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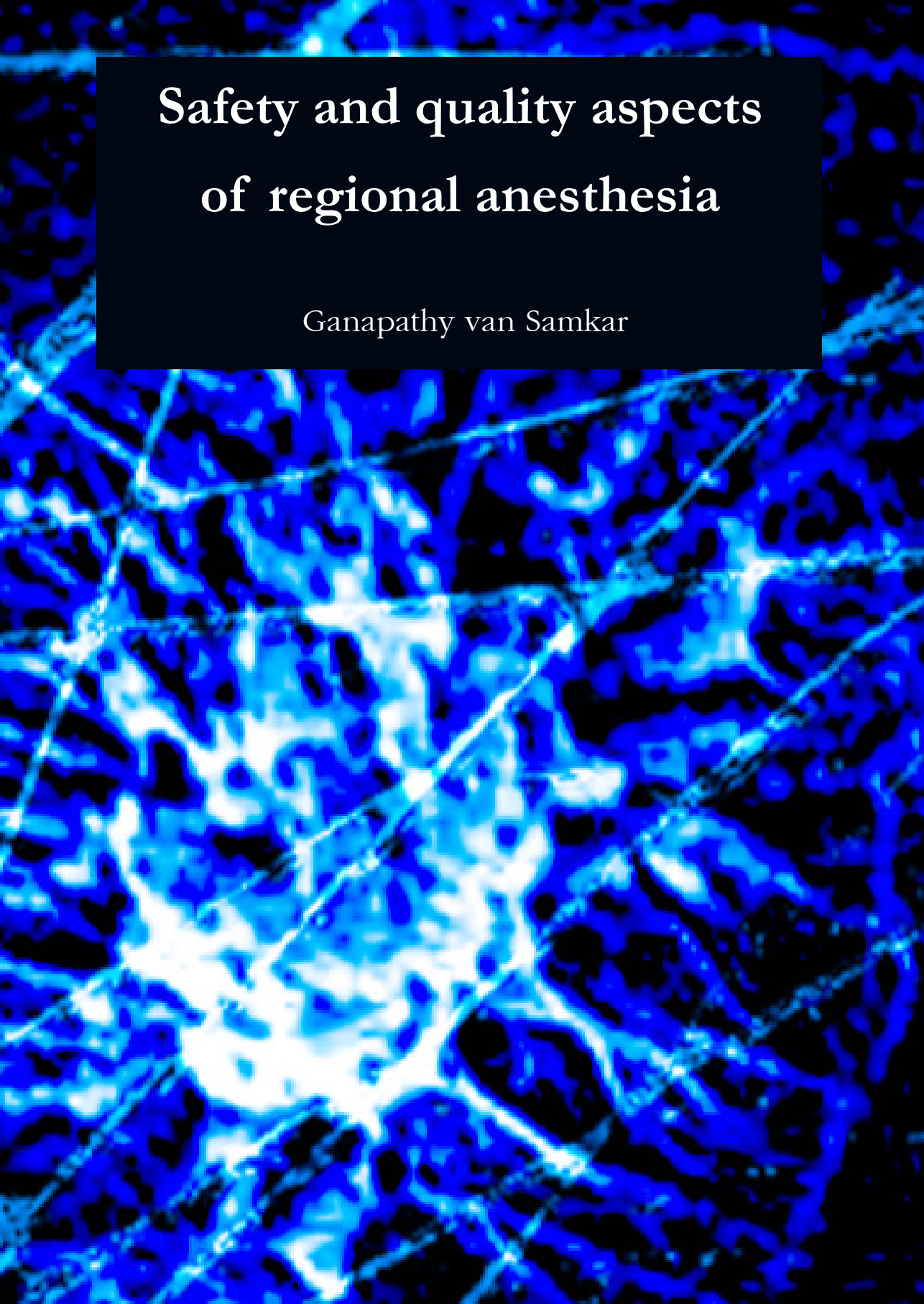

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Safety and quality aspects of regional anesthesia

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Faculteit der Geneeskunde

To my grandfather A.V. Ramaswami
and my grandmother Bhavani

Contents

Chapter 1

Introduction and outline of the thesis

G. van Samkar
H. Hermanns
M.W. Hollmann
B. Preckel

Introduction

Regional anesthesia (RA) has become an indispensable part of modern anesthesia concepts, either as alternative or adjunct to general anesthesia. Popularity of RA has increased in the past 20 years, driven partly by the need for increasingly cost effective health care, also available in outpatient surgery.[1] Recovery and discharge times can be shortened, and pain control for the postoperative phase is most often superior when using RA. Moreover, as the population is aging, the concomitant co-morbidity is challenging, but addressed properly by the use of RA.[2]

The evolution of ultrasound for RA has continued, and has currently become standard practice in the performance of peripheral nerve blocks.[3] Neurostimulators are still used to confirm proper location, in combination with ultrasound in cases with a more difficult anatomy.[4]

In addition, RA is indispensable in the multimodal approach to opiate sparing analgesia, and is an important part of enhanced recovery protocols targeted towards a more rapid recovery and rehabilitation.[5] [6]

Possible **advantages** of RA

Acute pain

The use of RA has been associated with positive effects on acute pain. A recent study examining the use of RA in patients with trauma of extremities concluded that use of RA improved average pain scores, for 24 months after the injury.[7] Early use of RA can have a positive effect on pain reported by the patient.

Meta-analyses regarding opioid consumption, pain scores, surgical site infections, post-operative nausea and vomiting, blood loss, length of stay, hypotension showed various advantages of regional anesthesia in patients undergoing different types of surgery.[8-10]

Chronic pain

Use of RA may also have beneficial effects on chronic pain.[11] [12] A systematic review of 32 randomized controlled trials (RCTs) concluded that “RA may be beneficial in reducing severity of both acute and chronic pain in patients undergoing amputation, mastectomy or thoracotomy”.[13] A meta-analysis of 39 studies including 3,027 patients undergoing breast cancer surgery, thoracotomy

and cesarean section also concluded that RA can lessen the chance of developing chronic postoperative pain, even if the evidence of chronic persistent pain was moderate.

Opioid consumption

In a large database study of more than 82,000 patients undergoing arthroscopic surgery, decreased opioid consumption during the first two weeks postoperatively was reported when surgery was performed under peripheral nerve blocks. However, only those patients with opioid use during the three months *preceding* the operation benefited, whereas no differences were present after one month postoperatively.[14] A review of eight RCTs (379 patients) after total knee arthroplasty (TKA) investigated the effect of sciatic nerve block, and concluded that "adding a single shot or continuous sciatic nerve block to a femoral nerve block led to a significant reduction in morphine consumption 8 hours (single shot) to 48 hours (continuous) postoperatively".[15] A systematic review including 170 patients analysed continuous peripheral nerve blocks and concluded that opioid use was less and patient satisfaction was better in patients with nerve block.[16]

Possible **disadvantages** of RA

Epidurals

Unfortunately, there are disadvantages to epidurals: the incidence of hypotension is higher in patients with effective epidurals (20.9% vs 2.3% of patients), and technical failures may occur.[17] Epidurals also lead to urinary retention, pruritus and motor blockade. In addition, epidural puncture can be difficult to perform, and lead to neurologic complications due to epidural hematoma, abscess, meningitis or spinal cord injury.[18] Learning how to perform an epidural puncture can also be difficult as well as time consuming. Therefore, tools have been developed to teach novices how to perform the procedure, employing software and hardware simulation.[19] [20]

Disadvantages of nerve blocks: toxicity

Peripheral nerve blocks have their own disadvantages, including even lethal outcome due to Local Anesthetic Systemic Toxicity (LAST) with fatal cardiac arrest.[21-23] LAST is frequently underreported: a recent review of databases estimated

an incidence of 30 per 100,000 patients.[24] Classic symptoms of LAST include: metallic taste, confusion, excitability, seizures, often followed by cardiovascular instability (excitation and collapse). Toxicity can also suddenly occur without prodromal symptoms.[25] Local anesthetics potentially cause arrhythmias and central nervous system toxicity. Intravascular injection and / or delayed systemic absorption of the local anesthetic also carries the risk of toxicity. As blocks are increasingly performed outside operating rooms, the monitoring of patients who have undergone a block is challenging: symptoms can occur hours after injection of the local anesthetic and especially sedation can mask LAST symptoms. Patient safety requires proper use of equipment and techniques, correct route and dosing of drugs, a safe environment with well trained personnel, adequate equipment and medical supplies suitable for treating complications if and when they arise.

Complications of RA and contribution of ultrasound: nerve injury, hemi-diaphragmatic paresis, pneumothorax, vascular puncture

Peripheral nerve injury, LAST, hemi-diaphragmatic paresis (HDP) and pneumothorax are potential complications of RA.[26] In recent years, the use of ultrasound guided nerve blocks reduced LAST by 65%. HDP can be encountered, especially in higher volumes of local anesthetics. Reducing the volume from 20 ml to 5 - 10 ml can decrease the risk of HDP.[27] [28] The historic incidence of pneumothorax as a consequence of classic supraclavicular block was estimated to be around 6%.[29] More recently, the incidence of pneumothorax has dropped to 0.4/1,000, possibly by utilization of ultrasound guidance.[30]

Unintended vascular puncture is a surrogate marker for LAST. Compared to peripheral nerve stimulation, ultrasound guidance can lessen the occurrence of vascular puncture.[26]

However, ultrasound guided regional anesthesia (UGRA) did not eliminate the overall risk of LAST, HDP and pneumothorax. The risk of HDP ranged between 0 - 34% of supraclavicular brachial plexus blocks, which is a reason for caution in patients with compromised pulmonary function. A recent study of 20 patients demonstrated that small volumes such as 5 ml of local anesthetic still can cause HDP.[31]

Ultrasound guidance and intraneural injection, nerve damage

The intention of using medical technology is to reduce risk of complications while maintaining or increasing efficiency. Ultrasound guidance usage in nerve blocks can reduce complications like nerve injury. The pathophysiological explanation of nerve injury after peripheral nerve block stresses the importance of avoiding intraneural injections. In particular, when LA is injected inside the fascicles, high intrafascicular pressure can exceed the capillary occlusion pressure, leading to ischemic nerve damage and permanent neurologic deficits.[32] A study of 257 patients after shoulder surgery reported 17% intraneural injection without peripheral nerve injury (plexus block with ultrasound).[33] An earlier study in 1,169 patients reported an incidence of post-operative neurological symptoms (PONS) of 0.4% for permanent nerve injury, respectively, for ultrasound guided supraclavicular and interscalene blocks.[34] A study of 1,000 ultrasound guided peripheral nerve blocks reported an all- cause PONS of 0.6% at six months postoperatively, and accompanying paraesthesia during the procedure increased the odds ratio for PONS to 1.69.[35] [36] When comparing other localization methods, ultrasound guidance has not shown to lower the incidence of PONS or peripheral nerve damage.[37] [38]

In spite of advantages offered by RA, only a small fraction of patients eligible for RA actually receive a nerve block.[39] [40] [41] Training all anesthesiologists to perform ultrasound guided RA remains important to gain the necessary skills.[42]

Aim of this thesis

The aim of this thesis was to investigate safety, efficacy and training aspects of currently employed RA techniques, and also to compare different clinically used methods with each other. At the beginning of this thesis, we provide an overview of developments in the field of RA. The underestimation of opioid addiction and possible causes of the current opioid crisis are discussed, with exploration of the value of RA in providing alternatives. We briefly touch the subjects of chronic postsurgical pain and the implementation of new approach called transitional pain service in helping opioid addiction prone patients in an early phase of peri- operative care. The subject of wrong sided blocks is discussed, with possible solutions such as a preoperative checklist. A severe complication of RA is LAST, and we present the updated guidelines by the American Society of

Regional Anesthesia as a tool to be used in emergencies. Another complication is the infection associated with the use of prolonged use of RA catheters for continuous RA, and explore this subject. Ultrasound guided regional anesthesia (UGRA) can reduce complications. We elaborate on which complications can be reduced by the use of UGRA. Application of RA medication can be done unintentionally through the wrong route, such as intravenous dosing of local anesthetic meant for epidural use. The use of dedicated connectors (called NRfit) can help to reduce the occurrence of this potentially lethal problem. We also discuss the advantages of RA during the SARS-CoV-2 pandemic: lessening the need for general anesthesia which potentially generates aerosols during airway management. Lastly, the use of RA can lead to rebound pain when the block wears off, especially when only RA is used without multimodal pain strategy, and we provide insight and possible ways to mitigate rebound pain (**Chapter 2).**

Patient controlled epidural analgesia is commonly used during labor and delivery. In this patient group of relatively young females, a multimodal analgesic approach combining diclofenac, ketamine, clonidine, intravenous lidocaine and intravenous opiates cannot readily be implemented because of the following reasons: (maternal) diclofenac is contraindicated during the last trimesters of pregnancy due to its association with premature closure of the fetal ductus arteriosus, can contribute to increase of peri-partum hemorrhage and has been associated with maternal vaginal bleeding in the third trimester.[43] [44] Ketamine can create hallucinations and disorientation; clonidine leads to hypotension in a situation already prone to hypotension due to peri-partum blood loss; intravenous lidocaine is generally only administered in environments where electrocardiographic monitoring is available, due to its potential sodium channel block and conduction disturbances; intravenous opiates can induce ventilatory depression, nausea and itching. Evidence shows the advantages of patient controlled epidural analgesia during labor.[17] [45] [46] The same approach has therefore been extrapolated to the postoperative patients after surgery of a non-obstetric nature, including major abdominal surgery and orthopedic surgery of elderly patients, male and female. However, the cyclic nature of delivery pain is different from postoperative pain. High quality evidence proving the superiority of patient-controlled analgesia is scarce in this non-obstetric patient group differing in age, sex, physiology, comorbidity, surgical procedure and length of stay. Our hypothesis, based on evidence in the obstetric population

was that employment of PCEA compared to CEA leads to reduced pain scores in rest and movement. In **Chapter 3**, we evaluate the effects of patient-controlled analgesia and systematically reviewed the literature on patient-controlled versus continuous epidural analgesia, exploring which of the two application modes is safer and has less disadvantages in patients undergoing non-obstetric surgery.

Epidural analgesia has been shown to fail in 30% of the cases.[17] An early sign of possible failure is inadequate analgesia in the postoperative period, requiring interventions: extra doses of local anesthetics, known as top-ups, or intravenous opiates. Both can cause problems: hypotension and respiratory depression being the foremost. Side-effects such as respiratory depression can be lethal, and frequent top-ups reflect inadequate analgesia. Further, frequent top-ups are time consuming and therefore costly. In **Chapter 4** we compare the number of top-ups and side-effects during the postoperative use of patient-controlled or continuous epidural analgesia (PCEA). Our hypothesis was that PCEA would reduce the number of top-ups, side-effects and workload. We further investigated whether PCEA could lead to an earlier termination of epidural analgesia.
Calcaneal and talar fractures are known to be painful in the postoperative period after open surgical reduction and internal fixation. Analgesia can be provided by intravenous opiates or continuous peripheral nerve blocks (CPNB). A meta-analysis of 19 studies including 603 patients has shown that CPNB in general provided better analgesia than opiates alone.[47] However, there is a paucity of evidence regarding the advantages of CPNB in the specific group of patients after calcaneal / talar fractures. Comparing the two methods could provide insight regarding advantages in analgesia, side effects, opiate use, and length of stay. In **Chapter 5** we focus on the postoperative treatment of pain in patients with fractures of the calcaneus and talus, comparing continuous nerve blocks to intravenous patient- controlled analgesia. Our goal was to generate hypotheses based on this retrospective study, to adequately power a randomized controlled blinded study.

Pain treatment of calcaneal fractures does not stop after discharge from hospital. Patients contact the hospital after discharge for a variety of reasons, and one out of five calls concerns postoperative pain.[48] Peripheral nerve blocks are a modality of treatment by the anesthesiologist. A variety of reasons can be present for abstaining from the nerve block, including patient consent, prior nerve damage,

logistic reasons (no equipment or personnel capable of doing the block, time pressure). Trauma surgeons have detailed knowledge of the anatomy of the ankle and can also perform an ankle block postoperatively. Comparing the anesthesiologist driven peripheral nerve block with the trauma surgeon's ankle block can add knowledge which can be used to increase efficiency of pain treatment in respective patients and reduce costs. In **Chapter 6** we compare two different blocks in the postoperative treatment of displaced calcaneal fractures: a popliteal block and an ankle block, evaluating which of the techniques is superior regarding pain management and length of hospital stay.

In major abdominal surgery, such as pancreatic or liver surgery, epidural analgesia is a common modality of pain treatment. Neuraxial blocks can be challenging to perform and carry a risk of epidural hematoma or abscess, a serious complication with an incidence varying from 1 in 1,000 to 1 in 6,000 patients.[49 50] Alternative treatments have evolved away from the proximity of the neuraxial plane, having less complications than neuraxial techniques and therefore could add pain relief with increased safety. One option is the use of continuous wound infiltration catheters. In abdominal surgery, the wound catheter is positioned pre-peritoneally and below the fascia of the transverse abdominis muscle. During the initial bolus of local anesthetics through wound catheters LAST might occur, as catheters could be in the proximity of vascular structures. In **Chapter 7** we investigated safety aspects of the continuous wound catheter technique, comparing bupivacaine plasma levels during bolus injection through pre-peritoneal wound catheters versus epidural catheters.

Technical skills have traditionally been learnt by novices on patients. Simulation training can steepen the learning curve of the novice in a safe environment without time pressure and allow feedback by the tutor. There are various simulators including epidural and spinal models. The look and feel of a simulator is important, it should measure what it is supposed to measure (face validity), and it should distinguish between experienced and novice anesthesiologists by behaving like a real case (construct validity). In existing literature, none of the simulators used for placement of epidural catheters was face or construct validated, and none used advanced MRI (magnetic resonance imaging) modeling scans.[51] In **Chapter 8**, we describe the face and construct validity of the TU-Delft epidural simulator, and advantages of real-time visualization using MRI modeling.

In teaching residents, the use of a simulator can prevent damage to patients and potentially steepen the learning curve. We hypothesized that a visualization aid would improve the performance during the actual procedure.

Infection of epidural catheters is a serious complication associated with their use. The documented incidence of superficial infections after placement of epidural catheters ranges from 5-12%. Deep tissue infections range from 1 in 1,000 to 1 in 100,000. [52-54] Colonization of epidural catheters can be a source of epidural infection, originating from bacterial skin flora, or from blood borne spread caused by bacteria elsewhere in the body. Despite adequate skin disinfection, bacteria can reside in hair follicles, which are not reached by the respective skin disinfectants. The common route of epidural catheter infection is assumed to be skin flora and their migration along the epidural catheter, inwards to the neuraxial space, eventually leading to tissue damage in surgical patients. Scanning electron microscopy of epidural catheters has never been described pertaining to bacterial colonization. In **Chapter 9**, we describe the results of bacterial culture and scanning electron microscopy of epidural catheters. In this observational study, we explored whether bacteria present *on* or *in* the skin are the primary source of colonization of the epidural catheter which progresses along the outer catheter surface towards the tip and from there potentially into its lumen.

To summarize, this thesis will give answers to the following clinically relevant questions:

1. Is PCEA superior to CEA in non-obstetric surgery?
2. Does PCEA reduce the number of top-ups, side-effects and workload and lead to a reduced duration of use of epidural analgesia?
3. In the postoperative treatment of pain in fractures of the calcaneus and talus, how do continuous nerve blocks compare to intravenous patient-controlled analgesia?
4. In the postoperative treatment of displaced calcaneal fractures, which block is superior regarding pain management: a popliteal block or an ankle block?
5. During use of continuous wound catheters, are bupivacaine levels below toxic levels but higher compared to epidural analgesia?
6. During use of the TU Delft epidural simulator, do participants rate it as realistic and useful for training purposes, and does a visualization aid improve the performance during the actual procedure and even in subsequent

procedures without visualization?

7. Can bacteria present *on* or *in* the skin be the primary source of colonization of the epidural catheter, by progressing along the outer catheter surface towards the tip and lumen?

Finally, the thesis concludes with a summary of findings and a general discussion and future perspectives on various aspects influencing the decision to use RA for pain management in the perioperative period.

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Chapter 2

Recent developments in regional anesthesia

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Submitted for publication

Abstract

Regional anesthesia (RA) techniques are still evolving rapidly, adapting to recent developments in medicine and society. While RA is ever improving its excellent safety record, hitherto unknown side effects are also newly discovered. In the past decades, the use of ultrasound guided techniques has become an indispensable part in the practice of RA. The focus of block performance has shifted from neuraxial techniques to peripheral nerve blocks and fascial plane blocks. Increased emphasis and efforts to reduce pain within and outside of the hospital have partially led to over-prescription of opioids and contributed to the opioid crisis, most prominent in the United States (US). RA techniques contribute to reduced peri-operative pain and opioid requirements.

During the recent Covid-19 pandemic RA was advertised and preferred wherever possible in order to avoid aerosol-generating procedures during induction, maintenance and emergence of general anesthesia in patients with suspected or proven SARS-CoV-2 infection.

