anforderungen aufgeklärt worden. Ich habe darüber hinaus den Text dieser Patientenaufklärung und Einwilligungserklärung, die insgesamt 4 Seiten umfasst gelesen. Aufgetretene Fragen wurden mir vom Prüfarzt verständlich und genügend beantwortet. Ich hatte ausreichend Zeit, mich zu entscheiden. Ich habe zur Zeit keine weiteren Fragen mehr.

Ich werde den ärztlichen Anordnungen, die für die Durchführung der klinischen Studie erforderlich sind, Folge leisten, behalte mir jedoch das Recht vor, meine freiwillige Mitwirkung jederzeit zu beenden, ohne dass mir daraus Nachteile für meine weitere medizinische Betreuung entstehen.

Ich bin zugleich damit einverstanden, dass meine im Rahmen dieser klinischen Studie ermittelten Daten aufgezeichnet werden. Um die Richtigkeit der Datenaufzeichnung zu überprüfen, dürfen Beauftragte der zuständigen Behörden beim Prüfarzt Einblick in meine personenbezogenen Krankheitsdaten nehmen.

Beim Umgang mit den Daten werden die Bestimmungen des Datenschutzgesetzes beachtet.

Eine Kopie dieser Patienteninformation und Einwilligungserklärung habe ich erhalten. Das Original verbleibt beim Prüfarzt.

.....

(Datum und Unterschrift des Patienten)

.....

(Datum, Name und Unterschrift des verantwortlichen Arztes)

(Der Patient erhält eine unterschriebene Kopie der Patienteninformation und Einwilligungserklärung, das Original verbleibt im Studienordner des Prüfarztes.)

6.3 Ethics committee [German]

Ethikkommission

Medizinische Universität Graz

Auenbruggerplatz 2, A-8036 Graz
ethikkommission@medunigraz.at
Tel.: +43 / 316 / 385-13928, Fax: -14348

VOTUM
gültig bis 17.05.2014

EK-Nummer:	25-387 ex 12/13
Studientitel:	Efficacy of a modified obturator nerve block technique by using only a single morphological landmark: A double-blinded randomised pilot study
Prüfer:	Prof.Dr. Andreas Sandner-Kiesling Univ.Klinik für Anästhesiologie und Intensivmed.
Sponsor:	-
CRO:	-
Antragsteller:	Univ.Klinik für Anästhesiologie und Intensivmed.
Ansprechpartner:	Dr. Holger Simonis, 8036 Graz, Auenbruggerplatz 29

Die o.a. Studie wurde von der Ethikkommission erstmals in der Sitzung 08-12/13 am 13.05.2013 behandelt.
Die Ethikkommission ist zu folgendem Schluss gekommen:

Es besteht kein Einwand gegen die Durchführung der Studie in der vorliegenden Form.

Stimmberechtigte bzw. anwesende Mitglieder bei der Behandlung waren: Siehe beiliegende Liste vom 13.05.2013.

Kommissionsmitglieder, die für diesen Tagesordnungspunkt als befangen anzusehen waren und daher gemäß Geschäftsordnung an der Entscheidungsfindung und Abstimmung nicht teilgenommen haben: keine

Zur Beurteilung vorliegende Dokumente:

Dokumente eingegangen am 22.04.2013, begutachtet in der Sitzung 08-12/13 am 13.05.2013	
✓ Antragsformular	22.04.2013
✓ Originalprotokoll VOB 1.3	20.04.2013
Informed Consent Form 1.0	18.04.2013
✓ Case Report Form 1.1	
Dokumente eingegangen am 25.04.2013, begutachtet in der Sitzung 08-12/13 am 13.05.2013	
✓ Antrag Teil B	25.04.2013
Dokumente eingegangen am 16.05.2013, begutachtet im 'expedited Review' am 17.05.2013	
✓ Informed Consent Form 1.1	16.05.2013

Die Ethikkommission geht – rechtlich unverbindlich – davon aus, dass es sich um die Anwendung einer neuen medizinischen Methode handelt.