Safety of RA has been improved by various techniques like the use of ultrasound, improved local anesthetic toxicity treatment and algorithms, avoidance of wrong-sided blocks by safety procedures, increased hygiene measures to avoid infection; and introduction of a specialized connector for application of local anesthetics to prevent medication errors. While the techniques and safety are continuously being improved and new advantages are being discovered, even yet under recognized side-effects such as rebound pain are being discovered.

Introduction

The field of regional anesthesia (RA) rapidly evolved during the last two decades with a shift from neuraxial anesthesia to more peripheral nerve blocks, and more recently to fascial plane blocks. These new developments became possible through the introduction of ultrasound guided RA. This narrative review will focus on the role of RA in eventually perioperative opiate-sparing effects, recent advances and developments regarding different safety issues, the advantages of RA during the SARS-CoV-2 pandemic and evaluate the role of rebound pain after RA.

Role of RA for perioperative opioid-sparing goals

During the 1980s, the risk of addiction to opioids in medical treatment was rendered negligible.[1-3] Since then the use of opioids for acute and chronic pain has increased tremendously and been advocated by slogans as "pain-free hospital" by doctors as well as pharmaceutical industry. Currently, however, over 2.1 million people suffer from opioid addiction in the USA alone, and over 128 deaths occur daily due to opioid overdose.[4 5] Two thirds of opioid-involved deaths are related to synthetic opioids.[5] Meanwhile, increased use of opioids and some indications of increased abuse have been signaled in the United Kingdom, Australia, South America, India and the Netherlands.[6 7-9] However, in these countries the opioid-abuse problem is several orders of magnitude smaller compared to the USA. The hitherto opioid naive patient is commonly exposed to opioids for perioperative or posttraumatic pain management for the first-time. Opioid-sparing perioperative and posttraumatic regimens will not only reduce exposure to opioids in the hospital, but most likely also after discharge.[10-12] While opioid administration for inpatients is highly controlled, the prescription of opioids outside the hospital is far less controlled and more fallible to mechanisms of misuse. Therefore, any methods reducing post-hospitalization opioid prescription will most likely also reduce the risk of opioid misuse. Naturally, RA is the most powerful candidate to minimize opioid use. A retrospective study of over 82,000 patients having (arthroscopic) shoulder operations found decreased use of opioids in the first two weeks following the operation in patients who were operated under nerve block.[13] A meta-analysis of eight randomized controlled trails (RCTs) including 379 patients undergoing total knee arthroplasty concluded that adding a sciatic nerve block to a femoral nerve block led to a significant reduction in morphine consumption up to 48 hours postoperatively.[14] Other studies found comparable

results using continuous infusion nerve blocks.[15] These are just a few examples of opioid sparing effects by different RA techniques. Actually, in most studies the effectivity of RA techniques is demonstrated by significant and clinically meaningful reductions of opioid consumption. However, the amount of opioid reduction is variable with the type of block and kind of surgery and generally is absent when the block wears off. Severe postoperative pain is associated with chronic post-surgical pain (CPSP), and chronic opioid use and misuse can lead to tolerance and opioid-induced hyperalgesia.[16-18] Epidural anesthesia for lateral thoracotomy can prevent or ameliorate development of chronic postoperative pain.[19 20] Likewise, RA can also reduce the incidence of CPSP after caesarian section and after breast cancer surgery.[20 21] Unfortunately, these results cannot be transferred to other types of RA and other types of operations. This is partially because the long-term results of RA are less frequently reported (absence of evidence), but also partially because no long-term effects of RA could be discovered in the three above mentioned surgical procedures (evidence of absence).[22]

However, only a very small minority of patients receiving opioids peri-operatively become opioid abuser or being addicted. In the general population a history of substance abuse and several psychological, psychiatric and psychosocial factors has a higher influence on the risk of becoming addicted to opioids than undergoing surgery with the use of opioids. In contrast, in surgical patients, preoperative opioid use and/or high pre- and/or postoperative pain levels are risk factors for long-term postoperative opiate use and abuse.[23 24] For this patient group a Transitional pain service (TPS) is a new multidisciplinary, individualized approach instituting not only multimodal pain treatment during hospital treatment, but also including non-pharmacological methods.[25 26] The TPS can be used in an early phase of peri-operative care, for risk assessment of patients on their admission to the hospital.[26] Implementation of TPS has demonstrated that opioid users can be weaned off the opioids even peri-operatively. TPS implementation can offer more control and lessen acute pain during hospital stay, reduce the duration of hospital stay, increase quality of life postoperatively, and even provide monetary savings for society.[27 28] Traditionally, face to face contact with the patient in hospital enhances mutual trust and is helpful in communication in difficult situations such as the discussion of opioid abuse. The SARS-CoV2 pandemic has dramatically reduced direct patient contact to the unavoidable, such as hands-

on treatment (such as surgery and nursing). Telehealth has replaced physical contacts where possible, to reduce risk to personnel and patients. Due to the desire to reduce physical contacts during the pandemic of SARS-CoV2 pandemic, telehealth initiatives have been adopted in the implementation of TPS.[29]

Safety aspects using RA techniques

Wrong Side Nerve Block (WSNB)

The Joint Commission considers any wrong-sided procedure, including a nerve block as sentinel event, i.e., an event requiring immediate action of the health care institution. [30 31] The incidence of a wrong sided nerve block has been reported to vary between 0 and 75 per 10,000.[31-33] Factors contributing to WSNB include: time pressure, personal factors, distraction and inadequate communication, not-visible or not existing site marking, as well as disobedience with local and global guidelines. After implementation of a pre-procedural checklist in a US hospital, the number of WSNB decreased from 4 (95% CI= 1.3-10) in 10,000 to 0 in 10,000 (95% CI= 0-1). Next to pre-procedure safety checklists a culture of safety within the department and hospital was equally important for achieving this reduction.[32] Important interventions to prevent WSNB are:

1. incorporation in a pre- (RA) procedure checklist including:
    a. Patient details (date of birth, check nametag)
    b. Operation planned
    c. Fasting status
    d. Allergies
    e. Medication such as anticoagulants, antibiotics needed
    f. *Block-site identification by visible marking*
    g. Equipment/ (emergency) medication needed for block procedure.
2. If the operation site is already marked by the surgeon before the procedure, for example on patient admission and before transport from the surgical ward to the operating or preparation room, this shall contribute to safety. As blocks are frequently performed outside the operating room it requires discipline of all staff members to perform the above checklist with only part of the team present (anesthesia).[34]

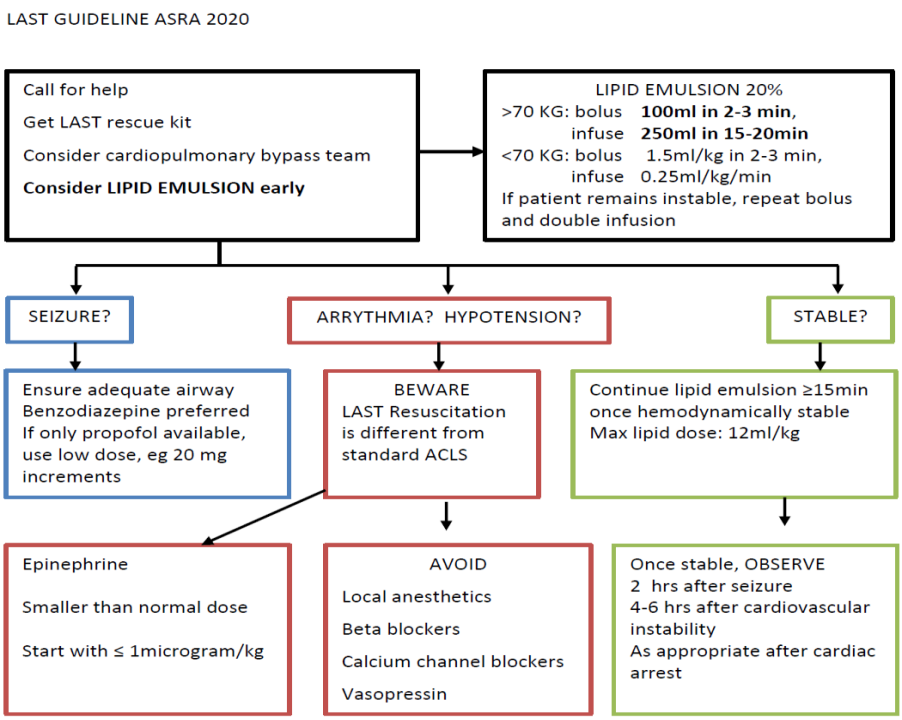
Local anesthetic toxicity

Local Anesthetic Systemic Toxicity (LAST) is a complication of RA, that can lead to mortality.[35-37] The incidence from registry and epidemiologic studies has

recently been estimated 0.27 (CI: 0.21-0.35) per 1,000 peripheral nerve blocks.[38 39] Classic symptoms of LAST described with increasing levels of LA concentrations are: metallic taste, numbness of the tongue, lightheadedness, visual and auditory disturbance, muscular twitching, unconsciousness, convulsions, coma, respiratory and cardiovascular arrest. Not all symptoms are presented in the patient in that order, but are more a general summary of possible symptoms as the plasma concentrations of local anesthetic rise. Especially neurologic symptoms not only depend on the absolute concentration but also on the steepness of rising local anesthetic concentration. Severe toxicity can also occur without any minor prodromal symptoms, especially during accidental intravascular injection.[40] Deep pharmacologic sedation can also mask these prodromal symptoms.

Updated guidelines regarding the treatment of LAST were recently published by the ASRA [41] (permission for Figure granted by ASRA)

Figure 1. Treatment of local anesthetic systemic toxicity (LAST).[41]



Recent changes are: Considering infusion of lipid emulsion 20% early even if only mild symptoms are observed. Dosing of lipid emulsion according to body weight up to 70 kg, but not higher. Changing the advanced cardiac life support (ACLS) algorithm during resuscitation with regards to adrenaline dosing (starting with ≤ 1 mcg/kg) and the recommendation to avoid other local anesthetic drugs, beta-blockers, Calcium-channel blockers and vasopressin. However, the most important change was the design of the algorithm by simulation experts, verified in simulation studies improving the readability by a less wordy version and a more process-flow format instead of a more traditional bullet-pointed design.[41]

Hygiene

Prolonged catheter use in continuous RA has been associated with infection: a prospective multicentre registry of 44,555 patients with peripheral or epidural catheters in 25 centers found an incidence of severe infections in 31 patients (0.07%).[42] Severe infection was defined as need for surgical intervention. The most important predictor of infection was the length of time that a continuous catheter technique was used, starting on the fourth day of use. Most cases with severe infection progressed from mild -being considered acceptable- to infections requiring surgical intervention. In continuous peripheral nerve block catheters, certain factors are associated with a higher infection percentage: patients on a surgical ward, the psoas compartment block site, Body Mass Index, femoral site and pre-existing diabetes mellitus. A propensity matched retrospective registry study in 11,307 patients found that single dose antibiotic prophylaxis, given as a surgical antibiotic prophylaxis, correlated with fewer infections in perineural as well as epidural catheters.[43] The 2017 ASA guidelines on neuraxial anesthesia recommendations include use of aseptic technique, sterile gown and gloves, mask and surgical cap, micropore filters for drug preparation, disposable packaging, sterile draping, chlorhexidine skin disinfection and regular block site inspection, as well as blood tests for early recognition of infection parameters.[44] Furthermore, medical equipment such as ultrasound machine, probes and gel should be free of contamination, since recent studies found a large portion of contaminations of ultrasound probes.[45 46] Covering the ultrasound machine and ultrasound probe with a sleeve is advised by the American Society of Regional Anesthesia (ASRA) during the SARS-CoV-2 pandemic, and leads to improved hygiene irrespective of an pandemic.[47] The cleaning and disinfection of all medical equipment with 80% alcohol should be a mandatory part of the hygiene measures. Ultrasound

probes are to be disinfected with designated materials such as H_2O_2 wipes or ClO_2 (Chlorine dioxide) foam. The Center of Disease Control (CDC) guideline additionally includes recommendations and alternative suitable disinfectants.[48] Ultrasound gel can in itself also be a source of contamination. Previous studies indicated that after switching from multiple-use gel dispensers to single use gel preparations the contaminations after continuous RA were vastly reduced.[49-52] Measures such as sealing multi-dose containers and not refilling containers after use are recommended to reduce risk of transmission of microorganisms.[52]

Ultrasound guided regional anesthesia (UGRA)

Ultrasound guided nerve blocks may reduce complications of RA, such as the damage of nerves. The pathophysiological explanation of nerve injury after peripheral nerve block stresses the importance of avoiding intra-neural injections. In particular, when the injections are inside the fascicles, the high pressure within the fascicle can exceed the capillary occlusion pressure, leading to ischemic and mechanical damage of the nerves and eventually permanent neurologic deficits.[53] However, even with intra-neural injection only very few patients develop any neurological damage. A study of 257 patients undergoing ultrasound guided plexus block for shoulder surgery reported 17% unintentional intra-neural injections after the block was re-reviewed by an expert, without any documented peripheral nerve injury.[54] An earlier study in 1,169 patients of ultrasound guided supraclavicular and interscalene blocks showed an incidence of post-operative neurological symptoms (PONS) of 0.4% (95% CI= 0.1-1%), and 0% (95% CI=0-0.3%) for permanent nerve injury.[55] A study of 1,000 ultrasound guided peripheral nerve blocks reported an all-cause PONS of 0.6% at six months postoperatively, and paraesthesia's during the procedure an odds ratio of 1.69 for development of PONS.[56] Recommended strategies to reduce complications of PONS include recognitions of at risk patients including pre-existent neuropathies (such as in patients with diabetes mellitus or hereditary polyneuropathy), obesity, trauma, pre-existent neurologic deficit, and nerve blocks performed in patients under sedation or general anesthesia.[57] Ultrasound guidance has not yet been proven to lower the rate of postoperative neurological symptoms or nerve injury.[58 59] To be able to prove a statistically significant reduction of long term nerve injury when comparing traditional nerve stimulation techniques with ultrasound guided nerve blocks would require about 70,000 patients in each study group (control versus intervention), assuming a long-term incidence of 4 injuries per 10,000 RA

procedures and a 50% reduction from 4 to 2 with α= 0.05 and a power of 0.80.[60] A recent analysis by ASRA focused on major complications of RA: peripheral nerve injury, local anesthetic systemic toxicity (LAST), hemi diaphragmatic paresis (HDP) and pneumothorax.[60] Propensity matched analysis demonstrated that the use of ultrasound guided nerve blocks reduced the incidence of LAST by 65%: Ten LAST events in 4,745 (2.1/1,000; 95% CI 1-3.9) non-ultrasound blocks vs. 12 events in 20,401 (0.59/1,000 95% CI 0.3-1.03) ultrasound blocks . Hemi diaphragmatic paresis (HDP) , as a consequence of interscalene and supraclavicular block is more frequently encountered when higher volumes of local anesthetic (LA) are used. Studies have shown that reducing the volume of LA from 20 ml to 5 - 10 ml decreases the incidence of HDP. Reduction of ropivacaine 0.75% from 10 to 5 ml lowered HDP (chest x-ray diagnosed) from the original 60% to a new 33%.[61 62] The historic incidence of pneumothorax as a consequence of classic supraclavicular block was estimated to be around 6%.[63] Recent estimates report the incidence of pneumothorax at 0.4/1,000 (95% CI 0.01-2.3).[64]

Unintended vascular puncture is a surrogate marker for LAST, as the intravascular injection of local anesthetics can cause symptoms associated with LAST. Vascular puncture has been reported as a secondary endpoint in 27 RCTs including a total of 1867 patients. Compared to peripheral nerve stimulation, ultrasound guidance significantly reduced the incidence of vascular puncture.[60]

Even if there was a reduction of LAST, HDP and pneumothorax, UGRA did not eliminate all complications or unintended effects. The risk of HDP ranged between 0 - 34% of supraclavicular brachial plexus blocks, which is a reason for caution in patients with compromised pulmonary function. A recent study of 20 patients demonstrated that LA volumes as low as 5 ml still can cause HDP.[65] The ASRA compared UGRA with other nerve localization techniques for regional nerve block performance and concluded: [66]

upper extremity anesthesia: UGRA superior regarding time to do the block, sensory onset time, number of needle attempts, and incidental vascular puncture.
lower extremity anesthesia: UGRA superior regarding block performance time, sensory onset time, decreased anaesthetic requirements, success rate.

truncal blocks: UGRA superior in pectoralis nerve block, transverse abdominal plane block, rectus sheath ilioinguinal and iliohypogastric block.
Neuraxial block: UGRA assistance improves accurate measurement and efficacy of neuraxial anesthesia (particularly: less technical failure and reduced amount of needle passes).

Medication errors and RA connectors, NR fit

The erroneous administration of medication through a wrong route has been described before and is a significant patient safety challenge. For example, intravenous instead of enteric administration of milk (due to the ordering of 'milk drip') was described.[67] Several other cases of fatal outcome have been published due to administration of enteral feed or medication through an intravenous route.[68] This was possible because the Luer-lock of intravenous and enteral lines could be mistakenly interchanged, as they all fitted each other. Meanwhile, the implementation of dedicated connectors has largely solved this problem.[69]

The Joint commission alert described adverse events due to other types of misconnections, and recommend the use of the dedicated ISO connectors for RA lines.[70] Transient spinal paralysis with tetraplegia and cardiac and respiratory failure have been described after continuous potassium chloride dosing epidurally.[71] [72] A review reported 4 maternal deaths from accidental intrathecal administration of tranexamic acid.[73] Another review of the literature between 1960 and 2018 described 21 cases of accidental spinal administration of tranexamic acid, with fatal outcome in 10 cases. In one patient the spinal catheter was mistaken for an intravenous line.[74] Drug administration errors in anesthesia have been reviewed in various studies.[75-79] Llewellyn found 66 medication error incidences per 30,412 cases. Dosing via incorrect route was found in 7 cases, with 2 cases of intravenous instead of epidural dosing of local anesthetics.[75] Webster et al. found 79 errors in 7,794 patients, of which 2 cases concerned local anesthetic dosed intravenously instead of epidurally.[77] Sakaguchi et al. found 50 medication errors in 64285 anesthesia cases, and 4 were wrong route errors.[79] Complications due to "wrong route medication errors" have also been documented in other studies.[80] [81] A recent review, including 133 "wrong route" case studies over a 20 year period found that epidural medication was given intravenously in 29% of events, intravenous medication administered epidurally in 28% and intravenous medication given intrathecally in 25% of cases.[82] The intravenous dosing of

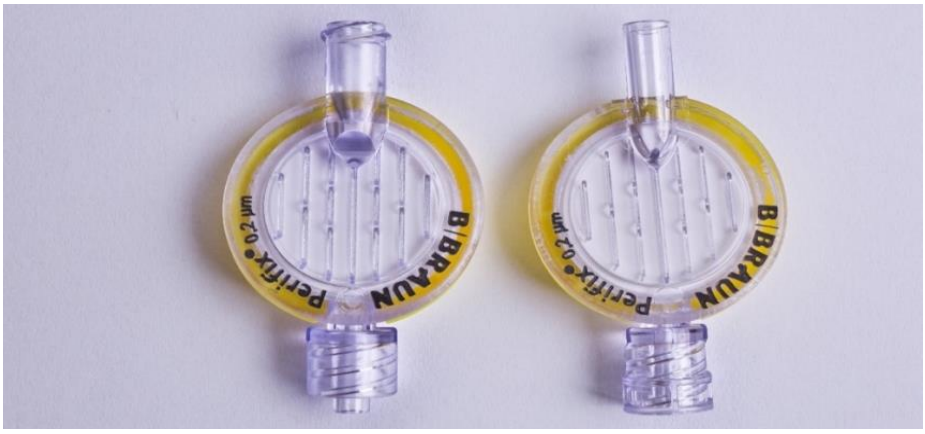
bupivacaine was lethal in 4 cases.[82] Due to underreporting of complications, it is difficult to know the exact incidence of accidental wrong route medication errors with catastrophic outcome. To prevent fatal events as described, specific connectors have been developed for various routes of access, recognized by the international organization of standardization (ISO). These include: enteral, cuff inflation, neuraxial, intravascular. There are different types of connectors, dependent on their route of administration A dedicated system was designed to be used solely with local anesthetics (neuraxial, nerve blocks) for single shot and continuous administration. It has been designed in such a way that it does NOT fit the classic Luer syringes, tubing and needles; the "NR fit" (ISO 80369-6) was developed for neuraxial and perineural use only.[73 81 83] A multicentre simulation study investigating ease of use and possible misconnections rated 109 out of 110 connections (simulating procedures cross-connecting Luer connections and non Luer neuraxial NR fit, and enteral EN fit connections) a good overall performance with easy connections, where Luer to non-Luer connections were non-functional or leaky.[84] An earlier study with an artificial back model compared a Luer with Non-Luer system, and found that the safety system was clinically acceptable for 93/ 98 procedures, and 48 /49 doctors agreed that the system would reduce the risk of misconnections, or even prevent them.[85]

Potential advantages of this system – if properly implemented – are the dedicated use of syringes, tubing and neuraxial connectors for RA procedures. If medication meant for RA is prepared in dedicated syringes and the entire system would be implemented universally, it would be almost impossible to unintendedly dose medication over an intravenous access, as the syringes are not interchangeable. Additionally, colour coding and bar coding of medication can add to patient safety.[86-89]

Disadvantages and risks of NR fit include: 1. Discipline is needed to use the system 2. There is a sparsity of clinical trials in patients concerning NR fit, proving its safety in daily use. It seems, however, nearly impossible to conduct such a trial, given the low incidence of these complications. 3. Single shot medication errors such as those described after spinal administration of tranexamic acid, can only be reduced by double checking the medication AND the route of its administration.[74 90] Implementation of the new NR fit system is slow, in spite of legislation and possible litigation, because of practical aspects of the introduction

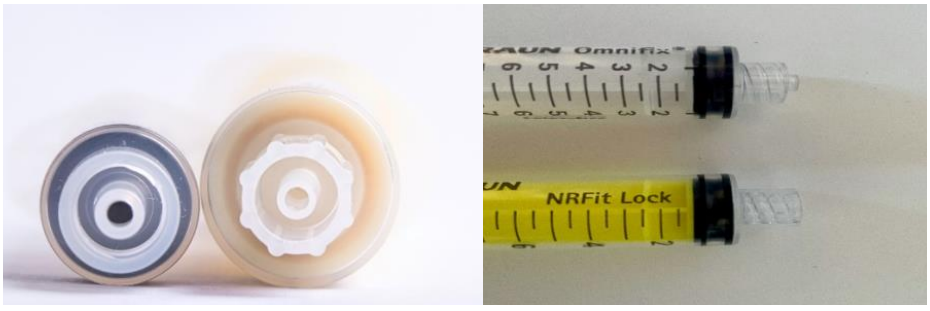
of a new system not only in one department, but all departments of a hospital and a whole country, which might play an important role in case of interhospital transfer of patients. Only a combined effort by anesthesiologists, in cooperation with nursing personnel, medical equipment manufacturers and in particular the national and international health organizations could make a significant difference and solve this problem.

Figure 2. Two types of epidural filter.



Left: standard luer lock ('old type' ISO 80369-7 connection); Right: new NR fit neural connector (ISO 80369-6) is 20% smaller

Figure 3. Comparison of old and new type, front and side view.



NR fit on the right side. **NR fit (yellow) at bottom**

Regional anesthesia during the SARS-CoV-2 pandemic [91,92] and patients with other droplet- or aerosol-transmissible diseases

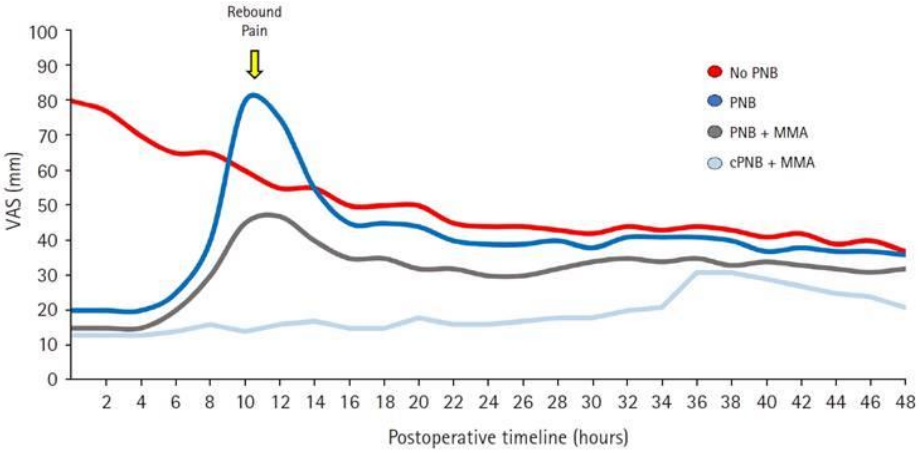
Diagnostic or therapeutic procedures performed under RA can avoid aerosol or droplets producing procedures during sedation or general anesthesia. The preservation of pulmonary function during RA and the decreased frequency of postoperative nausea and vomiting are advantageous for patients with pulmonary problems. Practice guidelines have recently been published by the European Society of Regional Anesthesia (ESRA) and ASRA, regarding RA in the potentially SARS-CoV-2 positive patient.[47] Neuraxial anesthesia and peripheral nerve blocks do not lead to increased aerosol or droplet formation, as there is no airway management involved. Therefore, RA procedures are not classified as aerosol generating procedures by the WHO and therefore considerably less infection preventions measures must be taken. In pulmonary compromised patients undergoing upper extremity surgery, axillary or infra-clavicular brachial plexus block are preferred over supraclavicular or inter-scalene brachial plexus block in order to minimize the chance of HDP or pneumothorax. The ultrasound machine and controls should be protected by a single use plastic cover.[91] Some disadvantages, however, also exist, including that trainees would not be the first choice in performing the blocks, as the success percentage is vital to avoid conversion to general anesthesia. The operating room will be in use by the anesthesiologist during block procedure, and will eventually cause delay since a specialized blocking room should be used for infected patients. The dosing of LA is of paramount importance, as the block will have to sufficiently last during the whole surgical procedure, while LAST should be avoided. Equipment will be considered contaminated and should meticulously be disinfected after treating a SARS-CoV-2 positive patient.

Rebound pain after RA

Rebound pain has been described as a quantifiable difference in pain scores between timepoints when the block is still working correctly, versus the scores after the block has worn off (Figure 4).[93 94 95]

(Figure adapted from: Levya et al., *Managing rebound pain after regional anesthesia, Korean Journal of Anesthesiology 2020; 73(5): 372-383*)

Figure 4. The phenomenon of rebound pain after RA



PNB, Peripheral nerve block; cPNB, continuous peripheral nerve block; MMA, Multi modal analgesia; VAS, Visual analogue scale of pain;

The rebound pain is disproportionately higher, *i.e.,* higher than in control group without nerve block. This may be related to lower dose of applied opioids or other analgesics until the block wears off, or the rapid onset of pain at the end of the block.[96-98] A meta-analysis showed rebound pain in patients undergoing a single-shot inter-scalene block for shoulder surgery, occurring between 16 and 24 hours after surgery.[99] In most clinical cases that will mean occurrence of pain during night hours with less distraction and a peri-operatively disturbed circadian rhythm leading to subjectively exaggerated pain sensation.[100-102] Apart from the local blockade of sodium channels, LA have a multitude of local and systemic actions.[103] Most of them will disappear synchronized after a single shot application and therefore their vanishing systemic action might also contribute to rebound pain. Risk factors for the development of rebound pain were younger age, bone surgery, as well as absence of perioperative dexamethasone use.[104]

Until today, the phenomenon of rebound pain is insufficiently understood and investigated to allow evidence-based advice to overcome or even better prevent rebound pain. However, a multimodal strategy including Non-steroidal anti-inflammatory drugs (NSAIDS), alpha 2 agonists, dexamethasone, esketamine, avoidance of short-acting opioids as well as the increased use of continuous

catheter techniques or single-shot blocks with adjuvants are candidates to ameliorate or abolish rebound pain.[94]

Conclusion

To summarize, RA technique is continuously evolving, while accuracy and safety of different blocks are also improving over time. In addition, RA can be used to help solve hitherto unknown problems. A typical example is the opioid crisis, promoting the perioperative use of RA techniques in order to decrease acute postoperative opioid requirement and avoid post-hospitalization opioid prescriptions. Similarly, during the SARS-CoV-2 pandemic the advantage of RA in leading to decreased transmission of airborne infections in comparison with general anesthesia was demonstrated. Transitional pain services are being established in order to preoperatively identify patients prone to a high risk of postoperative pain. Again, RA is one of the most powerful tools in these difficult patients to decrease and/or stop postoperative opioid requirement and improve pain treatment. Recent developments such as UGRA, avoidance of wrong sided nerve block, increased hygiene measures, improved algorithms to treat local anesthetic systemic toxicity and RA specific connectors (NR fit) are advances which could further improve safety of RA. Despite all these improvements in RA, unfortunately, new negative phenomena are being discovered, e.g. rebound pain, and we need to describe therapeutic strategies to avoid this side effect.

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Chapter 3

Comparison of patient controlled versus continuous epidural analgesia in adult surgical patients: A systematic review

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Abstract

Objective

To assess possible advantages of patient controlled epidural analgesia (PCEA) over continuous epidural analgesia (CEA) in surgical patients.

Background

Advantages of PCEA over CEA have been demonstrated in obstetric patients. Whether similar benefit applies to surgical patients is unclear.

Methods

Embase, PubMed and Cochrane library were searched, enabling systematic review of studies comparing PCEA and CEA in adult surgical patients (PROSPERO: CRD42018106644). Study quality was assessed using Cochrane Risk-of-Bias tool (RoB2). Primary outcome: pain score on postoperative day one (POD1). Secondary outcomes: 24- or 48-hour epidural or intravenous total analgesic dose, manual top-ups and patient satisfaction.

Results

Eleven trials (ten RCTs, one cohort-analysis, 1687 patients) with high heterogeneity of study characteristics were identified with a high to intermediate risk of bias. Three studies showed reduced pain scores on POD1 in PCEA compared to CEA patients (36-42%, $P<0.05$). Seven studies found comparable pain scores between groups, one study a higher pain score in PCEA patients. PCEA-use reduced epidural medication (28% to 76% reduction, $P <0.01$) in seven studies. Two studies found lower top-up frequency in PCEA; PCEA patients used less intravenous morphine (0.16 vs 3.45 mg per patient, $P<0.05$) in one study, and more satisfied with analgesia in two studies.

Conclusion

Regarding pain scores, rescue systemic analgesics and patient satisfaction, PCEA in surgical patients had limited advantages over CEA. PCEA reduced amount of epidural medication and top-up frequency. On the basis of current available evidence, we cannot conclude that PCEA offers major benefits over CEA in surgical patients.

Introduction

Epidural analgesia is still considered standard of care for major upper abdominal or thoracic surgery.[1-4] However, epidural analgesia is known to have a failure rate as high as 30% and therefore frequently requires epidural top-ups and/or systemic analgesic rescue medication.[5]

During labour the superiority of patient controlled epidural analgesia (PCEA) compared to continuous epidural analgesia (CEA) has been proven in numerous clinical studies, and has been confirmed in systematic reviews with meta-analyses.[6-9] PCEA during labour induced superior analgesia with reduced drug requirements when compared to CEA. PCEA is most commonly implemented by manual boluses of local anaesthetic on top of a baseline infusion, by the patient. One of the factors involved in inferiority of constant epidural infusion may be progressive regression of the block. A higher infusion rate is associated with more usage of local anaesthetic and more maternal block in obstetrics, possibly contributing to higher rate of instrumental deliveries.[8 10] The additional cost of purchasing special pumps and training of personnel is justified if PCEA is superior. In contrast, the efficacy of PCEA in a surgical (non-obstetric) population has been investigated less frequently, lacking systematic reviews or meta-analyses. Results from a relatively homogenous population of young and healthy females with uniform indication for short term peri-partum analgesia may not be justified in a totally different population including males, elderly, including higher ASA categories and concomitant medication for a variety of operations requiring a longer stay in hospital. Therefore, we performed a systematic review of studies comparing PCEA and CEA in the adult population undergoing non cardiac and non-obstetric surgery to examine evidence pertaining to: 1. pain scores; 2. Total 24- or 48-hour amount of epidural and intravenous medication used; 3. number of manual top-ups required; 4. use of additional systemic analgesics; and 5. patient satisfaction.

Our hypothesis, based on evidence in the obstetric population, was that employment of PCEA compared to CEA leads to reduced pain scores in rest and movement. Further, we expected reduced use of epidural medication, a reduction in top-ups and reduced use of systemic analgesics, with improved patient satisfaction in the PCEA group. Our aim was to investigate and compare

the existing methods of epidural analgesia in non-obstetric patients undergoing surgery. Our secondary aim was to ascertain which method offers the best analgesic benefit and least amount of side effects.

Methods

The review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with number: CRD42018106644. The guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were followed.[11] Embase (Ovid), PubMed and the Cochrane library were searched for studies performed before 23rd February 2021, to identify relevant trials. Search terms and search strategy are described in Appendix 1.

Inclusion criteria: **P**atients: adult surgical patients receiving perioperative epidural analgesia; **I**ntervention: patient controlled epidural analgesia (PCEA, with or without continuous background infusion); **C**omparator: conventional CEA; **O**utcome parameters: Our primary outcome was post-operative pain *during rest* on day 1 (Visual analog scores or comparable scores, and/or Numeric Rating Scale). Secondary outcomes were: 1. Postoperative pain *during movement* on day 1; 2. amount of epidural medication used; 3. number of top-ups required; 4. use of systemic analgesics; and 5. patient satisfaction. We defined a difference of 2 in mean pain scores (in a scale of 0-10) between groups as a meaningful clinically important difference, when one of the mean scores is ≥4, signifying the threshold of treatment.[12] To enable better comparison with the obstetric studies which have a relatively short duration of epidural treatment, we chose day 1 pain scores as primary endpoint.

Exclusion criteria: patient age < 18 years, obstetric patients during labour, language not native to at least two team members (Chinese, Spanish, French, Russian, Korean, Japanese), conference abstracts or communications, comparison using PCEA followed by CEA or vice versa in the same patient, use of Programmed Intermittent Epidural Bolus instead of PCEA, type of publication other than a randomized controlled trial (RCT) or cohort analysis. We included cohort analyses to enable a more complete comparison in case there was an insufficient amount of RCTs found in the search. Titles and/or abstracts of studies retrieved using the

search strategy were screened on Rayyan.qcri.org independently by two review authors (GvS and YRT) to identify studies that met the inclusion criteria. Conflicts in this stage were resolved by a third reviewer (MFS). The full text of potentially eligible studies was retrieved and independently assessed for eligibility by two review authors (GvS and YRT). Any disagreement between them over the eligibility of particular studies were resolved by discussion with a third reviewer (MFS). After final selection of studies to be included, a predefined data extraction form was used (by GvS and YRT) to extract data from the respective studies for assessment of study quality and evidence synthesis (Appendix 2).

The risk of bias in included studies was assessed according to the guidelines of the Cochrane collaboration, using the Cochrane risk of Bias tool (RoB2).[13 14]

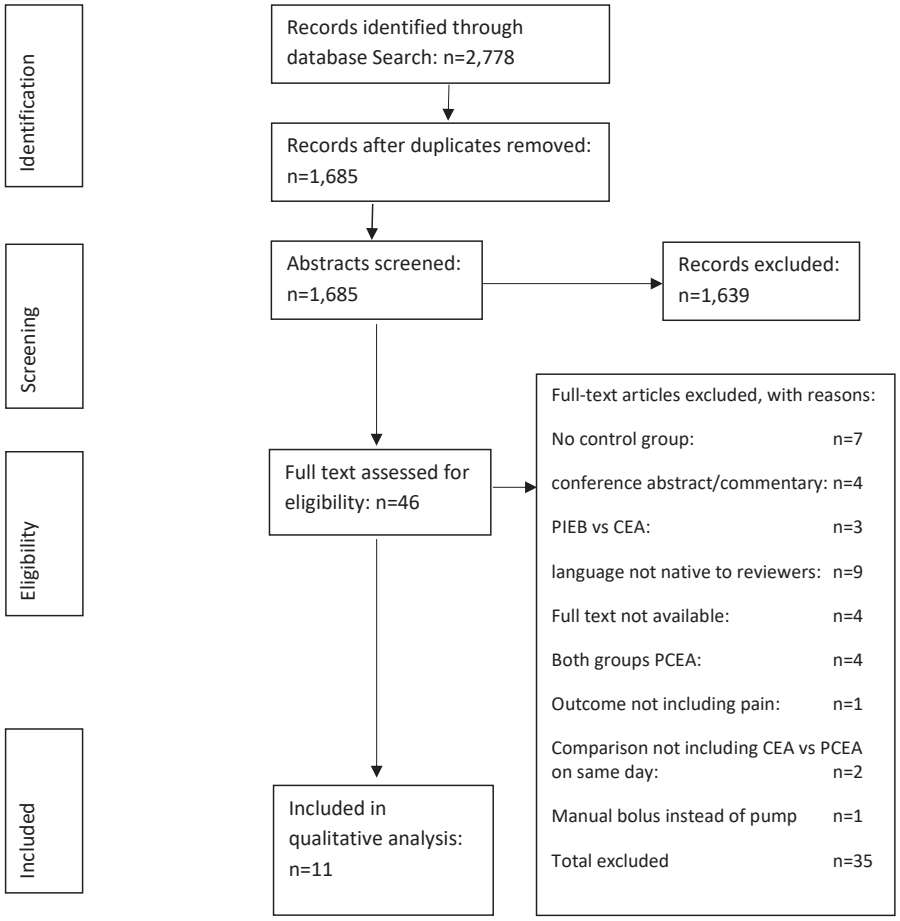
Meta-analysis

Meta-analysis of data was to be performed using Review Manager 5.4 software of the Cochrane center, when two or more RCTs were available for a specific outcome. Between-study variance (Tau^2) and the statistic I^2 was to be computed to estimate the percentage of variability in effect sizes that cannot be explained by sampling error. We defined statistical heterogeneity as high when $I^2>50$. Forest plots were to be used to present data when appropriate for specific outcomes. We intended to perform type of surgery specific sub analysis if 4 or more studies were retrieved in patients undergoing the same type of surgery. If studies had multiple arms using different epidural medication in comparing PCEA and CEA, we analyzed outcome of the arms separately in tables and Forest plots.

Results

The systematic search (1989- 23 Feb 2021) yielded a total of 2,778 studies. The PRISMA study selection flow diagram is depicted in **Figure 1**. After deduplication, 1,685 studies were screened for title and abstract. Finally, we were able to select eleven studies including 1,687 patients (ten RCTs and one cohort analysis).[15-25] Reasons for exclusion are specified in **Figure 1**. The methodological quality of the studies was mostly moderate with the exception of three studies. Two studies had a low risk of bias, and one study had a high risk of bias (no randomization). The risk of bias assessment is specified in **Figure 2**.

Figure 1. Study selection flow diagram.

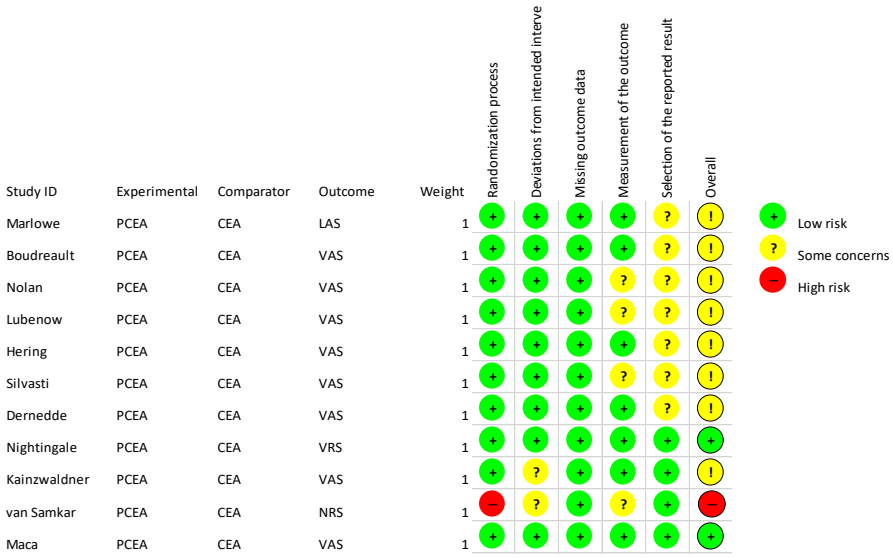


Outcomes

Baseline characteristics (type of surgery, patient population, location of epidural, PCEA/CEA regimen) are described in **table 1**. The studies were heterogeneous in nature, including colonic, upper and lower abdominal surgery, total knee replacement, total hip replacement, pelvic surgery, major abdominal surgery, urological, breast, orthopedic, thoracic and vascular surgery. ASA categories of included patients ranged from I-III. The mean age of included patients ranged from 33 to 74 years. The levels of insertion of the epidural catheter varied from T7 to L4. Epidural solutions used were: bupivacaine (0.1-0.125%) or levobupivacaine

(0.15-0.5%) or ropivacaine (0.2%), with or without addition of opiates (fentanyl 1-10 micrograms/ml or sufentanil 1 microgram/ml). Continuous infusion rate of PCEA regimens varied from 4-10 ml/h and bolus rates varied from 1-5 ml/bolus.

Figure 2. Risk of Bias assessment



PCEA: patient controlled epidural analgesia, CEA: continuous epidural analgesia, LAS: Linear Analog Scale, VAS: Visual Analog Scale, NRS: Numeric Rating Scale.

Primary endpoint

Pain scores: All studies reported resting pain scores. Nightingale et al. presented area under the curve (AUC) in for pain (PCEA 15.6 vs CEA 32, P<0.001). We calculated means of Wessex VRS score (0-3 scale) from the original diagram to enable comparison with a 1-10 score as used by other authors.[25]

Of the eleven studies included, three studies found significantly reduced pain scores on the first postoperative day in patients treated with PCEA (**table 2**): pain scores were reduced by 36-53% in favor of PCEA. However, none of these studies found a meaningful clinically important difference between groups (predefined as a difference of 2 in mean pain scores in a 0-10 scale),[17] all studies showed an average pain score <3 in both groups, indicative of adequate pain control.