Das Votum der Ethikkommission berührt in keiner Weise die alleinige Verantwortung der Prüferin / des Prüfers / der Prüfer für die ordnungsgemäße Durchführung der Studie unter Einhaltung aller einschlägiger gesetzlicher Bestimmungen und Richtlinien.

Weiters machen wir darauf aufmerksam, dass der Kommission unverzüglich zu melden sind:

- Abweichungen vom Protokoll aus Sicherheitsgründen oder Protokolländerungen

Medizinische Universität Graz, Auenbruggerplatz 2, A-8036 Graz. www.medunigraz.at
Rechtsform: Juristische Person öffentlichen Rechts gem. Universitätsgesetz 2002. Information: Mitteilungsblatt der Universität und www.medunigraz.at. DVR-Nr. 210 9494.
UID: ATU 575 111 79. Bankverbindung: Bank Austria Creditanstalt BLZ 12000 Konto-Nr. 500 948 400 04, Raiffeisen Landesbank Steiermark BLZ 38000 Konto-Nr. 49510.

- Änderungen, die das Risiko der Teilnehmer/-innen erhöhen oder die Durchführung der Studie wesentlich beeinflussen

- Mutmaßliche unerwartete schwerwiegende Nebenwirkungen - SUSARs (AMG-Studien ab 1.5.2004) oder schwerwiegende unerwünschte Ereignisse - SAEs (andere Studien)

- Jegliche Information über sonstige Umstände, die die Sicherheit der Teilnehmer/-innen oder die Durchführung der Studie beeinträchtigen können

Dieses Votum gilt für ein Jahr ab dem Datum der Ausstellung. Bei längerer Studiendauer ist rechtzeitig vor Ablauf der Gültigkeit des Votums ein Zwischenbericht vorzulegen (Berichtsformular), um eine etwaige Verlängerung zu erlangen.

Graz, 17. Mai 2013

Univ.Prof.DI Dr.Josef Haas
Vorsitzender

Univ.Prof.DDr.Hans-Peter Kapfhammer
Stv. Vorsitzender

Achtung: Bitte bei allen das Projekt betreffende Schreiben oder telefonischen Anfragen die EK-Nummer angeben!

6.4 Protocol Registration Receipt - ClinicalTrails.gov

ClinicalTrials.gov PRS
Protocol Registration and Results System

Protocol Registration Receipt
03/20/2014

Efficacy of a Modified Obturator Nerve Block Technique

This study has been completed.

Sponsor:	Medical University of Graz
Collaborators:	
Information provided by (Responsible Party):	Andreas Sandner-Kiesling , MD, Medical University of Graz
ClinicalTrials.gov Identifier:	NCT01875289

Purpose

Efficacy of a modified obturator nerve block technique by using only a single morphological landmark, a double-blinded randomised pilot study.

Condition	Intervention	Phase
Hip Surgery Knee Surgery	Procedure/Surgery: obturator nerve block	N/A

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), Randomized, Safety/Efficacy Study

Further study details as provided by Andreas Sandner-Kiesling , MD, Medical University of Graz:

Primary Outcome Measure:

- Adductor strengths [Time Frame: pre operative, 30 minutes before start surgery] [Designated as safety issue: No]

  Adductor muscle strength is measured with a sphygmomanometer. Patients are instructed to squeeze a blod pressure cuff, already inflated to 40 mm Hg, between their extended knees. The maximal sustained

pressure is taken as the baseline adductor strength.

Estimated Enrollment: 36
Study Start Date: July 2013
Primary Completion Date: March 2014

Arms	Assigned Interventions
Experimental: Ropivacain Local anaesthesia	Procedure/Surgery: obturator nerve block
Placebo Comparator: NaCl 0.9% Saline	Procedure/Surgery: obturator nerve block

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both

Inclusion Criteria:

- American Society of Anesthesiologists 1-3, older than 18 y, cooperative patient

Exclusion Criteria:

- infection, neuromuscular deficits of the lower extremities,pregnancy, neurologic disease

Contacts and Locations

Locations

Austria

Medical University Graz
Graz, Austria, 8036

More Information

Publications:

Feigl GC, Ulz H, Pixner T, Dolcet C, Likar R, Sandner-Kiesling A. Anatomical investigation of a new vertical obturator nerve block technique. Ann Anat. 2013 Jan;195(1):82-7. doi: 10.1016/j.aanat.2012.05.008. Epub 2012 Aug 10. PubMed

Responsible Party: Andreas Sandner-Kiesling , MD, Prof. Dr. med. univ., Medical University of Graz
Study ID Numbers: VOB-Studie EK 25-387 ex 12/13

Health Authority: Austria: Federal Office for Safety in Health Care

6.5 Example of the production log for study medication

6.5.1 Verum group

[German]

Produktionsdatum: Di, 4.3.2014, von 08:43 bis 08:45 Uhr

Hergestellt von: PIA

1 [08:43:29] HERSTELLUNG NR. 422897 GESTARTET AM Di, 4.3.2014 UM 08:43 (Cato-VERSION: 2.29.8.5), XPM aktiviert

2 [08:43:29] Zugeordnete Flaschen:

3 [08:43:29] >>> 1. Flasche Vorrat Nr.282 Naropin (Ch.Nr.: LABU): Restmenge: 36,53mg, Volumen: 4,87ml (4,87g)

4 ----------

5 [08:43:30] Med. Nr. 602856: Naropin 37,5mg (5ml) Bolus perineural, Studie VOB Pilot (UNI-KL. - Chir.Kl. Ambulanz allg.) für 4.3.2014

6 ----------

7 [08:43:30] MELDUNG: "Bitte stellen Sie die 1. Flasche Vorrat Nr.282 Naropin (Ch.Nr.: LABU) auf die Waage. <F2> Diese Flasche nicht verwenden <F3> um diese Medikation zu überspringen"

8 [08:43:46] IDENTIFIKATION OK: '1. Flasche Vorrat Nr.282 Naropin (Ch.Nr.: LABU)' wurde mittels bereits bekanntem Gewicht
identifiziert. Erwartetes Gewicht: 7,350g, Tatsächliches Gewicht: 7,34g.

9 [08:43:46] MELDUNG: "Aus dieser Flasche zu entnehmen: ALLES: 4,87ml Bitte legen Sie eine leere 5ml Bolus auf die Waage dazu! <F3> um diese Medikation zu überspringen"

10 [08:43:51] Gesamtgewicht von Spritze und Flasche: 11,71g

11 [08:43:51] Spritzengewicht vor Entnahme: 4,370g

12 [08:43:52] MELDUNG: "Verordneter WS: 37,5mg, Bisher erreicht: 0mg Ziehen Sie den gesamten Inhalt (=ALLES: 4,87ml) auf. Legen Sie die Spritze danach wieder auf die Waage. <F3> um diese Medikation zu überspringen"

13 [08:44:04] MELDUNG: "Verordneter WS: 37,5mg, Bisher erreicht: 0mg Ziehen Sie den gesamten Inhalt (=ALLES: 4,87ml) aus der 1. Flasche Vorrat Nr.282 Naropin auf. Legen Sie die Spritze danach wieder auf die Waage. <F1> wenn keine

Entnahme mehr möglich (4,9ml Verlust) <F3> um diese Medikation zu überspringen"

14 [08:44:33] Gewicht der Spritze(n) nach Entnahme: 9,56g g, Differenz: 5,19 g

15 [08:44:33] SOLL-ENTNAHME: alles entnehmen, Flasche Nr. 1, befüllt mit 36,53mg, Dichte = 1g/ml, Konzentration = 7,5mg/g, zu entnehmende Gesamtmasse = 4,87g, entspr. Volumen = 4,87ml, Wirkstoffmasse = 36,525mg, Dosis = 36,53mg, Spritze: eine leere 5ml Bolus

16 [08:44:33] IST-ENTNAHME: ACHTUNG! Entnahmestatus: "außerhalb Entnahmetoleranz", Gesamtmasse 5,19g, das sind 0,32g (0,32ml) zuviel (bezogen auf die Einzelentnahme), entspr. Volumen 5,19ml, Wirkstoffmasse = 38,925mg, Dosis: 38,92mg