Table 1. Basic characteristics of included studies.

Author Year	Marlowe 1989	Boudreault 1991	Nolan 1992	Lubenow 1994	Hering 1997
Study type	RCT	RCT	RCT, PB	RCT	RCT
N: PCEA/CEA	8 / 8	8 / 8	11 / 12	31 / 31	15 / 15
ASA category	NR	1-2	1-2	1-3	1-3
Age: PCEA/ CEA	55/54	54/59	33/35	57/60	62/63
Surgery	ORT/TH/ UABD LABD	ABD	PEL	TH/GEN/ URO/ORT GYN	MABD
Epidural	L2-4	T7	L2-4	NA	T10-L4
PCEA medication, speed, Bolus LOP	Hydro-morphone BOL 0.15-0.3mg; LOP 15-30min	Bup 0.1% + Fen 10µg/ml; 0.1ml/kg/h; BOL 2ml; LOP 12 min	Bup 0.125% + Fen 1µg/ ml; 4ml/h; BOL 3ml; LOP 15min	Bup 0.1% + Fen 10µg/ ml; 5ml/h BOL 1ml; LOP 10min	Bup 0.125% + Suf 1µg/ml + clo 3µg/ ml; 3ml/h BOL 5ml; LOP 20min
CEA medication, speed	Hydromor-phone 0.15-0.3mg/ h constant.	Bup 0.1% + Fen 10 µg/ml; 0.1 ml/kg/h	Bup 0.125% + Fen 1µg/ ml. 10ml/h	Bup 0.1%+ Fen 10µg/ ml: 5ml/h; increase by nurse.	Bup 0.125% Suf 1µg/ ml+clo3µg/ ml; 5-8 ml/h
Rescue opiates	NR	No	NR	Mor: 1-2mg /2h	No
Co analgesics	NR	No	NR	NR	NR
Pain Service	Research nurse	No	APS	APS	NR

Abbreviations: RCT=Randomized Controlled Trial; PB=Patient blinded; DB=Double blinded; PCEA=Patient controlled epidural analgesia; CEA=Continuous epidural analgesia; NR=Not Reported; ASA=American Society of Anesthesiologists; ORT=Orthopedic; TH=Thoracic; ABD=Abdominal; UABD=Upper Abdominal; LABD=Lower Abdominal; PEL=Pelvic; GEN=general; MABD=Major Abdominal; GYN=Gynecological; TKA=Total knee arthroplasty; COL=Colonic resection; BR=Breast; VAS=Vascular; THR=Total hip replacement; Bup=bupivacaine Lbup=Levobupivacaine; Ropi=Ropivacaine; Fen=Fentanyl; Suf=Sufentanil; Mor=Morphine; Oxy=Oxycodone; LOP=Lock out period; BOL=Bolus dose; clo=clonidine; Par=paracetamol; PPar=Proparacetamol; KL=ketorolac; Dicl=diclofenac; Met=Metamizole; ICU=hourly evaluation at intensive care unit.

Silvasti 2001	Dernedde 2006	Nightingale 2007	Kainzwaldner 2013	v. Samkar 2017	Maca 2018
RCT, DB	RCT	RCT	RCT	Cohort	RCT
26 / 23	21/20[#] 21/21	104 / 101	305 / 401	187 / 199	55 / 56
1-3	1-3	NR	NR	1-3	1-3
71/74	55/60[#] 54/60	68/69	61/61	62/60	66/70
TKA	LABD	COL	PCEA:URO/ ABD/BR CEA:ABD/ ORT/TH/VAS	MABD/TH	THR
L2-3	T8-10[#]/ T10-L1	TH	NA	T6-L2	L2-3
Bup 0.11% + Fen 5µg/ml; 0.1ml/kg/h; BOL 0.05ml/ kg; LOP 10min	Lbup 0.15% 3.3ml[#] or 0.5% 1ml BOL only; LOP 20min	Bup 0.125% + Fen 4µg/ ml; 8ml/h; BOL 3ml; LOP 20min	Ropi 0.2% + Suf 0.24µg/ml; 4-10ml/h; BOL 3ml/h; LOP 1h	Bup0.125%+- Suf 1µg/ml; 6ml/h; BOL 2ml; LOP 20min	Lbup 0.1% + Suf 1µg/ ml; 3ml/h; BOL 4ml; LOP 20min
Bup 0.11% +Fen 5µg/ ml;0.1ml/kg/h BOL 0.2ml, LOP 10min	0.5% Lbup 3ml/h[#] or Lbup 0.15%; 10ml/h	Bup 0.125% + Fen 4µg/ ml; 15 ml/h	Ropi 0.2% + Suf 0.24 µg/ ml ; 4-10ml/h	Bup 0.125% + Suf 1µg/ml ; 10ml/h	Lbup 0.1% + Suf 1µg/ ml, 5ml/h BOL: 8ml; physician
Oxy 0.15mg/ kg im.	Mor sc. 1x/4hrs.	NR	NR	No	Tramadol
Par 3x1g/d.	PPar 4x2g/d. KL 60mg 4x/d.	NR	NR	Par 4x1g/d; Dicl 3x50/d or Met 4x1g/d	Par; Met
APS	APS	APS	APS	APS	ICU

Table 2. Outcome parameters of included studies

Author Year	**Marlowe 1989**	**Boudreault 1991**	**Nolan 1992**	**Lubenow 1994**	**Hering 1997**
	PCEA / CEA	PCEA / CEA	PCEA / CEA	PCEA / CEA	PCEA / CEA
Primary end-point	Pain score LAS (0-10)	Pain score VAS (0-10)	Pain score VAS (0-10)	Pain score VAS (0-10)	Pain score VAS (0-10)
24h Pain score resting mean (sd)	1.3(1.7)/ 1.6(1.0)	1.7(0.2)/ 1.0(0.2) (SEM)	2.6 (0.4-7.2)/ 1.4 (0-7.8) range	2.7(2.9)/ 4.2(2.3)	0.4(0.4)/ 0.4(0.5)
P	NS	NS	NS	P<0.05	NS
24h Pain score motion	*	*	*	*	3.4(1.1)/ 1.9(1.1)
P					P<0.01
Mean(sd)pcea/ cea epid.drug [time]	4.6(2.2)/ 10.2(3.6) Hydroxy-morphone mg [48h]	405(110)/ 1600(245) Fen µg [24h]	316(34)/ 341(41) Bup ml [24h] SEM	219(140)/ 307 (80) Bup ml [48h]	112(33)/ 135(20) ml [24h]
P value	0.005	0.001	NS	<0.01	<0.01
Side effects	NS	NS	NS	NS	NS
Patient satis-faction	NS	NS	NS	NR	93%/100% NS
Other				Mean iv morphine 0.16(0.9)/ 3.45(7.7) mg per patient P<0.05	

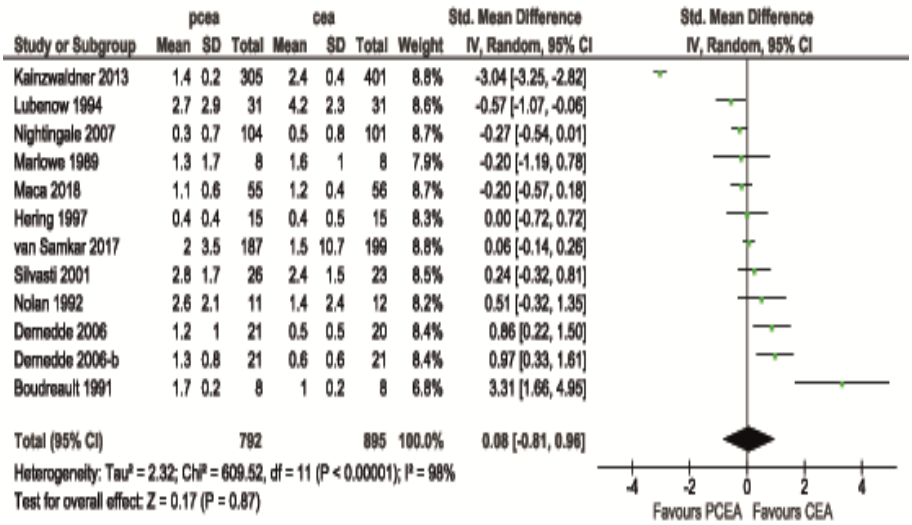
NS=No Significant difference SEM=standard error of mean is reported instead of sd.*Not specified if pain scores were measured in rest or movement. #=0.15% (2 concentrations of local anesthetic used in study, 0.5% is without marking) ^=AUC of Wessex pain score ^^=Mean Wessex Pain score.(0-3 scale) ~lower abdominal surgery, values from figure .

Silvasti 2001	**Dernedde 2006**	**Nightingale 2007**	**Kainzwaldner 2013**	**v. Samkar 2017**	**Maca 2018**
PCEA / CEA	PCEA / CEA 48h	PCEA / CEA	PCEA / CEA	PCEA / CEA	PCEA / CEA
Pain score VAS (0-10)	Pain score VAS (0-10)	Pain score VRS (0-3)	Pain score NRS (0-10)	Top-ups	Pain score VAS (0-10)
2.8(0-6.8)/ 2.4(0-6.0) Range NS	1.2(1)/0.5(0.5)# 1.3(0.8)/0.6(0.6) P=0.01# P=0.03	15.6(24)/ 32.2(34.7)^ (AUC all scores were <1) P<0.001	1.4(0.2)/2.4(0.4) From figure~ P=0.006	2(1.5_2.5)/ 1.5 (0-3) NS	1.1(0.6)/ 1.2(0.4) NS
3(0-10)/ 4.6(0-8) Range NS	NR	0.81(0.6)/ 1.23(0.7)^^ P<0.001	3(0.2)/4.1(0.4)~ P=0.006	3(1_5) / 3(2_5) P=NS	NR
74(24)/ 124(20) Bup ml [20h]	170(103)/720# 182(110)/720mg [48h]	NR	NR	NR	0.9(0.3)/ 1.3(0.4) ml/kg/d
<0.001	<0.001	-	-	-	<0.001
NS	NS	NR	NS	24/35% P=0.02	
NS	NS	76/43% P<0.0001	95%/91% NS	NR	4.3(1)/ 2.8(0.7) P<0.001
VAS (0-50) recalculated to 1-10 score	Motor block (n) 0 / 2 (P=0.48)# 1 / 8 (P=0.04)	Top-ups: 13%/36% P=0.0002	Adjustment epidural: 10%/23% of patients P= 0.0001 (calculated)	Top-ups: 10%/29% P=0.0001 Rate adjust: 1.6%/8.5% P=0.002	Satisfaction in 0-5 Likert scale, higher is better.

One study with a PCEA regimen without background infusion found statistically *higher* mean pain scores in the PCEA group (at 20 hours in 1.5 mg levobupivacaine /ml group and at 5 hours in 5 mg levobupivacaine/ml group).[24] All pain scores in this study had a mean value below two, suggestive of clinically adequate analgesia. Five studies provided information about pain scores during motion,[19 20 22 23 25] from which two studies observed that PCEA patients had lower pain scores during motion compared to CEA treated patients.[19 25] One study found higher pain scores in PCEA patients during motion (3.4 vs 1.9 on VAS).[22]

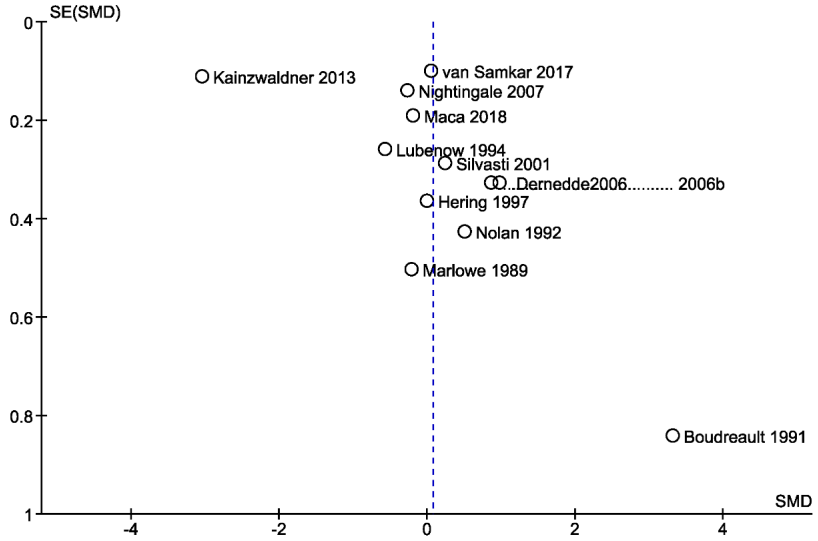
The Forest plot (**Fig3**) is arranged in order of studies favoring PCEA followed by studies favoring CEA, and suggests different effect sizes in the different types of populations. Four arms of the study by Dernedde et al. are represented separately for sake of analysis, as different local anesthetic concentrations were used in the arms.[24] The degree of heterogeneity is high, signified by Tau^2 (2.32) and I^2 (98%). Therefore, significance testing in combined effect size is not meaningful.

Figure 3. Forest plot of studies comparing PCEA vs CEA



PCEA, patient controlled epidural analgesia. CEA, continuous epidural analgesia.

The heterogeneity is further illustrated by the funnel plot (**Fig4**).

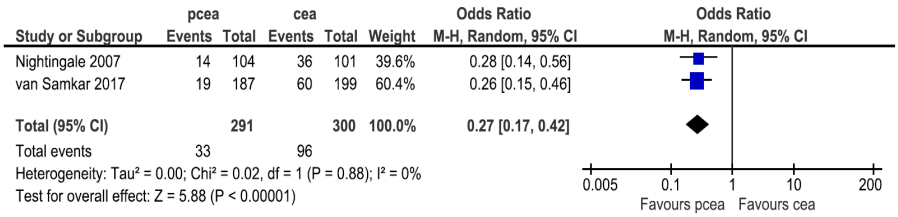


Secondary endpoints:

Epidural medication: Seven out of eight studies found a significant reduction in epidural drug use by 25-75% in PCEA patients.

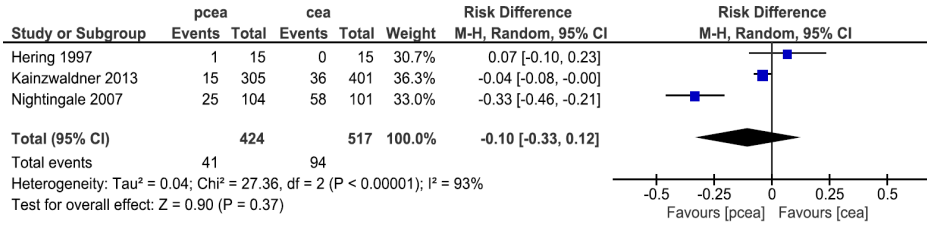
Top-ups: Two studies found a reduced number of epidural top-ups in PCEA patients from 23% to 10% and from 29 to 10%, respectively (**Fig5**).[20 25]

Figure 5. Epidural top-ups



Patient satisfaction: In two studies, the percentage of good patient satisfaction was higher in PCEA patients (76% vs 43%, and a Likert score of 4.3 vs 2.8).[21 25] Two other studies did not find a difference in patient satisfaction; however, the control groups of these studies already showed a satisfaction percentage of 90% or higher (**Fig 6**).

Figure 6. Patient satisfaction



Use of intravenous rescue medication: One study found lower requirement of intravenous morphine (mean dose per patient: 0.16 vs 3.45 mg) in PCEA patients.[18]

Discussion

In surgical patients there is little evidence that PCEA has significant and clinically relevant advantages when compared to CEA in regards to pain scores, amount of medication used for epidural analgesia or rescue analgesia, or patient satisfaction. PCEA does reduce the dose of epidural medication and the requirement for additional top-ups. Furthermore, PCEA can increase patient satisfaction if the satisfaction with CEA is not already above 90%.

While eight studies found no difference in pain score between groups, three studies found lower scores in the PCEA groups: Firstly, Lubenow et al. found mean scores of 2.7 vs 4.2 in a study of 62 patients undergoing various surgical procedures. Secondly, Nightingale et al. calculated an area under the curve of the Wessex pain score (0-3 scale) and found that PCEA halved the area under

the curve of pain scores in patients undergoing colonic surgery. However, all average pain scores at rest were below 0.5 in both groups at any time and thus the statistically significant differences are not clinically meaningful. Thirdly, Kainzwaldner et al. performed a four-armed study, with two arms concerning PCEA and CEA. A subgroup analysis of patients undergoing lower abdominal surgery showed lower pain scores for PCEA in the first three days postoperatively (1st day: 1.4 vs 2.4). Thus, in none of the three cited studies the difference in pain scores was a meaningful clinically important difference. In contrast, Dernedde et al. found *higher* pain scores in PCEA at some time points. But again, both groups had average pain scores < 3. Thus, PCEA did not provide a clinically meaningful difference in any study.

Hering et al. found that patients receiving PCEA had higher pain scores during motion (3.4 vs 1.9), which again has limited clinical relevance.[26] Nightingale et al. found that pain scores in motion were lower in PCEA (Wessex scores: 0.81 vs 1.23). As a rating of one is mild and two is moderate in the Wessex score, the clinical relevance of this difference seems of limited importance. Similarly, Kainzwaldner et al. found lower pain scores in PCEA (3 vs 4.1). Thus, although PCEA significantly decreases the pain score in motion, again the difference is small and clinically negligible because of relatively low pain scores in the control (CEA) group.

A significant reduction of epidural medication by PCEA has been demonstrated in seven studies. Although that may be a theoretical advantage regarding side effects or possible local anesthetic toxicity, no study could demonstrate an advantage regarding side effects of a lower versus higher epidural medication dose.

Reduction of additional i.e. manual top-ups may lead to cost savings depending on hospital logistics around epidural top-ups.[20] This may be offset by the additional cost of PCEA devices compared to a standard CEA pump.[27] Our analysis showed that PCEA patients had a time investment regarding top-ups of 16 minutes per patient versus 56 minutes per patient for CEA patients.[20]

Analysis of the retrieved studies showed that PCEA can increase patient satisfaction, however a difference could only be shown if the control (CEA) group does not yet have a high patient satisfaction (> 90%). This seems surprising as pain scores

or other side effects were not meaningfully different between the treatment groups. A psychological effect of PCEA through placebo effect and impression of self-control for pain treatment could have contributed to these findings.

A recent Cochrane review demonstrated the benefit of PCEA in obstetrical patients in reducing the amount of epidural medication, improving satisfaction, and reducing breakthrough pain.[6] Since only obstetric patients and delivery were investigated the studies are much more homogenous than the surgical patients we included in our analyses. Furthermore, the process of delivery is much more characterized by increasing pain with periodic breakthrough episodes. Contrastingly, the average postsurgical patient has slowly decreasing pain levels and less frequent breakthrough pain. However, similar to obstetric patients, PCEA also decreased the requirement for additional top-ups. This may explain why PCEA in obstetric patients seems more advantageous.

Limitations: The overall quality of the studies included was moderate and the number of studies/patients included was limited. More importantly, there was a tremendous heterogeneity in the primary outcome parameter (pain scores, I^2 98%) and in patient populations and type of surgery, and epidural site and medication used, as well as in the specific PCEA regimen applied.

In surgical patients, PCEA compared to CEA does not improve pain management in a clinically relevant degree. However, in clinical pathways using CEA where patient satisfaction is low or demand for additional top-ups is high, switching from CEA to PCEA may be useful.

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Appendix 1. Search terms.

PubMed

("Analgesia, Epidural"[Mesh] OR "Anesthesia, Epidural"[Mesh] OR epidural an*[tiab]) AND ("Analgesia, Patient-Controlled"[Mesh] OR patient controlled[tiab] OR PCEA[tiab] OR intermittent bolus[tiab] OR intermittent epidural bolus[tiab] OR alternative analgesic technique*[tiab] OR other analgesic technique*[tiab]) AND (continuous epidural*[tiab] OR continuous infusion*[tiab] OR epidural analgesia[ti])

EMBASE (Ovid)

#	Searches
1	epidural analgesia/ or epidural anesthesia/ or epidural an*.ti,ab,kw.
2	patient controlled analgesia/ or (patient controlled or PCEA or intermittent bolus or intermittent epidural bolus).ti,ab,kw. or ((alternativ* or other) adj analgesic technique*).ti,ab,kw.
3	continuous epidural anesthesia/ or (continuous epidural* or continuous infusion*). ti,ab,kw. or epidural analgesia.ti.
4	1 and 2 and 3
5	limit 4 to conference abstract status
6	4 not 5

Cochrane Library

ID	Search Hits
#1	MeSH descriptor: [Analgesia, Epidural] explode all trees
#2	MeSH descriptor: [Anesthesia, Epidural] explode all trees
#3	(epidural an*):ti,ab,kw
#4	#1 or #2 or #3
#5	MeSH descriptor: [Analgesia, Patient-Controlled] explode all trees
#6	(patient controlled or PCEA or intermittent bolus or intermittent epidural bolus or alternative analgesic technique* OR other analgesic technique*):ti,ab,kw
#7	#5 or #6
#8	(continuous epidural* or continuous infusion*):ti,ab,kw
#9	#3 and #7 and #8

Appendix 2.

Author	
Year of publication	
study type and blinding	RCT, Patient blinded, Double blinded, Cohort
Number of participants: PCEA/CEA	
ASA categories	1,2,3,4
Age distribution: PCEA/CEA	
Surgery type	Orthopedic, Thoracic, upper abdominal, lower abdominal, pelvic, general, urologic, major abdominal, gynecological, total knee arthroplasty, colonic resection, breast, vascular, total hip replacement
Epidural level	level op epidural catheter insertion
Patient controlled epidural analgesia medication, speed,	
Bolus (mg/ ml)	
Lock out period	
Continuous Epidural Analgesia medication	
speed	
Rescue opiates	
Co analgesics	
Pain Service	type of pain service
Primary endpoint	Pain score (types: visual analog scale, Numeric Rating scale
24h Pain score resting, mean (sd), SEM, IQR.	
P value	
24h Pain score in motion	
P value	
Mean(sd)pcea/cea epid.drug [time]	
P value	
Side effects (nausea, pruritus, hypotension, motor weakness)	
Patient satisfaction	
Other	

Chapter 4

Influence on number of top-ups after implementing patient controlled epidural analgesia: A cohort study

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Abstract

Postoperative epidural analgesia often needs rate readjustment using top-ups. Patient-controlled epidural analgesia (PCEA) is said to reduce the requirement of epidural top-ups when compared to continuous epidural analgesia (CEA). We compared CEA and PCEA in major thoracic and abdominal surgery, in a cohort study. The primary endpoint was the required number of epidural top-ups. Secondary endpoints were pain scores, side effects and workload differences. We analysed 199 patients with CEA and 187 with PCEA. Both groups had similar pain scores. The total number of top-ups was 75 in 57 patients (CEA) versus 20 top-ups in 18 patients (PCEA). (p= 0.0001) Sedation tended to occur more frequently in patients with CEA versus PCEA, 5.5% vs 1.6% (p=0.05). Implementation of PCEA led to a decreased number of top-ups, fewer side-effects and decreased use of the postoperative care unit.

Introduction

Epidural analgesia is regularly applied perioperatively for major abdominal or thoracic surgery.[1 2] However, epidural analgesia can have a failure rate as high as 30%, frequently requiring re-adjustment by increasing the speed of infusion and/or top-ups with a bolus of local anaesthetic.[3-5] Nevertheless, top-ups with larger doses of local anaesthetics and/or opioids can cause hemodynamic or respiratory depression and therefore require intensified monitoring.

A refinement of continuous epidural analgesia (CEA) is patient controlled epidural analgesia (PCEA) where a basal epidural infusion rate can be supplemented by an on-demand bolus. The efficacy of PCEA has already been investigated in numerous clinical studies, and confirmed in a systematic review.[6-14] PCEA induced superior analgesia with fewer side effects and a decrease in drug requirement. However, many hospitals and anaesthesiologists continue using CEA for reasons of simplicity, scarcity of PCEA pumps and intricacy of handling of these pumps. In our institution CEA was the standard of care before we introduced PCEA. Monitoring of an epidural top-up can be challenging to manage, given the logistics of a large hospital and teaching centre: response time, transport time, time to contact a physician to do the top-up, and assessment, supervision, and monitoring time. We investigated whether the introduction of PCEA infusion pumps on the regular postoperative wards decreased the need for postoperative top-ups. Thus - in contrast to previous studies - the primary aim of this study was to reduce the number of top-ups after implementation of PCEA. Secondary outcome measures were: pain score (numeric rating scale, NRS), side effects (sedation, itching, motor block, nausea and vomiting) and calculated hours of differences in workload. Our hypothesis was that PCEA would reduce the number of top-ups, side effects and workload. Further, it could lead to a reduced duration of use of epidural analgesia.

Materials and Methods

In this retrospective cohort study, we investigated adult patients who had undergone thoracic and upper abdominal surgery during 2012-2013. The institutional medical ethics committee provided a waiver (W14-051 # 14.17.005)

for this anonymized investigation. Patient consent was not required, as data used for this cohort analysis was already present, and patients were not subjected to study measures. Epidural catheters were placed preceding the induction of general anaesthesia by a consultant or a registrar in anaesthesia with adequate experience, and proper placement was confirmed, according to local standard operating procedures. The epidural catheter was used for analgesia during the operation, infusion of bupivacaine 0.25% at the rate of 8-10 ml per hour. Patients received only standard CEA for nine months in 2012 (N=199). After educating all care givers about the technique of PCEA, patients received PCEA for nine months in 2013 (N=187). Itching (tolerable or needing medication), motor weakness (Bromage score), sedation (Ramsay score) and nausea (tolerable or needing medication) were scored. For safety reasons (e.g., monitoring of hypotension and respiratory depression), top-ups (top-ups: lidocaine 1%, dosed at 1mg/kg body weight) were given by a physician under basic monitoring (by means of non-invasive blood pressure, ECG and saturation). In patients not needing top-ups, the standard rate of epidural infusion was as per protocol (see below). Primary and secondary epidural failures were scored in both groups: primary failure was defined as: the epidural was not working immediately after the operation in spite of top-up, and secondary failure was defined as: initially good analgesia, but in the course of time a failed epidural (no analgesia) in spite of top-ups. Peak NRS scores were registered before top-ups in both groups. Both, primary and secondary failures were included in an intention-to-treat analysis. Workload was calculated as the amount of time spent by medical professionals to treat inadequate postoperative epidural analgesia.

CEA protocol

Standard epidural medication was bupivacaine 0.125% with 1 microgram sufentanil per ml solution. In patients older than 70 years or weighing less than 60 kg, sufentanil was omitted from the epidural. The epidural pump was set at a constant speed of 10 millilitres per hour (ml/h). The rate was increased by 2 ml/h if indicated by pain scores (see below), after a top-up dose. Maximum dose was 0.3 mg/kg per hour of bupivacaine. The rate was decreased by 2 ml/h if analgesia was adequate or in the presence of hypotension.

PCEA protocol

Epidural solution was identical to the CEA protocol. The epidural infusion speed was 6 ml/h with a patient-controlled bolus of 2 ml and a lockout time of 20

minutes. The maximum bupivacaine dose was defined as 0.3 mg/kg per hour. In case of inadequate analgesia, the bolus was primarily increased from 2 ml to 4 ml. In case of arterial hypotension, the rate was decreased by 2 ml/h (as above).

Both groups

Standard additional medication (unless they were contraindicated) included acetaminophen 4 grams (g) daily in 4 doses, and diclofenac 150 milligrams (mg) daily in 3 doses or dipyrone 4 grams (g) daily in 4 doses. We used the following pump: BBraun PerfusorSpace with special module for PCEA. This enabled us to use the same pump for continuous epidural and patient controlled epidural analgesia by adding an extra module with button for patient control.

Pain scores

The first pain scores were routinely taken at the post anesthesia care unit (PACU). After transferring the patients to the surgical wards, the level of epidural analgesia was judged by the staff of the acute pain service daily, and if inadequate (resting NRS score above 4 in the operated location, inadequate block height) the patient received an epidural top-up bolus with lidocaine 1%, dosed at 1 mg/kg. This was done after transferring the patient to the PACU under extended hemodynamic and neurologic monitoring, because of the complexity of the patient population with underlying diseases in a university hospital. This is partially reflected in ASA class distribution in table 1, bearing in mind that a pancreatic resection or transthoracic esophageal resection remains a high-risk procedure even in patients categorized as ASA 1 and 2. In addition, NRS scores were documented by the ward personnel 3-4 times daily, and if scores were above 4, the acute pain service was called. Patients could also alert the nurses if they felt uncomfortable due to pain. In both groups, successful top-ups were followed by an increase in basic epidural infusion speed (in case of pain during rest). In the PCEA group pain during activity was treated by an increase in bolus dose. Total failure of epidural analgesia (insufficient effect of top-up) was followed by removal of the epidural catheter and the initiation of patient-controlled analgesia with morphine (PCA).

Endpoints

Primary endpoint was the cumulative frequency of top-up rescue interventions per therapy group throughout the entire period of postoperative epidural analgesia. Secondary endpoints were: NRS pain scores, side effects (hypotension,

nausea, vomiting, itching, motor weakness, sedation) and estimated differences in workload. Hypotension was generally defined as: when mean arterial pressure decreased more than 20% from the normal mean arterial pressure of the patient as commonly measured in normal circumstances. Additionally, for the workload calculation, we measured the average time involved in a top-up of a surgical ward patient. Including transport, this was 2.5 hours per patient. (30 min transport to and from the PACU, 2 hours observation including top-up of epidural on PACU).

Statistics

SPSS version 22 (IBM software, New York, USA) was used to analyze our data. Normality of distribution was evaluated using the Shapiro-Wilk test. Student's t-test or Mann-Whitney U test was used to calculate differences in mean or median where appropriate. Continuous data not normally distributed were analyzed by a Kruskal-Wallis test and if significant followed by Mann-Whitney U test. Categorical data and frequencies were analyzed by Fisher's exact test. Confidence intervals of 95% are given where appropriate, otherwise data are presented as means with standard deviations (SD) or median with interquartile range (IQR), respectively. A p-value of < 0.05 was considered statistically significant.

Results

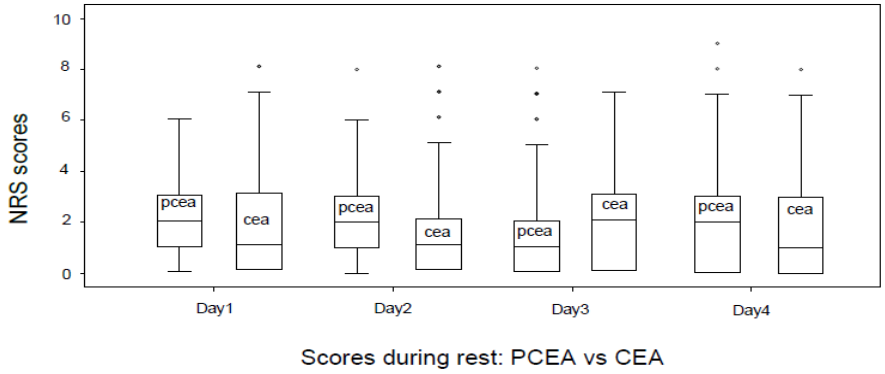
A total of 386 patients were analysed from 2012 to 2013: 199 in the CEA and 187 in the PCEA group. There were no significant differences between the two groups regarding age, weight, distribution of sex. Regarding type of surgery, there were significantly more oesophageal resections with CEA. On the other hand, significantly more patients underwent pylorus preserving pancreatoduodenectomy with PCEA. More than 80% of epidurals were placed at thoracic level in both groups. (Table 1) In the group of patients with CEA, 75 top-ups were necessary, compared to 20 in the PCEA group (p=0.0001). There were no significant intergroup differences in NRS scores on Postoperative day 1 to 4. (Fig 1, Fig 2). Peak NRS scores before top-up did not differ between groups.

Table 1. Patient and treatment characteristics

	CEA* N=199	PCEA† N=187	P-Value
Male/Female N (%)	63/136 (32/68)	45/142 (24/76)	0.131‡
Mean weight kg (SD)	73 (15)	73 (14)	0.824§
Median age (IQR)	60 (47-68)	62 (52-70)	0.566
ASA class** N (%)			0.08‡
1	55 (28)	70 (38)	
2	122 (61)	94 (50)	
3	22 (11)	23 (12)	
Operation type N (%)			¶
PPPD, pancreatic surgery	18 (9)	42 (23)	0.000
Thoracic oesophagus resection	25 (13)	7 (4)	0.000
Trans hiatal oesophagus resection	8 (4)	1 (0.5)	0.04
Laparotomy	58 (29)	45 (24)	0.30
Debulking tumour load	31 (16)	42 (23)	0.16
Wertheim	25 (13)	18 (11)	0.42
Hemihepatectomy	10 (5)	12 (6)	0.66
Liver hilus resection	3 (2)	0	0.25
Gastrectomy	3 (2)	6 (3)	0.32
Pelvic exenteration	3 (2)	0	0.25
Liver segment resection	4 (2)	5 (3)	0.74
Colonic surgery	11 (6)	8 (4)	0.64
Level of Epidural N(%)			
T6-T7	24 (12)	11 (6)	0.05
T7-T8	36 (18)	20 (11)	0.04
T8-T9	41 (21)	31 (17)	0.36
T9-T10	38 (19)	35 (19)	1
T10-T11	18 (9)	46 (25)	0.000
T11-T12	5 (3)	17 (9)	0.007
T12-L1	5 (3)	6 (3)	0.76
L1-L2	28 (14)	20 (11)	0.36

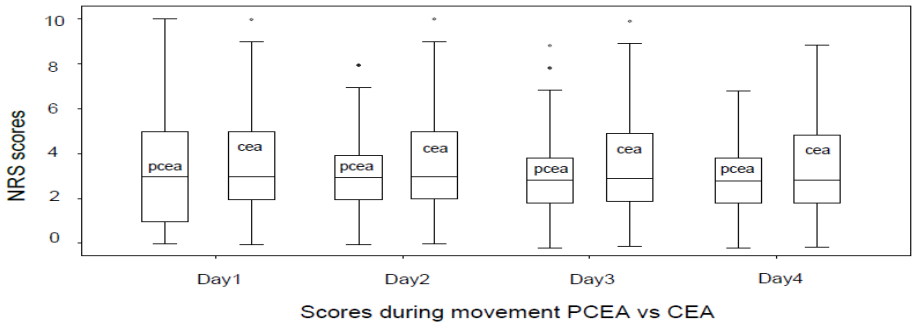
**ASA class, American Society of Anesthesiologists physical status classification ; *CEA, Continuous Epidural Analgesia; †PCEA, Patient Controlled Epidural Analgesia; PPPD, Pylorus Preserving Pancreato Duodenectomy; ‡2 sided Pearson Chi Square test. §t Test Bias Corrected Accelerated . ¶ Fisher exact two tailed.

Figure 1. NRS* resting pain scores postoperative day 1 to day 4, CEA† (N=199) vs PCEA‡ (N=187)



*NRS, Numeric rating scale of pain. †CEA, continuous epidural analgesia, ‡PCEA, patient controlled epidural analgesia. Depicted in the boxes are resting postoperative pain scores of 4 days in patients with continuous and patient controlled epidural analgesia. Top of box is third quartile, bottom is first quartile. The horizontal line in box is median value; whiskers at the end of lines are minimum and maximum values. Dots are outliers.

Figure 2. NRS* pain scores during movement postoperative day 1 to day 4, CEA† (N=199) vs PCEA‡ (N=187)



*NRS, Numeric rating scale of pain. †CEA, continuous epidural analgesia, ‡PCEA, patient controlled epidural analgesia. Depicted in the boxes are postoperative pain scores during movement, of 4 days in patients with continuous and patient controlled epidural analgesia. Top of box is third quartile, bottom is first quartile. The horizontal line in box is median value; whiskers at the end of lines are minimum and maximum values. Dots are outliers.

Primary and secondary endpoints are compared in Table 2. Itching, nausea and motor weakness was not significantly different between groups.

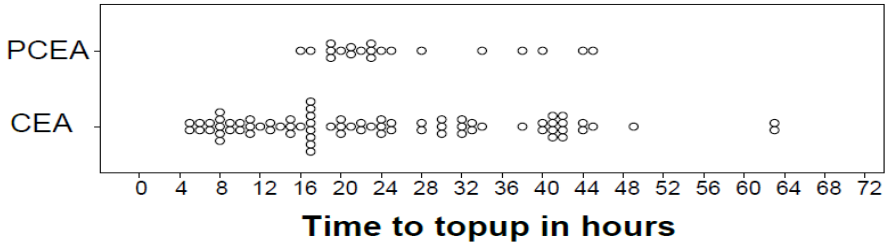
Table 2. Comparison of endpoints between CEA* and PCEA†

	CEA* (N=199)	**PCEA†** (N=187)	**p value ‡**
Total number of patients with Top-ups N (%)	57 (28.6)	18 (9.6)	0.0001
Requiring One top-up N	41	16	0.001
Two top-ups N	14	2	0.004
Three top-ups N	2	0	0.49
Mean days duration epidural analgesia (SD)	3.3 (1.5)	3 (1)	0.07
Median Peak NRS scores (95% CI)	8 (7-8)	8 (7-8)	0.75
Primary failure of epidural	6	1	0.12
Secondary failure of epidural	2	4	0.44
Side effects			
Itching untreated N (%)	4	3	0.57
treated	4	2	
Nausea untreated N (%)	11	10	0.52
treated	14	9	
Motor weakness total N (%)	28	19	0.27
Bromage level 2	13	9	
Bromage level 3	11	9	
Bromage level 4	4	1	
Sedation total N (%)	11 (5.5)	3 (1.6)	0.05
Ramsay score 3	3	2	
Ramsay score 4	2	1	
Ramsay score 5	6	0	
Any side effect (%)	72 (36.1)	46 (24.5)	0.02

*CEA, continuous epidural analgesia. †PCEA, Patient controlled epidural analgesia. Explain CI SD ‡ Fisher exact.

The timings of top-ups are represented in figure 3.

Figure 3. Top-up administration in CEA and PCEA groups



†CEA, continuous epidural analgesia, ‡PCEA, patient controlled epidural analgesia. Each circle represents one top-up. The time-interval is given in hours. In order to visualize each patient data points were mildly shifted in time and stacked to improve readability of the figure.

Post-hoc exclusion of pancreatoduodenectomies and oesophagectomies to control for non-random distribution of these procedures between groups resulted in 148 patients with CEA and 137 patients with PCEA with 32 top-ups in the CEA group, and 16 top-ups in the PCEA group (p=0.03). Thus, the difference remains significant even in the patients with presumably less painful operations.

Table 3 presents reasons for decreasing the rate of the epidural infusion. We decreased rates in 17 patients (8.5%) in the CEA group and in 3 patients (1.6%) in the PCEA group (p=0.002).

Table 3. Rate adjustment due to side effects

Number of patients for whom:	CEA* (N=199)	PCEA† (N=187)	p value‡
rate was decreased due to motor blockade	5	3	0.5
rate was decreased due to sedation	5	0	0.02
rate was decreased due to arterial hypotension	7	0	0.006
Total N (%)	17 (8.5)	3 (1.6)	0.002

*CEA, continuous epidural analgesia. †PCEA, Patient controlled epidural analgesia. ‡Fisher exact

Workload calculation

In our hospital, the average time spent on the monitoring ward, was 2 hours. Transport to and from the surgical and gynecological wards required on average 30 minutes per patient. This sums up to an average workload per (patient) top-up of 2.5 hours in our setting. We had 20 top-ups in our PCEA group of 187 epidurals, and 75 in our CEA group of 199 patients. 20 top-ups result in 50 hours per 187 patients receiving PCEA, this is 16 minutes per patient in this group. 75 top-ups result in 187.5 hours per 199 patients receiving CEA, this is 56.5 minutes per patient in this group.

Discussion

Our main finding in this retrospective cohort study was that the use of PCEA significantly reduced the number of patients requiring top-ups, while NRS scores did not differ between groups. The total numbers of top-ups in our study are in accordance with other studies: a Swedish study encompassing seven years of PCEA and 4,912 epidurals had a failure rate of 11%, resulting in termination of the epidural.[15] Recent literature gives a failure rate of up to 30% in CEA epidurals.[3 16] Our study investigates the effect of implementation of PCEA on the total number of rescue top-ups, which form a logistically important and costly aspect of postoperative epidural analgesia. The finding that the PCEA group did *not* improve pain scores is in contrast to other studies.[7 9] However, most studies comparing PCEA and CEA were done before the introduction of multimodal pain concepts. Thus, the fact that all patients continued preoperative pain medication with the addition of acetaminophen and diclofenac or dipyrone may have also worked in favour of the pain scores in the CEA group. Well in accordance to the quoted comparative studies between CEA and PCEA, we noticed more side effects in the CEA group. There was a significant difference between groups, in the number of patients requiring reduction of infusion rate due to side effects such as sedation, motor block or hypotension. The degree of sedation was considerably lower in patients with PCEA. Also, fewer patients were sedated. Since our pumps only register drug consumption over the last 4 hours, unfortunately we were not able to obtain results regarding the applied doses, but it is likely that the increased percentages of side effects in the CEA group were caused by high local anaesthetic and opioid doses applied. Regarding hypotension and possible

respiratory complications after epidural analgesia, these frequencies may be under reported. Due to the retrospective nature of the study, we can only show the actual documentation of these events. Furthermore, the incidence of hypotensive episodes may have been influenced by the the epidural level. In the CEA group midthoracic epidural levels (T6-T8) were more frequent than in the PCEA group where low thoracic levels (T10-T12) were more frequent. Therefore, these are limitations of the study.