17 [08:44:39] MELDUNG: "Verordneter WS: 37,5mg, Bisher erreicht: 0mg Ziehen Sie den gesamten Inhalt (=ALLES: 4,87ml) aus der 1. Flasche Vorrat Nr.282 Naropin auf. Es sollten dann 4,87ml Lösung in der Spritze sein. Legen Sie die Spritze danach wieder auf die Waage. "

18 [08:44:47] Gewicht der Spritze(n) nach Entnahme: 9,33g g, Differenz: 4,96 g

19 [08:44:47] SOLL-ENTNAHME: alles entnehmen, Flasche Nr. 1, befüllt mit 36,53mg, Dichte = 1g/ml, Konzentration = 7,5mg/g, zu entnehmende Gesamtmasse = 4,87g, entspr. Volumen = 4,87ml, Wirkstoffmasse = 36,525mg, Dosis = 36,53mg, Spritze: eine leere 5ml Bolus

20 [08:44:47] IST-ENTNAHME: Entnahmestatus: "Okay", Gesamtmasse 4,96g, das sind 0,04g (0,04ml) zuwenig (bezogen auf die notwendige Gesamtmenge), entspr. Volumen 4,96ml, Wirkstoffmasse = 37,2mg, Dosis: 37,2mg, innerhalb Zuspritztoleranz

21 [08:44:47] VERBUCHTE ENTNAHME: Entnahmestatus: "Okay", Gesamtmasse 4,96g, innerhalb Zuspritztoleranz, Restdosis in Flasche = 0mg

22 [08:44:47] MELDUNG: " Erreichte Wirkstoffmenge: 37,2mg Verordnete Wirkstoffmenge: 37,5mg Erreichte Menge: 99,2% Nehmen Sie die Spritze von der Waage."

23 [08:44:56] Etiketten für Medikation Nr. 602856 werden gedruckt.

24 [08:45:06] DIE PRODUKTION WURDE BEENDET

6.5.2 Control group

[German]

Produktionsdatum: Di, 4.3.2014, von 08:49 bis 08:53 Uhr

Hergestellt von: PIA

1 [08:49:36] HERSTELLUNG NR. 422900 GESTARTET AM Di, 4.3.2014 UM 08:49 (Cato-VERSION: 2.29.8.5), XPM aktiviert

2 [08:49:36] Zugeordnete Flaschen:

3 [08:49:36] >>> 1. Flasche NaCl 0,9% 100ml Infusionsflasche Glas Fresenius 100mg (Ch.Nr.: 19GG11WB): Soll-Volumen: 100ml, Dichte: 1g/ml

4 ----------

5 [08:49:36] Med. Nr. 602859: NaCl 0,9% 100ml Infusionsflasche Glas Fresenius 5mg (5ml) Bolus perineural, Studie VOB Pilot (UNI-KL. - Chir.Kl. Ambulanz allg.) für 4.3.2014

6 ----------

7 [08:49:37] MELDUNG: "Bitte stellen Sie die 1. Flasche NaCl 0,9% 100ml Infusionsflasche Glas Fresenius 100mg (Ch.Nr.: 19GG11WB) auf die Waage. <F2> Diese Flasche nicht verwenden <F3> um diese Medikation zu überspringen"

8 [08:49:41] IDENTIFIKATION OK: '1. Flasche NaCl 0,9% 100ml Infusionsflasche Glas Fresenius 100mg (Ch.Nr.: 19GG11WB)' wurde mittels Chargendurchschnittsgewicht identifiziert. Erwartetes Gewicht: 207,800g, Tatsächliches Gewicht: 207,74g.