Our PCEA algorithm is rather conservative, and there are studies with more successful algorithms; especially those with integrated mandatory and automatic bolus.[17]

Nevertheless, we noticed a significant improvement in our in-hospital logistics after the introduction of PCEA pumps. Perhaps the feeling of being in control positively adds to the success of PCEA, as suggested in an earlier publication.[18] More than a decade ago, Schuster and co-workers calculated the cost of PCEA and demonstrated that most of the money is spent on staff costs, although in their calculation they did not include expenses for top-ups at medium- or high-care units.[19] In an earlier study of 6349 patients, Brodner and co-workers demonstrated significant cost savings due to the implementation of a multimodal pain management including PCEA.[20] Furthermore, in the last decennium, the percentage of staff cost in developed countries increased further while drug and material costs tended to decrease. In our hospital the transport and admittance of patients for epidural top-ups is not only time-consuming, but because of its urgent character it cannot be scheduled or planned and can create logistic problems for the ward, transport service and the postoperative care unit. The introduction of PCEA did significantly ameliorate this problem.

In our hospital, we calculate 16 minutes per patient in the PCEA group versus 56.5 minutes in the CEA group. Even though this is specific to our hospital and may not reflect the situation in other hospitals, top-ups are always time consuming, and efficiency is welcome. Top-ups are often done in the wards, but even then, if the frequency of top-ups can be drastically reduced, it is beneficial to workload.

Thus, not only patient comfort and success rate were increased (decrease in sedation and less top-ups) but also hospital investment of costly urgent medium or high care space.

Our study has several limitations: Patients with oesophageal and pancreatic surgery were not equally distributed between cohorts. However, excluding these patients in a post-hoc analysis revealed even in the remaining and presumably less painful operations, a significant difference in the number of top-ups between groups ($p=0.03$). In this subgroup the number of side-effects leading to changes in management was significantly more in the in CEA group than in the PCEA group. Thus, the non-randomized nature of the study leads to an uneven distribution of operations between groups, but the results were robust enough, when controlled for the uneven distribution.

Furthermore, due to the nature of the study (not an RCT, no blinding) there are many possible causes of bias: the effect of the PCEA may be due to the psychological factor of "self-control", resulting in less complaints, nurses may call the pain service earlier in case of CEA, or delay because of the hassle involved in a top-up dose. Irrespective of whether the effect of PCEA was caused by psychological or pharmacologic factors, in clinical practice it will have a benefit. Whatever bias may have been involved, it did not seem to result in a significant difference in NRS scores between groups. Although our results may need validation in a prospective randomized trial, we demonstrated for the first time that PCEA could reduce the frequency of top-ups and thereby reduce inconvenience for the patient, workload for the staff and costs for the hospital.

Conclusion

We conclude that PCEA can reduce the frequency of top-ups and side effects, compared to CEA. This may lead to reduced logistic workload and hospital costs.

Appendix 1. Ramsay score

	Ramsay	
Awake	1	Anxious, agitated, restless
	2	Cooperative, oriented, tranquil
	3	Responsive to commands only
Asleep	4	Brisk response to light glabellar tap or loud auditory stimulus
	5	Sluggish response to light glabellar tap or loud auditory stimulus
	6	No response to light glabellar tap or loud auditory stimulus

Appendix 2. Bromage score

Bromage	Criteria	Degree of block
1	Free movement of legs and feet	Nil
2	Just able to flex knees with free movement of feet	Partial
3	Unable to flex knees, but with free movement of feet	Almost complete
4	Unable to move legs or feet	Complete

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Chapter 5

Comparison of continuous nerve block versus patient-controlled analgesia for postoperative pain and outcome after talar and calcaneal fractures

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Adapted from ***Foot Ankle Int. 2014 Nov;35(11):1116-21.***

Abstract

Background

Talar and calcaneal fractures and their treatment can cause severe postoperative pain. We hypothesized that a continuous peripheral nerve block (CPNB) would reduce pain scores more effectively than systemic analgesics, improve recovery, and lead to reduced length of stay (LOS).

Methods

Over a 3-year period, patients undergoing open reduction and internal fixation (ORIF) of a talar or calcaneal fracture were retrospectively analyzed. Patients received a CPNB catheter preoperatively or intravenous patient-controlled analgesia (PCA) postoperatively. Primary endpoint was Numerical Rating Scale (NRS) scores on postoperative day 1. Secondary endpoints were NRS scores up to day 3, opioid requirement, analgesia-related side effects, intraoperative blood loss, infection, and LOS. Eighty-seven patients were analyzed; 70 with calcaneal fracture, 21 with talar fracture, 4 with both. In all, 40 patients received CPNB, 47 patients PCA.

Results

Median NRS scores on day 1 were 1.0 (IQR 3) in the CPNB group and 2.0 (IQR 3) in the PCA group (*ns*). Median LOS for patients with CPNB was 5 days (IQR3) and PCA 4 days (IQR 2 *ns*). Blood loss and incidence of local infections were comparable in both groups. Opioid requirement was significantly increased in the PCA group ($P < .01$).

Conclusion

Significant advantages or disadvantages were not seen in either group. However, the PCA group required about 30-fold more opioids compared to the CPNB group on day 1, although that did not lead to an increased number of side effects.

Level of Evidence

Level III, retrospective comparative series.

Introduction

The operative treatment of talar and calcaneal fractures can result in significant postoperative pain.[1 2] There are several available methods of postoperative pain management to ensure as much comfort as possible following the operative treatment of these fractures. Most commonly, continuous peripheral nerve block (CPNB), patient-controlled analgesia with morphine (PCA), and combinations of oral and intravenous analgesic drugs are used. A prospective study in 2003 showed that Visual Analog Scale scores were lower in patients who had CPNB.[3] In a more recent retrospective study of 106 patients undergoing open reduction and internal fixation (ORIF) of calcaneal fractures, CPNB led to a reduction in costs by means of a reduction in hospital length of stay (LOS). However, in this study it was the policy to discharge people with a CPNB in situ.[2] A meta-analysis of a total of 603 patients led the authors to conclude that CPNB provided better postoperative analgesia compared to opiates alone.[4] Even though CPNB might facilitate an early discharge due to better pain control, it is current policy at our institution to delay discharge until wound inspection at day 3 after surgery, and weight-bearing is mostly restricted for up to 3 months following talar and calcaneal fractures. This distinguishes the calcaneal/talar fracture surgery from other lower extremity surgery such as total knee or total hip replacement. Therefore, continuous sciatic nerve block seems to be a preferable technique for these patients, since they have no increased risk of falling such as patients undergoing total knee arthroplasty with immediate postoperative mobilization.[5]

Considering the above, there is a limited amount of research on the efficacy of CPNB compared with multi- modal oral and intravenous analgesics in this particular patient group.

The aim of the study was therefore to compare the efficacy of analgesia with CPNB and PCA in patients undergoing isolated ORIF of the foot and ankle during the past 3 years in our institution. Our goal of this retrospective study was to generate hypotheses and set a framework to adequately power a future randomized controlled blinded study.

Methods

In this retrospective analysis, we analyzed data of patients who had undergone an ORIF of a calcaneal or talar fracture between August 2010 and August 2013 at a level 1 trauma center, which functions as a tertiary referral center for complex foot and ankle injuries. A total of 87 patients were included: 70 calcaneal and 21 talar fractures (including 4 patients with both). In 40 patients a CPNB was used and in 47 a PCA (Table 1). There were no significant differences between the 2 groups regarding age, weight, sex, ASA (American Society of Anesthesiologists) category, or surgery type (Table 1). The Sanders classification of the intra-articular fractures was as follows: 3 type I, 49 type II, 10 type III, and 1 type IV. There were 6 extra-articular calcaneal anterior process fractures.

Table 1. Demographic Characteristics, Surgery

Variable	CPNB, n=40	PCA, n=47	P Value
Age	45.6	42	.291
Median weight, kg	76	75	.508
Male n (%)	25 (62)	34 (72)	.364
Female n (%)	15 (38)	13 (28)	
ASA status (1/2)	26/14	34/13	.493
Surgery			
Calcaneus ORIF	32	34	.614
Talus ORIF	6	11	
Calcaneus + talus ORIF	2	2	

ASA, American Society of Anesthesiologists; CPNB, continuous peripheral nerve block; ORIF, open reduction and internal fixation; PCA, patient-controlled analgesia. *P* values based on Pearson chi-square and Fisher's exact test

The primary outcome parameter was numeric rating scale (NRS) score on postoperative day 1. NRS is a verbally administered pain rating scale in which a patient can rate his or her pain ranging from 0 (no pain) to 10 (maximum pain).[6] NRS measurements on the first postoperative day were by protocol and were therefore complete and valid. NRS measurements on day 2 and day 3 were not as complete as at day 1 and therefore represent secondary endpoints. Patients were operated between 1 to 2 weeks post trauma to allow for adequate swelling resolution. The operative approach of the calcaneal fractures was via an

extended lateral approach in most cases or a sinus tarsi approach in some. The talar fractures were treated via 2 incisions in the 8 talar neck fractures or via a single incision in other fracture types. Fifteen patients received a medial incision due to talar neck or combined fractures. Postoperatively, 3 of these patients received an additional saphenous nerve block (only in patients specifically complaining of pain on the medial side of the ankle in spite of their analgesic treatment we performed an additional saphenous nerve block). The institutional medical ethics committee provided a waiver for this retrospective study. We excluded patients who had concomitant traumatic injuries in other parts of their body. Patients underwent surgery under general anesthesia with a postoperative pain therapy either by means of CPNB or PCA. All patients were proposed CPNB initially in the preoperative phase, but only patients who consented to CPNB actually received the regional block. The CPNB was initiated by a single shot local anesthetic under ultrasound guidance (sciatic or popliteal block was used according to the preference of the attending anesthesiologist, as the incision was not in the medial part of the foot in the majority of patients), followed by placement of a peripheral nerve catheter preoperatively. Failure of CPNB was defined as lack of pain relief, with an NRS score above 4, with documented lack of sensory block even after an extra bolus dose of 100 mg of lidocaine via the catheter. Patients with a failed CPNB received PCA postoperatively. Standard medication of the CPNB was levobupivacaine 0.125% starting at an infusion rate of 8 ml/h postoperatively. The PCA contained morphine with a bolus of 1 mg, a lockout of 5 minutes and a maximal dose of 30 mg in 4 hours. Standard medication included acetaminophen 4 g daily in 4 doses, and diclofenac 150 mg daily in 3 doses or dipyrone 4 g daily in 4 doses. If analgesia was inadequate, patients received additional intravenous S-ketamine (0.1mg/kg/h). All patients were visited daily by our acute pain service to record, evaluate and adjust analgesic requirements. All patients receiving CPNB had an “as required” opioid prescription, but no PCA. Antiemetics were prescribed when indicated by nausea or vomiting.

For our analysis of opioid requirement, we calculated the equipotent dose of morphine for all opioids used in the individual patient. The following postoperative data were obtained: Numerical Rating Scale (NRS) scores, opioid consumption, nausea and vomiting, hallucinations, itching, motor block, blood loss during surgery, infection, and duration of hospital stay.

Statistics

SPSS version 20 (IBM, New York, NY, USA) was used to analyze our data. Normality of distribution was calculated using Kolmogorov–Smirnoff and Shapiro–Wilk tests. Student's *t* test or the Mann–Whitney *U* test was used to calculate differences in mean or median where appropriate. Continuous data not normally distributed were analyzed by a Kruskal–Wallis test and, if significant, followed by a Mann–Whitney *U* test. Categorical data and frequencies were analyzed by Fisher's exact test. Data are presented as means with standard deviations (SD) or median with interquartile range (IQR) defined as third quartile minus first quartile, depending on normality of distribution. A *P* value ≤.05 was considered statistically significant. nQuery 7.0 advisor (Janet Elashoff, Ireland) was used in the post hoc power analysis calculations.

Results

There were no significant differences in median NRS scores (interquartile range, IQR) between groups at rest on postoperative day (POD) 1: CPNB: 1 (IQR 3) versus PCA: 2 (IQR 3), and during activity: CPNB: 2.5 (IQR 4) versus PCA: 3.0 (IQR 2). On POD 2 the median NRS scores at rest were CPNB 2 vs PCA 2. On POD 3 these NRS scores were CPNB 1 vs PCA 1 (Table 2).

Table 2. NRS Scores Days 1-3

Variable	NRS day 1R	NRS day 1A	NRS day 2R	NRS day 2A	NRS day 3R	NRS day 3A
CPNB	1.0 (3)	2.5 (4)	2.0 (4)	3.0 (4)	1.0 (2)	3.0 (2)
PCA	2.0 (3)	3.0 (2)	2.0 (2)	4.0 (3)	1.0 (4)	3.0 (3)
P value	.070	.055	.917	.106	.612	.893

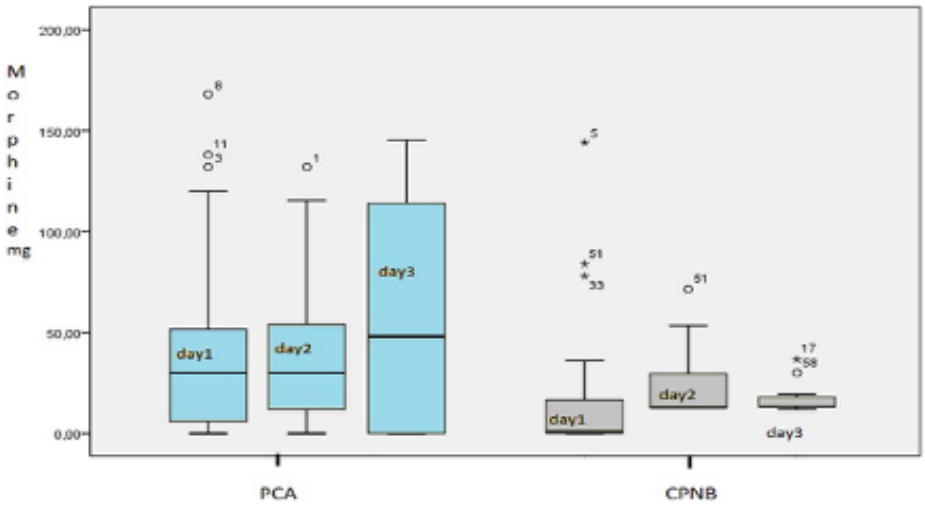
Values are medians, with interquartile ranges in parentheses. *P* values are based on Mann–Whitney *U* test. A, score during activity; CPNB, continuous al Rating Scale; PCA, patient-controlled analgesia; R, score at rest.

Six patients receiving CPNB had a failed block. These patients were analyzed in an intention-to-treat analysis; elimination of these patients from the CPNB cohort did not change the results. Fourteen patients had a sciatic nerve block and 20

patients had a popliteal block. The median NRS score in sciatic block was 2 (IQR of 3) versus a median NRS score of popliteal block of 1 (IQR of 3).

A significant difference was found in opiate requirements between groups on POD 1: a median of 1.1 mg of morphine (IQR 16.7) in the CPNB group versus 30 mg (IQR 46.8) in the PCA group (P = .005). On the following days this difference was less pronounced, but still considerable (Table 2, Figure 1).

Figure 1. Morphine consumption per group



Values are shown as medians with interquartile range.

CPNB, continuous peripheral nerve block; PCA, patient-controlled analgesia.

There was no significant difference in duration of hospital stay in the CPNB group (5 days vs 4 days in PCA group; P = .342; Table 3). The incidence of side effects was not significantly different between groups, although patients in the PCA group received an approximately 30-fold higher morphine dose (Table 4). No case of neuropathy was reported. On POD 1, 12 patients in the PCA group received S-ketamine versus 1 in the CPNB group. There was no significant difference in postoperative infections between the 2 groups: 6 minor infections in both groups requiring oral antibiotics and wound care and 3 major infections in the PCA group versus 2 in the CPNB group requiring intravenous antibiotics and operative debridement. Blood loss was comparable in both groups (Table 3).

When comparing the different fracture types we found no significant difference in NRS scores (P = .913).

Table 3. Clinical Outcomes

Variable	CPNB, n=40	PCA, n = 47	P Value
Morphine in mg day 1,median (IQR)	1.1 (16.7)	30.0 (46.8)	.005
Morphine in mg day 2,median (IQR)	13.3 (16.6)	30 (57)	.078
Morphine in mg day 3,median (IQR)	13.3 (6)	48 (129)	.305
Days of hospital admission, median (IQR)	5.0 (3)	4.0 (2)	.342
Side effects, n	6	13	
Motor block, n	13	1	
Blood loss during surgery ml (mean, SD)	287	299	.865

P values based on Mann–Whitney *U* test and Student's *t* test. CPNB, continuous peripheral nerve block; PCA, patient-controlled analgesia.

Table 4. Side Effects of Analgesics

Side Effect	CPNB, n = 6	PCA, n = 13
PONV	3	5
Hallucinations	1	2
Vertigo		3
Itch		1
Drowsiness + itching	1	1
PONV + hallucinations		1
PONV + drowsiness + itch	1	

CPNB, continuous peripheral nerve block; PCA, patient-controlled analgesia; PONV, postoperative nausea and vomiting.

Discussion

Our findings show that the placement of continuous peripheral nerve catheters in the postoperative treatment of pain after surgery for fractures of the calcaneus or talus resulted in a significant reduction of the required opiate dose only on POD 1. All other primary and secondary outcomes were not significantly changed by the choice of postoperative pain therapy.

In comparison to other studies, the PCA control group had remarkably low NRS scores for pain, possibly due to the multimodal pain concept: use of acetaminophen, dipyrone, and when indicated S-ketamine. Although the NRS score was reduced by 0.5 to 1 point, this did not reach significance levels given the current number of patients. Post hoc power analysis revealed that to demonstrate a significant reduction in NRS by CPNB, a group size of approximately 166 patients would be required, assuming an alpha of .05 and a power of 90% in a 2-sided Mann–Whitney *U* test with the distribution of the observed NRS data. However, even if the reduction would be significant with a larger number of patients, the difference in NRS would not be considered clinically relevant by the International Association for the Study of Pain.

The use of local or regional anesthetic block techniques has been advocated to improve the quality of analgesia, and has been shown to reduce hospital days in an ambulatory setting when patients are discharged with elastomere pumps.[2 6-8] However, it is our policy to discharge patients without invasive catheters. Discharge criteria were pain at acceptable level (NRS of below 3) and no wound leakage at wound inspection at 48 to 72 hours. Therefore, the longer duration of hospital stay may be biased by this policy, and a change in policy may significantly change the results for length of hospital stay. The consumption of opiates also depends on prescription by the physician and may vary between countries. Patients with ankle fractures get a high amount of opiate prescriptions during their hospital stay, and this amount has been shown to be much higher in the United States than in the Netherlands.[9]

A randomized controlled trial (RCT) in the United Kingdom including 54 patients undergoing major ankle surgery compared CPNB and single shot popliteal block and found that opiate consumption was significantly less in the patients with CPNB, and also that overall pain scores were low in both groups.[10] Several other studies involving lower extremity fractures came to the same conclusion: CPNB provides better analgesia and reduces morphine consumption.[1 11-13] A Swiss RCT showed that a continuous block of the saphenous nerve in addition to the continuous popliteal block not only further reduces pain scores in the postoperative period, but that this effect was still measurable after 6 months.[14] The importance of a saphenous nerve block in ankle surgery may sometimes be underestimated.[15] Unfortunately, there is always a chance of neuropathic

symptoms, sometimes initiated by additives to the local anesthetic solutions.[16] There are various pathophysiological mechanisms to explain this.[17] A prospective study of 147 patients (predominantly female) with CPNB for foot and ankle surgery reported 24% neuropathy at 8 months after surgery. Severe neuropathy was present in 4%. However, patients were very satisfied with the block, even with the neuropathy.[18]

There are several limitations of our study. First, due to the retrospective and nonrandomized nature of the trial, our results are subject to known and unknown bias. Second, the follow-up period with complete NRS data was 1 day. The registration on the second day and third day was less complete and possibly biased. However, the scores reconfirmed the values on POD 1. Furthermore, while patients in the PCA group had free access to opioids, patients in the CPNB group had to ask for additional opioids, which might have somewhat exaggerated the difference in opioid consumption. However, since there was no difference in NRS scores, this effect must have been minor to negligible. Most studies comparing CPNB could demonstrate a difference between groups over the first 72 hours, while in others the difference decreased or disappeared over time.[4 19] Finally, it is known that the length of hospital stay is multifactorial, and the most effective way to reduce this is the use of clinical pathways, which address all issues of the patients' well-being within and outside of the hospital.

Conclusion

Our retrospective analysis of calcaneal and talar fractures demonstrated only a significant opiate sparing effect favoring the CPNB group. No other advantages regarding pain therapy, blood loss, infections, or side effects were found. Differences in length of hospital stay between groups were not significant. In both groups the patients had low pain scores. However, the PCA group had a 30-fold increased opioid consumption that could have made the patients at risk of severe respiratory depression or more severe nausea, but our study population was too small to find these potential effects.

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Chapter 6

Comparable post-operative pain levels using two different blocks in operative treatment of displaced intraarticular calcaneal fractures

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Abstract

Background

The aim of this study was to compare the postoperative pain levels in patients undergoing osteosynthesis of the calcaneus, with either a popliteal nerve block or an ankle block and to compare duration of hospital stay between the above groups.

Methods

A retrospective analysis of all consecutive patients undergoing surgical fixation of a calcaneal fracture between August 2012 and April 2017 in a single foot/ankle specialized center was performed. Single shot popliteal blocks were placed using ultrasound guidance by an anesthesiologist, ankle blocks were placed by a foot/ankle specialized surgeon. Pain levels were measured through the numerical rating scale (NRS).

Results

In total 83 patients were included in this study, 33 received a popliteal block and 50 received an ankle block. No statistically significant differences were present in baseline characteristics between the two groups. Comparable postoperative pain levels were observed in both groups. There was no statistically significant difference in amount of morphine used between the two groups. The duration of hospital stay was 0.5 day longer in the ankle block group.

Conclusion

No significant differences were found in postoperative pain levels between patients receiving a single shot popliteal block and patients who received a single shot ankle block following calcaneal fracture surgery. The length of hospital stay was shorter in patients after a popliteal block, this difference was statistically significant.

Introduction

The operative treatment of calcaneal fractures can result in significant postoperative pain.[2] This is reflected in a recent study regarding orthopedic trauma surgery, in which over 20% of the patient- initiated telephone calls after discharge concerned postoperative pain.[9] Multiple options are available in managing postoperative pain after foot and ankle surgery. A nerve block is part of a multimodal approach in the treatment of pain. As the affected area is innervated by the sciatic nerve, a nerve block can be performed at different levels: upper sciatic, popliteal region block, ankle block, or simply local infiltration of the wound. Popliteal or ankle blocks are used most frequently in foot and ankle surgery.

Disadvantages of a popliteal nerve block are the duration of the procedure and the additional costs associated with placement and follow-up.[5,6,11] Therefore if an ankle block provides comparable analgesia a reduction in resource use and costs may be achieved. However, to this date, we were unable to find any studies comparing a peripheral (popliteal) nerve block with an ankle block in calcaneal fracture surgery.

Thus, the primary aim of the study was to compare the postoperative pain levels in patients undergoing osteosynthesis of the calcaneus via sinus tarsi approach (STA), using a popliteal block or an ankle block. Secondary aim was to compare duration of hospital stay between the above groups.

Patients and Methods

All consecutive adult patients between August 2012 and April 2017 who were operated due to an isolated calcaneal fracture via a Sinus Tarsi Approach (STA) at a single academic level 1 trauma center were retrospectively analyzed. Exclusion criteria were: bilateral fractures, use of a block other than popliteal or ankle block, patients sustaining multiple injuries, continuous nerve blocks and missing postoperative pain data at more than two sample points. We retrospectively reviewed electronic patient hospital charts. The following characteristics were obtained; gender, age at time of procedure, American Society of Anesthesiologists Score (ASA-score), fracture side, Sanders classification, (non-) smoker and use of

tourniquet. The following characteristics were collected regarding postoperative pain management: location of the block (i.e., popliteal or ankle), block placed by surgeon or anesthesiologist and type of postoperative analgesia (i.e., patient-controlled analgesia (PCA) or oral (Oxycodone). Furthermore, the cumulative amount of morphine used by patients during admission was registered (starting on the day following surgery). For our analysis of the cumulative amount of morphine used, we calculated the equipotent dose of morphine for all opioids used using a formula described by others.[21] The popliteal nerve block was placed by the anesthesiologist preoperatively using ultrasound guidance, at the popliteal fossa. An ankle block was performed intraoperatively by the trauma surgeon in the event that a popliteal nerve block was not placed by the anesthesiologist.

The primary outcome parameter was postoperative pain which was measured using the numeric rating scale (NRS). The NRS is a verbally administered pain rating scale in which a patient can rate his or her pain ranging from 0 (no pain) to 10 (maximum pain).[10] The NRS was scored routinely preoperatively (t=0), postoperatively at the surgical ward after transfer from the postoperative care (t=1), evening of the operation day (t=2), morning on the day following surgery (t=3) and afternoon on the day following surgery (t=4). The assessment of pain was done by the nurse on call and registered in the electronic patient chart.

Popliteal blocks were placed using a bolus of local anesthetic (levobupivacaine 0.25% or 0.5%, 10-20 ml). Standard medication of the ankle block was 10-20 ml bupivacaine 0.5%. The ankle block was placed by placed by a trauma surgeon specialized in foot and ankle surgery. The block was placed after positioning of the patient in a supine or lateral decubitus position. Patients had already received general- or spinal anesthesia. The block was placed using anatomical landmarks nearby the sural-, tibial-, saphenous-, superficial peroneal- and deep peroneal nerve as described by Schurman and Dhukaram.[3,19] Ultrasound guidance was not used for placing the ankle block.

Standard postoperative pain medication for all patients included Paracetamol (acetaminophen) 4 g daily in 4 doses and Metamizole (dipyrone) 4 g daily in 4 doses. Additionally, all patients either received PCA with morphine 1mg/ml or slow-release Oxycodone (oxycontin) 10 mg, twice daily and standard Oxycodone (oxynorm) 5mg up to 6 doses daily depending on the postoperative NRS.

The PCA was standardly discontinued on the morning following surgery when usage was below 10mg/4 hours and only restarted in case of inadequate analgesia. All patients were standardly discharged with oral paracetamol (acetaminophen), non-steroid anti-inflammatory drugs (NSAIDs) and Oxycodone for one week. Based upon a hospital wide protocol, patients were only discharged when their NRS-score was below 4.

Statistics

Statistical analysis was performed with *SPSS v. 24.0* (SPSS Inc. Chicago, Ill.). Categorical data are presented as frequencies and percentages. Continuous data are presented as means and standard deviations or standard error of the mean (SEM) (in case of use of imputed data) or medians and interquartile ranges where appropriate. Missing data was handled through imputation. To avoid bias, multiple imputation through predictive mean matching and using gender and age as predictor, with 10 imputed data sets was performed for the missing data. Data were subsequently pooled using Rubin's rule.[18] Differences in baseline characteristics, postoperative pain and hospital stay were analyzed with the Chi-square, independent t-test or Mann-Whitney U-test where appropriate. Significance levels are derived from two-tailed tests and were set at $p < 0.05$.

Results

Patient and treatment characteristics are displayed in Table 1.

A total number of 150 patients were eligible. Sixty-seven patients were excluded due to: bilateral fracture (n= 5), block differs from standard (n= 9), multiple injury patients (n= 3), continuous block instead of single shot (n= 28) and missing NRS-scores on > 2 time points (n= 22). A total number of 83 patients were included for analysis. Of these patients, 33 received a popliteal block by the anesthesiologist and 50 received an ankle block by the trauma surgeon. Intergroup differences were absent regarding gender, age, ASA, Sanders classification and smoking habits (Table1).

In total 8% of the postoperative pain scores were missing at the various time points, these were handled through multiple imputation. There were no significant differences in the pre-operative pain scores; mean NRS pre-operative popliteal block versus ankle block: 1.35 versus 1.53 (p= 0.64). Postoperative NRS scores did not differ significantly between the popliteal and ankle block on any of the time points (Table 2).

Table 1. General descriptives

	Ankle block (n= 50)	Popliteal block (n= 33)	p-value
Gender			.31[a]
Male (%)	36 (72)	27 (82)	
Female (%)	14 (28)	6 (18)	
Age (mean) [sd]	48.1 [13.5]	41.9 [15.0]	.06[b]
ASA –score			.51[a]
ASA 1 (%)	33 (66)	25 (76)	
ASA 2 (%)	16 (32)	8 (24)	
ASA 3 (%)	1 (1)	0 (0)	
Side			.08[a]
Left (%)	19 (38)	19 (58)	
Right (%)	31 (62)	14 (42)	
Sanders classification			.37[a]
Type 2 (%)	38 (76)	26 (79)	
Type 3 (%)	9 (18)	3 (9)	
Type 4 (%)	3 (6)	4 (12)	
Smoking habits			.12[a]
Smoking (%)	16 (32)	16 (50)	
Not smoking (%)	34 (68)	16 (50)	
Missing		1	
Tourniquet use			.70[a]
Yes	36 (74)	25 (76)	
No	14 (26)	8 (24)	
Type of anesthesia			.99[c]
General anesthesia (%)	49 (98)	32 (97)	
Spinal anesthesia (%)	1 (2)	1 (3)	

[a] = Chi-square test

[b] = Independent Samples T-test

[c] = Fishers exact test

ASA: American Society of Anesthesiologists sd: standard deviation

Twelve percent of patients with a popliteal block received an additional PCA postoperatively, in the ankle block group this was 38% (p= 0.01). In two patients with a popliteal block, analgesia was insufficient and a new single shot popliteal

block was placed postoperatively. No patients in the ankle block group required a re-block, this difference was not statistically significant (6% versus 0% p= .16). For 87% (72 out of 83) of the patients, data on the cumulative amount of morphine used was available. The cumulative amount of morphine used during admission did not statistically significantly differ between the two groups: 13 mg (median) [IQR: 13 – 17, range: 0 – 40] versus 13 mg (median) [IQR: 3 – 26, range: 0 – 94] p = 0.69 (popliteal versus ankle block respectively).

Smoking did not statistically significantly influence postoperative pain scores. The duration of operation was shorter in the ankle block group, but this difference was not statistically significant. There were no intergroup differences in the frequency of wound complications.

Median hospital stay in days after surgery popliteal block versus ankle block was 1.0 [IQR: 1 – 1.5] versus 1.5 [IQR: 1 – 3] (p= 0.01) (Table 3).

Table 2. Postoperative pain scores

	Ankle block (n=50)	Popliteal block (n=33)	p-value
NRS T0 (mean) [SEM]	1.53 [0.24]	1.35 [0.29]	.64[a]
NRS T1 (mean) [SEM]	2.30 [0.24]	2.41 [0.46]	.82[a]
NRS T2 (mean) [SEM]	2.39 [0.33]	1.53 [0.34]	.09[a]
NRS T3 (mean) [SEM]	3.11 [0.29]	2.63 [0.43]	.34[a]
NRS T4 (mean) [SEM]	2.31 [0.21]	2.21 [0.29]	.76[a]

NRS: Numeric rating scale T0: preoperative T1: at return to ward T2: evening following surgery T3: morning following surgery T4: afternoon following surgery

a = Independent Samples T-test SEM: standard error of the mean

Table 3. Operation characteristics and outcomes

	Ankle block (n=50)	Popliteal block (n=33)	P-value
Operation duration (min) (mean, [sd])	84 [26]	91 [28]	.26[a]
Wound dehiscence (%)	1 (2)	1 (3)	.99[b]
Wound infection (%)	2 (4)	3 (9)	.38[b]
Length of hospital stay (days) (median, [IQR])	1.5 [1 – 3]	1 [1 – 1.5]	.01[c]

a = Independent Samples T-test b: Fisher's exact test c: Mann-Whitney U test

min: minutes sd: standard deviation IQR: interquartile range

Discussion

The aim of the current study was to investigate the differences in postoperative pain between two types of postoperative pain management. We observed no significant differences in postoperative pain score between patients with a popliteal block or an ankle block, patients with a popliteal block group were discharged earlier compared to patients with an ankle block.

The popliteal and ankle block have a similar direct analgesic effect as shown by the NRS on T1 (first pain score measured at the ward). The analgesic effect seems to last a little longer in the popliteal group as reflected by the NRS on T2. However, this difference is not statistically significant. It has been shown before that a peripheral block may last a little longer compared to a regional block.[15] The clinical relevance of this difference however is not clear, as a reduction in NRS of 1.3 – 3 points or 33% is needed to be clinically relevant.[7,12,17] As the aforementioned difference in NRS between the two methods is absent at all time points, we considered it clinically irrelevant. Another important point is that the cumulative amount of morphine used between the two groups did not statistically significantly differ between the two groups. In our study the ankle block apparently provided adequate analgesia without increasing the use the of intravenous or oral morphine. This especially important in the light of the abuse of morphine observed in the United States in the last decade.[1]

In a randomized study by Migues et al. a single shot popliteal block was compared with a single shot ankle block.[15] They found that both methods provided adequate analgesia in patients undergoing elective forefoot procedures. Monsy et al. found the same in a group 3,050 patients undergoing minor foot surgery.[16] This comes at an expense as the use of popliteal block has been shown to actually result in a higher incidence of rebound pain after it wears off.[8]

The majority of the patients were discharged after 1 day (median 1, interquartile range 1 – 2) and maximum length of stay was 13 days. A small statistically significant difference in hospital stay was observed between the two groups. However, as this was only half a day the clinical relevance is unclear.

Furthermore, prolonged hospital stay was never because of insufficient pain management but because of logistical reasons, questioning the attribution of the ankle block to the prolonged hospital stay.

Several studies have compared a single shot nerve block with a CPNB in foot and ankle surgery.[2,4–6,11,14,20] Only Elliot et al. found a significantly lower postoperative pain score in patients with a CPNB.[5] All other authors however reported prolonged total procedure time due to the placement of a CPNB compared to a single shot block. These results question the added value of continuous blocks over single shot blocks. Furthermore, these blocks require extra resources as extra equipment is needed and patients are sometimes even discharged with a continuous block in situ demanding extra home care. Therefore, continuous blocks may be reserved for more severe cases in which persistent pain is expected and additional analgesia may be warranted.

This study has several limitations. First, our study is retrospective, which may introduce selection bias. However, we have included all consecutive patients to reduce this problem. Second, the data of the pain scores was not complete, approximately 8% of the NRS-scores were missing. We have overcome this problem by using multiple imputation for the missing pain scores which has shown to be a reliable method in case of missing data.[13] Interestingly PCA was applied more often in patients with an ankle block. We believe this was mainly as a precaution as patients had not received a block by the anesthesiologist. As a result of this, in almost all cases the PCA could be discontinued on the morning following surgery which is also reflected by the fact that the cumulative amount of morphine used did not statistically significantly differ between the two groups. Strength of this study is that it is the first to use the ankle block as an alternative to more elaborate analgesia techniques in the surgical treatment of displaced intra-articular calcaneal fractures. We have shown that the two regimes of postoperative analgesia resulted in similar pain levels. A reduction in hospital costs may be achieved when using ankle blocks in calcaneal fracture surgery. This may also be true in other foot ankle trauma procedures as the additional investment of equipment and personnel to perform a nerve block did not lead to better analgesia. The actual time needed to perform a block outside the operation room is an investment of time and use of scarce resources. We therefore question the need for nerve blocks for these specific procedures as a routine.

Conclusion

We found no differences in postoperative pain levels between patients receiving a popliteal block and patients who receive an ankle block following calcaneal fracture surgery. This may suggest that ankle blocks deliver adequate analgesia in routine cases, and in selective cases, a step up to a popliteal nerve block may be performed if prolonged analgesia is expected. In daily practice, this can lead to a more efficient use of resources and personnel. The results of the present study may serve as a basis for a prospective study on this subject to provide more definitive answers.

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Chapter 7

Serum levels of bupivacaine after preperitoneal bolus vs. epidural bolus injection for analgesia in abdominal surgery: A safety study within a randomized controlled trial

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Abstract

Background

Continuous wound infiltration (CWI) has become increasingly popular in recent years as an alternative to epidural analgesia. As catheters are not placed until the end of surgery, more intraoperative opioid analgesics might be needed. We, therefore, added a single pre-peritoneal bolus of bupivacaine at the start of laparotomy, similar to the bolus given with epidural analgesia.

Methods

This was a comparative study within a randomized controlled trial (NTR4948). Patients undergoing hepato-pancreato-biliary surgery received either a pre-peritoneal bolus of 30ml bupivacaine 0.25%, or an epidural bolus of 10ml bupivacaine 0.25% at the start of laparotomy. In a subgroup of patients, we sampled blood and determined bupivacaine serum levels 20, 40, 60 and 80 minutes after bolus injection. We assumed toxicity of bupivacaine to be >1000 ng/ml.

Results

A total of 20 patients participated in this sub-study. All plasma levels measured as well as the upper limit of the predicted 99% confidence intervals per time point were well below the toxicity limit. In a mixed linear-effect model both groups did not differ statistically significant (p=0.131). The intra-operative use of opioids was higher with CWI as compared to epidural (86 (SD 73) µg sufentanil *vs.* 50 (SD 32).

Conclusions

In this exploratory study, the pre-peritoneal bolus using bupivacaine resulted in serum bupivacaine concentrations well below the commonly accepted toxic threshold. With CWI more additional analgesics are needed intraoperatively as compared to epidural analgesia, although this is compensated by a reduction in use of vasopressors with CWI.

Introduction

Adequate pain treatment is an important component of modern perioperative care and essential for a fast recovery. Choosing the optimal analgesic modality remains a topic of debate especially in major abdominal surgery. Epidural analgesia is considered by many to be the reference standard.[1] However, besides its excellent analgesic effect, there are some disadvantages associated with epidural analgesia. This includes the risk of epidural hematoma/abscess (incidence 1:1,000-6,000 in surgical patients),[2-4] failure rates of up to 30%,[5] and the need for preoperative placement in awake patients, which patients often seem to dislike and sometimes even refuse .[6]

Continuous wound infiltration (CWI) -with pre-peritoneal catheters- has become increasingly popular in recent years because of fewer alleged disadvantages, and offers a good alternative. A meta-analysis showed comparable pain scores with CWI as compared to epidural analgesia in abdominal surgery.[7] There is also evidence that CWI leads to decreased perioperative hypotension, reduced urinary retention[7] and a fast recovery,[8 9] although the latter conclusion has been challenged.[10] In a recent randomized controlled trial, we showed CWI to be non-inferior regarding quality of analgesia as well as patient-reported outcomes in patients undergoing hepato-pancreato-biliary surgery.[6] Since earlier studies have shown CWI to be inferior to alternatives in the early postoperative phase (<24h)[11] we added a pre-peritoneal bolus after incision to improve intraoperative analgesia and decrease the use of substituting analgesics including opioids. An earlier study in laparoscopic hernia surgery showed a pre-emptive pre-peritoneal bolus with local anesthetic to be effective in reducing postoperative pain.[12] In another study an opioid bolus was combined with CWI, however this combination did not result in as effective early pain control compared to epidural analgesia.[13]

In the mentioned RCT[6] we had a case suggestive of local anesthetic toxicity after this bolus was given. After this needle bolus, one patient immediately showed ECG changes (arrhythmias) and became hypotensive (blood pressure suddenly dropped from 130/70 to 60/30). The noradrenaline infusion was already being given, and 10 mg of ephedrine was administered intravenously. That was followed by 200 micrograms of adrenalin to restore circulation. Further measures were not needed. As this patient was already under general anesthesia and intubated, and

as there was no surgical event at that time excepting the injection, we assumed a (partially) intravenous dose of local anesthetic resulting in high plasma levels. This bolus was not given according to the protocol, since it was done without aspiration and the needle was inserted several centimeters instead of 1-2 mm. Thus, this bolus was very likely given into the muscle. Since it is unclear to what plasma levels this needle-bolus leads when done correctly, our aim was to assess plasma levels after injection done according to protocol. We hypothesized that bupivacaine levels, when correctly applying this method, are below toxic levels but higher compared to epidural analgesia.

Methods

Participants

The TREND guidelines were followed for the reporting of this manuscript.[14] This was a prospective comparative open-label substudy in 20 of 105 patients who participated in the randomized controlled POP-UP trial (Netherlands Trial Registry number NTR4948). This substudy had a two-arm, open-label, parallel group design and was conducted in the main center of the original trial (Academic Medical Center). Inclusion of participants from the main trial for this substudy was done when it was logistically feasible to collect and process these samples. Analysis was done after all samples had been collected. Approval of the medical ethical committee (Medisch Ethische Toetsings Commissie AMC Amsterdam) was obtained (MEC2014_329). The trial protocol and rationale have been described elsewhere.[15] All patients gave both written and oral consent for study participation and additional blood samples. Eligible were adult patients undergoing subcostal or midline laparotomy for hepato-pancreato-biliary indications at the Academic Medical Center, Amsterdam. If any of the following criteria were present, patients were excluded: American Society of Anesthesiologists status of >3, chronic opioid use (>1 year), renal failure (an estimated glomerular filtration rate <40ml per min), contraindication for epidural analgesia, allergy for study medication, liver cirrhosis (Child-Pugh class C), or coagulopathies (international normalized ratio >1.5, partial thromboplastin time of >1.5x the mean of the normal range, platelets <80 x 10^9 per L).

Interventions

General anesthesia was induced in the operating room with 2-3 mg·kg^{-1} propofol (Fresenius Kabi, Zeist, the Netherlands). Besides, sufentanil was given for analgesia (Bipharma, Almere, the Netherlands), and for paralysis 0.6 mg·kg^{-1} rocuronium was given (Fresenius Kabi, Zeist, the Netherlands). The trachea was intubated, and the lungs were mechanically ventilated with pressure regulated volume-controlled ventilation. After the induction, general anesthesia was maintained with sevoflurane (AbbVie, Hoofddorp, the Netherlands) at a minimal alveolar concentration of 1 and was supplemented by an additional bolus of sufentanil when deemed necessary. An arterial line was inserted into the left or right radial artery. A right jugular tri-lumen central line was inserted at the discretion of the anesthesiologist. A double lumen gastric tube and an urinary catheter were inserted. Cefazoline (Kefzol™) 1-2 gram and metronidazol (Flagyl™) 500 mg were given prophylactically (around 30 minutes prior to incision).

Besides sufentanil, additional analgesia was at the discretion of the anesthesiologist and was done according to local protocols. This included paracetamol, Metamizol, or esketamine (Eurocept Pharmaceuticals, Ankeveen, the Netherlands).