9 [08:49:42] MELDUNG: "Aus dieser Flasche zu entnehmen: 5ml Bitte legen Sie eine leere 5ml Bolus auf die Waage dazu! <F3> um diese Medikation zu überspringen"

10 [08:49:48] Gesamtgewicht von Spritze und Flasche: 212,09g

11 [08:49:48] Spritzengewicht vor Entnahme: 4,350g

12 [08:49:48] MELDUNG: "Verordneter WS: 5mg, Bisher erreicht: 0mg Ziehen Sie 5ml Lösung auf. Legen Sie die Spritze danach wieder auf die Waage. <F3> um diese Medikation zu überspringen"

13 [08:50:01] MELDUNG: "Verordneter WS: 5mg, Bisher erreicht: 0mg Ziehen Sie 5ml Lösung aus der 1. Flasche NaCl 0,9% 100ml Infusionsflasche Glas Fresenius 100mg auf. Legen Sie die Spritze danach wieder auf die Waage. <F1> wenn keine

Entnahme mehr möglich (100ml Verlust) <F3> um diese Medikation zu überspringen"

14 [08:50:38] Gewicht der Spritze(n) nach Entnahme: 9,63g g, Differenz: 5,28 g

15 [08:50:38] SOLL-ENTNAHME: Flasche Nr. 1, befüllt mit 100mg, Dichte = 1g/ml, Konzentration = 1mg/g, zu entnehmende Gesamtmasse = 5g, entspr. Volumen = 5ml, Wirkstoffmasse = 5mg, Dosis = 5mg, Spritze: eine leere 5ml Bolus

16 [08:50:38] IST-ENTNAHME: ACHTUNG! Entnahmestatus: "außerhalb Entnahmetoleranz", Gesamtmasse 5,28g, das sind 0,28g (0,28ml) zuviel (bezogen auf die Einzelentnahme), entspr. Volumen 5,28ml, Wirkstoffmasse = 5,28mg, Dosis: 5,28mg

17 [08:50:44] MELDUNG: "Verordneter WS: 5mg, Bisher erreicht: 0mg Spritzen Sie 0,28g (0,28ml) Lösung zurück. Es sollten dann 5ml Lösung in der Spritze sein. Legen Sie die Spritze danach wieder auf die Waage. "

18 [08:50:49] Gewicht der Spritze(n) nach Entnahme: 9,46g g, Differenz: 5,11 g

19 [08:50:49] SOLL-ENTNAHME: Flasche Nr. 1, befüllt mit 100mg, Dichte = 1g/ml, Konzentration = 1mg/g, zu entnehmende Gesamtmasse = 5g, entspr. Volumen = 5ml, Wirkstoffmasse = 5mg, Dosis = 5mg, Spritze: eine leere 5ml Bolus

20 [08:50:49] IST-ENTNAHME: Entnahmestatus: "Okay", Gesamtmasse 5,11g, das sind 0,11g (0,11ml) zuviel (bezogen auf die notwendige Gesamtmenge), entspr. Volumen 5,11ml, Wirkstoffmasse = 5,11mg, Dosis: 5,11mg, innerhalb Zuspritztoleranz

21 [08:50:49] VERBUCHTE ENTNAHME: Entnahmestatus: "Okay", Gesamtmasse 5,11g, innerhalb Zuspritztoleranz, Restdosis in Flasche = 94,89mg

22 [08:50:49] MELDUNG: " Erreichte Wirkstoffmenge: 5,11mg Verordnete Wirkstoffmenge: 5mg Erreichte Menge: 102,2% Nehmen Sie die Spritze von der Waage."

23 [08:50:55] Etiketten für Medikation Nr. 602859 werden gedruckt.

24 [08:51:05] MELDUNG: "Einwiegen der Reste Stellen Sie die 1. Flasche, NaCl 0,9% 100ml Infusionsflasche Glas Fresenius 100mg auf die Waage. <F1> um Rest zu verwerfen"

25 [08:53:06] TASTE: Es wurde die 'F1' Taste gedrückt!

26 [08:53:06] Flasche wurde VERWORFEN! NaCl 0,9% 100ml Infusionsflasche Glas Fresenius 100mg Charge Nr.: 19GG11WB Restmenge: 94,89mg (94,9ml (94,9g))

27 [08:53:06] DIE PRODUKTION WURDE BEENDET