Fluid management was primarily done according to a stroke volume-, stroke volume variation- or pulse pressure variation-guided, goal-directed fluid therapy protocol.[16]. Relevant parameters were obtained by means of FloTrac (Edwards Lifesciences) or trans-esophageal Doppler monitoring (EDM).

We monitored heart rate, blood pressure, arterial blood oxygen saturation and toxicity signs. The enhanced recovery program included preoperative nutritional optimization, normal oral nutrition up to 6 h and clear liquids up to 2 h before surgery, anti-thrombotic prophylaxis, normothermia and glycemic control.

Pre-peritoneal bolus group

Patients received a single-shot bolus injection by the surgeon of 30 mL bupivacaine 0.25% at the start of the procedure after laparotomy in the pre-peritoneal space (i.e., between the peritoneum and the posterior transverse fascia). This procedure has been described before.[15] Step 1. After laparotomy, stretch the posterior transverse fascia manually or using a Kocher clamp. Step 2. Insert needle tip 1mm in the pre-peritoneal space. Step 3. Aspirate to exclude

intra-vascular placement. If no blood is aspirated inject slowly, 10ml (in subcostal incision) or 15ml (in midline incision), in aliquots of 5 ml without using high pressure. Step 4. Repeat this 1 or 2 times on the designated locations. When in the correct plane, one should see the spreading of local anesthetic through the pre-peritoneal plane. This is the same plane in which the catheter tip is placed at the end of the procedure (see appendix). This dosage was chosen because it is also given as a bolus immediately after placement of the catheters.[9] Adherence to the standard operating procedure of this bolus was checked in the operating room (by T.M.).

Epidural bolus group

Other patients were treated with thoracic epidural analgesia. The epidural catheter was placed between the levels of T7 and T10 at the discretion of the anesthesiologist and topped up using bupivacaine 0·25% and sufentanil 1 µg/ml before incision. This was with a total of 10 ml in 2 boluses of 5 ml as is standard practice in our institution. After 30 minutes a continuous epidural pump was started at 6-10 ml/h bupivacaine 0·25%, resulting in a cumulative dosage in 80 minutes of 15 – 18.3 ml of bupivacaine 0·25%.

Objective

To assess safety of bupivacaine after pre-peritoneal needle-bolus injection and compare them pragmatically with the plasma levels after standard epidural bolus.

Outcomes

Our primary endpoint was plasma levels of bupivacaine after pre-peritoneal single shot needle-bolus or epidural bolus. Analysis was by intention-to-treat. Arterial blood samples were collected intraoperatively into heparin vials at 20, 40, 60, and 80 minutes after the pre-peritoneal bolus of bupivacaine in the pre-peritoneal bolus group and after epidural bolus in the epidural group. Plasma was separated and frozen at -80 degrees Celsius. We used the MaxSignal bupivacaine ELISA kit for immunoassay (Bio Scientific, Austin, Texas, USA) (See appendix). Symptoms of toxicity of bupivacaine can occur from 1,000-1,500 ng/ml and seizures are associated with levels > 4,500 ng/ml.[17 18]

Baseline variables included: Gender, age, BMI, American Society of Anesthesiologists (ASA) physical status, creatinine. Secondary outcomes included:

intraoperative noradrenaline use, fluids administered, intraoperative sufentanil and esketamine usage, and operative time.

Sample size

This was an exploratory study. Due to the absence of literature regarding this pre-peritoneal needle-bolus, there was lack of evidence to facilitate a sample size calculation with confidence. The sample size of 20 patients (10 in each arm), which was decided beforehand, seemed reasonable for the goal of this exploratory analysis.

Statistical analysis

Regarding the primary and secondary endpoints, we calculated based on 1,000 bootstrap samples the mean and SD. For the primary endpoint we chose to display the upper limit of the 99% CI interval of the mean instead of for example the 95% CI since this seems more relevant to us because of the aim of our study. For baseline data we expressed median and IQR for continuous variables if non-Normally distributed, or mean and standard deviation (SD) when Normally distributed. The normal distribution was checked by visually inspecting the histograms. Missing data was considered missing at random. Dichotomous data were presented as numbers and percentages. For continuous variables, differences between groups were tested with Student's *t*-test for normally distributed data. For non-normally distributed data the Mann-Whitney *U*-test was used. A linear mixed effect model was used using time with group interaction. P-value of significance was set at <0.05. Fisher's exact test was used for proportions for all categorical data. Data was collected in, and analyzed with SPSS Version 22.0 (SPSS Inc., Chicago, IL, USA).

Results

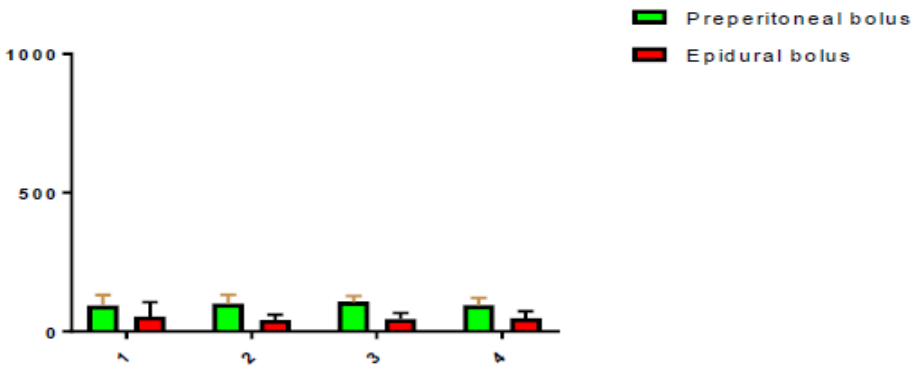
Twenty patients were included in this study between April 2015 and September 2015. All patients which were considered for these additional blood samples, agreed to participate in this substudy. Data was complete except for measurements in 2 patients in the epidural group at the 80-minute time point. There were no serious adverse events reported in these patients. For baseline data see table 1.

Table 1. Baseline characteristics of the 20 participants

	Pre-peritoneal bolus (N=10)	Epidural bolus (N=10)
Gender		
- Male	7 (70%)	5 (50%)
- Female	3 (30%)	5 (50%)
BMI (in kg/m^2)	24.0 [21-29.5]	24.7 [21.9-26.7]
Age (in years)	60 [47-72]	75 [57-85]
ASA class		
1	2 (20%)	1 (10%)
2	7 (70%)	8 (80%)
3	1 (10%)	1 (10%)
Creatinine (in µmol/L)	73 [64-81]	75 [68-91]

Data are median (interquartile range) and counts (%). ASA = American Society of Anesthesiology physical status. Groups did not differ statistically significant for all baseline variables.

Figure 1. Mean plasma levels of bupivacaine per time point in ng/ml



Time points 1-2-3-4 are 20, 40, 60 and 80 minutes after bolus injection. The green bar is the mean, the error line the upper limit of the 99% confidence interval. Since toxicity symptoms can occur from 1000 ng/ml we chose that as the upper limit of the Y-axis.[17 18]

The time course of bupivacaine concentrations is shown in Figure 1. All plasma levels measured were well below toxic levels. The highest measurement in the pre-peritoneal bolus group was 177 ng/ml compared to 201 ng/ml in the epidural

group. Also, the upper limit of the 99% confidence interval of the mean per time point never exceeded 132 ng/ml (figure 1), which is well below toxicity.

Plasma levels of pre-peritoneal bolus injection vs epidural bolus and continuous infusion were: at 20 minutes a mean of 94 (SD 54) *vs.* 54 (54) ng/ml (p=0.110), at 40 minutes a mean of 100 (SD 47) *vs.* 41 (21) ng/ml (p=0.005), at 60 minutes mean of 108 (SD 28) *vs.* 45 (25) ng/ml (p<0.001) and at 80 minutes a mean of 95 (SD 35) vs 48 (28) ng/ml (p=0.007).

The intra-operative use of additional analgesics was higher in the pre-peritoneal bolus group (sufentanil and esketamine), (table 2). The mixed effect model groups did not differ significantly (p=0.131).

Table 2. Operative data

	Pre-peritoneal bolus (N=10)	Epidural bolus (N=10)	p
Duration of surgery	319 (SD 55)	222 (SD 41)	0.288
Norepinephrine (in mg)	0.76 (SD 1.2)	1.3 (SD 1.0)	0.325
Fluids administered (in ml)	3099 (SD 1507)	3285 (SD 1237)	0.890
Sufentanil (in µg)	86 (SD 73)	50 (SD 32)	0.206
Esketamine (in mg)	27 (SD 32)	1 (SD 3)	0.039

Discussion

This comparative sub-study within a randomized controlled trial found that plasma levels of bupivacaine in patients receiving pre-peritoneal bolus injections are well below toxic levels. Furthermore, the intraoperative amount of analgesics used is still higher in patients with CWI compared to patients with epidural analgesia. This is indicates the pre-peritoneal bolus does not totally compensate intraoperatively for lack of epidural analgesia.

In our study, all measured levels were well below the toxic threshold on the different time points. In 51 RCTs, no cases of local anesthetic toxicity have been reported with continuous wound infiltration.[19] However, there are documented reports of toxicity; after malfunctioning of an elastomeric balloon pump,[20] and

after a TAP block following partial intramuscular injection.[21]

In our POP-UP trial we experienced one serious adverse event probably linked to an accidental intravascular injection. This bolus was not given according to the protocol. Instead of inserting the needle 1-2mm, the needle was inserted 2-3 centimeters, and the bolus was given without prior aspiration. When the bolus is given in the correct plane, there is visual feedback when the local anesthetic spreads through the pre-peritoneal plane. We advise to routinely aspirate prior to injection and inject slowly in aliquots of 5 ml, without high pressures, as is common practice in regional analgesia. At the end of the operation, when the bolus is given through the pre-peritoneal catheters, there is visual and tactile feedback when the catheters curl up in the pre-peritoneal plane and the risk of intravascular injection would seem negligible.

We showed that a pre-peritoneal needle-bolus with 30ml bupivacaine 0.25% to cover the early intra-operative period results in serum bupivacaine concentrations well below the concentration commonly accepted as toxic. However, close attention needs to be paid to the execution in operating theatres. Benefits during the intraoperative period include a decrease in perioperative hypotension.[6] In our trial, this manifested as reduced use of perioperative vasopressors. No difference was found in the use of iv-fluids, which we contribute to the use of perioperative goal directed fluid therapy. Without this method, this would probably lead to infusion of more iv fluids including all associated risks.

This study has several limitations. First, multiple testing might have influenced results of our analysis. We chose to not use the Bonferroni correction, since this is not advised by some, but chose to instead report our results unadjusted.[22] Second, we only have an exploratory sample size of 20 patients. To draw definitive conclusions and declare safety a larger-scale trial is needed. However, in our opinion these results provide relevant exploratory information related to this novel addition to the technique of CWI. Besides, our results can be used in the planning of such a large-scale study. Third, the plasma levels in the epidural group are influenced by the continuous infusion of epidural bupivacaine, started 30 min after epidural bolus. However, we made the pragmatic choice to compare 2 different dosages to evaluate the plasma levels as they are with the use of both methods in daily practice. Our goal was not to compare these measurements

directly, since for that purpose an equipotent dosage would be needed. Instead, we aimed to give the reader an idea to what extent these levels differ with the use of these methods as they are in daily practice. Besides, there are only measurements on the chosen time points (20, 40, 60, 80 minutes). These were chosen because of the expected epidural resorption peak at around 30 minutes, so peaks outside these time points could have been missed, but are very unlikely. A comparable study in transversus abdominis plane block showed a comparable curve, suggesting these time points were chosen correctly, without for example a very early peak.[23] However, because all measurements as well as the predicted upper limits of the 99%-CI of the mean are well below toxicity, (<180 ng/ml compared to a toxicity limit of 1,000 ng/ml), we feel confident that the current intervention when correctly executed does result in relatively low levels of local anesthetic. This is the first study in which this bolus injection is evaluated, studies evaluating the pharmacokinetics and precise method of action are warranted.

Conclusions

In this exploratory study, the pre-peritoneal bolus using bupivacaine resulted in serum bupivacaine concentrations well below the commonly accepted toxic threshold. With CWI additional analgesics are still needed intraoperatively as compared to epidural analgesia, although this is compensated by a reduction in use of vasopressors with CWI.

Appendix

S1. Original text of manufacturer

The MaxSignal® Bupivacaine ELISA Kit uses a competitive immunoassay method to determine the amount of bupivacaine present in the blood. The MaxSignal® Bupivacaine ELISA Kit uses a competitive immunoassay method to determine the amount of bupivacaine present in the blood or urine sample. Test plate wells are coated with bupivacaine. Blood or urine sample is added for analysis, along with anti-bupivacaine antibody. Bupivacaine in the sample will compete for the primary antibody, thereby preventing the antibody from binding to the drug attached to the well. After incubation, the sample is removed, the wells are washed and a secondary HRP-conjugated antibody is added. The intensity of the absorbance at 450 nm is directly proportional to the amount of Bupivacaine in the urine sample.

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Chapter 8

Face and Construct Validity of TU-Delft Epidural Simulator and the Value of Real-Time Visualization

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Abstract

Background and objectives

Learning epidural anesthesia traditionally involves bedside teaching. Visualization aids or a simulator can help in acquiring motor skills, increasing patient safety and steepening the learning curve. We evaluated face and construct validity of the TU-Delft Epidural Simulator and effect of needle visualization.

Methods

68 anesthesiologists, anesthesia residents and final year medical students tested the epidural simulator. Participants performed six epidural simulations with and six without needle visualization. We tested face validity on a Likert scale questionnaire. We collected data with the simulator software (spinal taps, dura contacts, bone contacts, attempts and time) and tested for correlation with the performers' experience (construct validity). A visualization aid was tested in a randomized cross-over design.

Results

Face validity as rated by the participants was above average with a mean of 3.7(2.0-4.8) on a 5-point scale. Construct validity was indicated by significantly more more spinal taps (0.4 (0-4) vs. 0.07(0-2), p=0.04) and more dura contacts (0.58(0-6) vs. 0.37(0-3), p=0.002) by the inexperienced group compared to the expert group.

The visualization aid improved performance by reducing the number of bone contacts, the number of attempts and by decreasing the procedure time. Prior visualization training reduced the total procedure time from 279 s(69-574) to 180 s(53-605) (p=0.01) for the 'blind' procedure.

Conclusions

The TU-Delft Epidural Simulator is a useful tool for teaching motor skills during epidural needle placement. Prior use of a visualization tool improves performance even without visual support during consequent simulations.

Introduction

Epidural catheter placement requires motor skills and experience. These are generally acquired during hands-on training, subjecting the patient to (unnecessary) risks. Although a variety of teaching methods for gathering technical skills have been described there is no widely accepted method to test manual skills of anesthesiologists during epidural needle placement.[1] Simulators can provide a safe environment for teaching residents and can also be used as a valuable tool for assessing the resident's proficiency in a systematic and consistent way, before performing this procedure on patients. An extensive technical review of thirty-one different epidural and spinal simulators was done by Vaughan and colleagues, comparing their features and highlighting their advantages and shortcomings.[2] However, neither construct nor face validity was available in this review for any of the described simulators. More recently, a banana was suggested as a teaching model for loss of resistance after comparison to three simulators.[3] Another study describing a recently developed simulator uses pressure guidance for detection of loss of resistance but lacks the advantage of MRI modeling.[4] The TU-Delft Simulator for Epidural Needle Skills (SENS) with two degrees of freedom was used in our study. It has the advantage of modelling a variety of MRI scans. Thus, varied constitutions, anatomies and possible pathologies of the vertebral column can easily be implemented in the simulator software. High fidelity simulators have not proven to be superior to low fidelity ones in terms of clinical impact. A study by Friedman and colleagues suggests no difference in learning curve between residents taught on low fidelity "greengrocers' model" and the ones taught on a high-fidelity simulator. [5 6] However, the study did not include a control group. High fidelity simulators offer up to six degrees of freedom, allowing the user to choose insertion point and needle trajectory in all plains and axes, while low fidelity simulators mimic only relevant clinical features. Which features are mandatory in a simulator and which are superfluous, still remains a topic of discussion. The purpose of our study was to test the 'TU-Delft Simulator for Epidural Needle Skills' considering three different issues: Face validity (the relevance of a test as it appears to test participants), construct validity (the degree to which a test measures what it claims to be measuring) and effect of a visualization aid. We hypothesized that participants would rate the simulator as realistic and useful for training purposes (mean score on the Likert Scale > 2.5). Furthermore, our test for construct validity was that experienced anesthesiologists

would perform better than inexperienced residents or students. We expected decreased bone contacts, dural contacts, spinal taps and also fewer attempts and less time spent until completion of procedure. We regarded the number of spinal taps as being clinically most relevant. The other measures for safety and quality of performance were added, because we expected the incidence of spinal taps to be too low to reach significance. Finally, we hypothesized that a visualization aid not only improves the performance during the actual procedure, but also in subsequent procedures without visualization.

Methods

The TU-Delft Simulator for Epidural Needle Skills is a computer-controlled learning tool that provides force feedback based on a virtual patient model. It consists of a metal plate representing the dorsal side of the patient, with a vertical opening. A syringe with needle can be introduced through this opening at a fixed point of entry. The needle can be rotated, and can be angled at different angles in respect to the vertical plane. The needle can be advanced anterio-posteriorly, towards the virtual front of the model (patient). Once the needle is advanced, the angle cannot be changed. Data are acquired electronically through a computer. The loss of resistance is felt through force feedback, and so is the bone contact. MRI simulation shows actual (real time overlay) advancement of the needle in the MRI model of the spine. The simulator (**Figure 1 and Figure 2**) allows the trainee to insert a needle into a virtual patient's back, following the midline approach with loss-of-resistance (LOR) technique.

The simulator software offers a flexible insertion point on the computer screen with visible spinous processes, while the hardware has a fixed insertion point and offers two degrees-of-freedom. The needle can be angled with respect to the back (vertical plane), mimicking the insertion (first degree of freedom). The needle can also be advanced inward towards the epidural space (second degree of freedom). The simulator allows training of several features of epidural needle placement: selection of the needle insertion point and angle (in the sagittal plane), insertion of the needle with variable resistance simulating fat, supraspinous ligament, interspinous ligament, bone, epidural space, dura and intrathecal space. Additionally, it provides tactile identification of epidural space entry by

loss-of-resistance with air or saline. For didactic reasons changing the angle of the needle after passing the supraspinous ligament is not possible. The forces model and the loss-of-resistance-pressure model are based on a combination of actual force and pressure measurements (porcine specimens, in vivo and in vitro), data from literature and expert opinion.[7-10] There are no experimental studies on the force measurement during real epidural needle insertion on live humans and therefore a realistic force range has been determined from animal studies.[9] The technical setup and exact mechanism of action of the TU Delft simulator is described in detail in a previous study.[10]

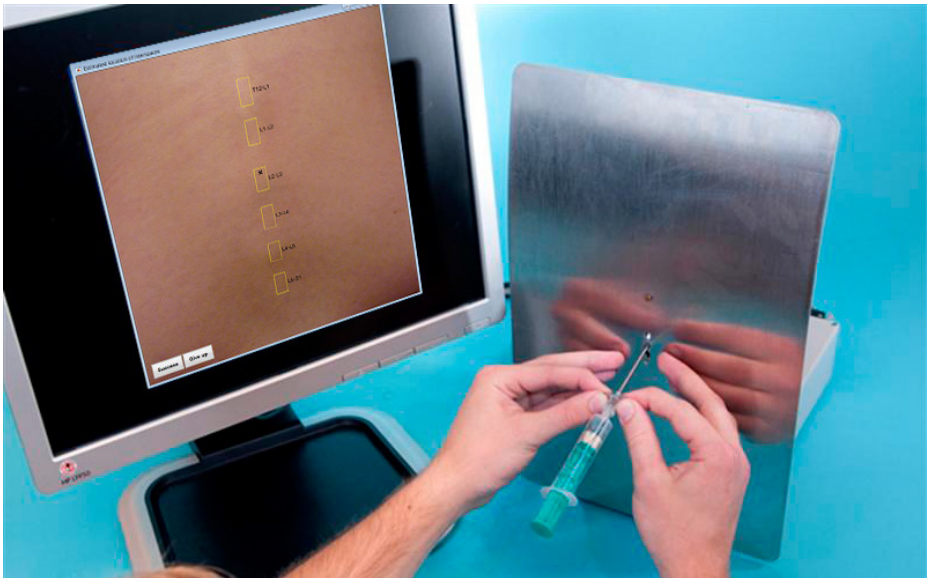

Figure 1. Hardware of the simulator showing monitor, metal plate with needle and syringe.

The anatomical model is based on segmented CT and MRI-data. Although the system database contains anatomical models of 52 different patients, in this study we used a single patient model of six consecutive vertebral interspaces from T12-L1 to L5-S1 in order to keep these variables constant. The simulator software allows visual support to be displayed in form of a MRI image with representation of the needle during the procedure (**Figure 3**). This allows the user to correct the angle of the needle, if necessary, before contacting the bone. The optimal point and angle of insertion was recently studied in a computerized model.[11] This interface can be turned off or on.

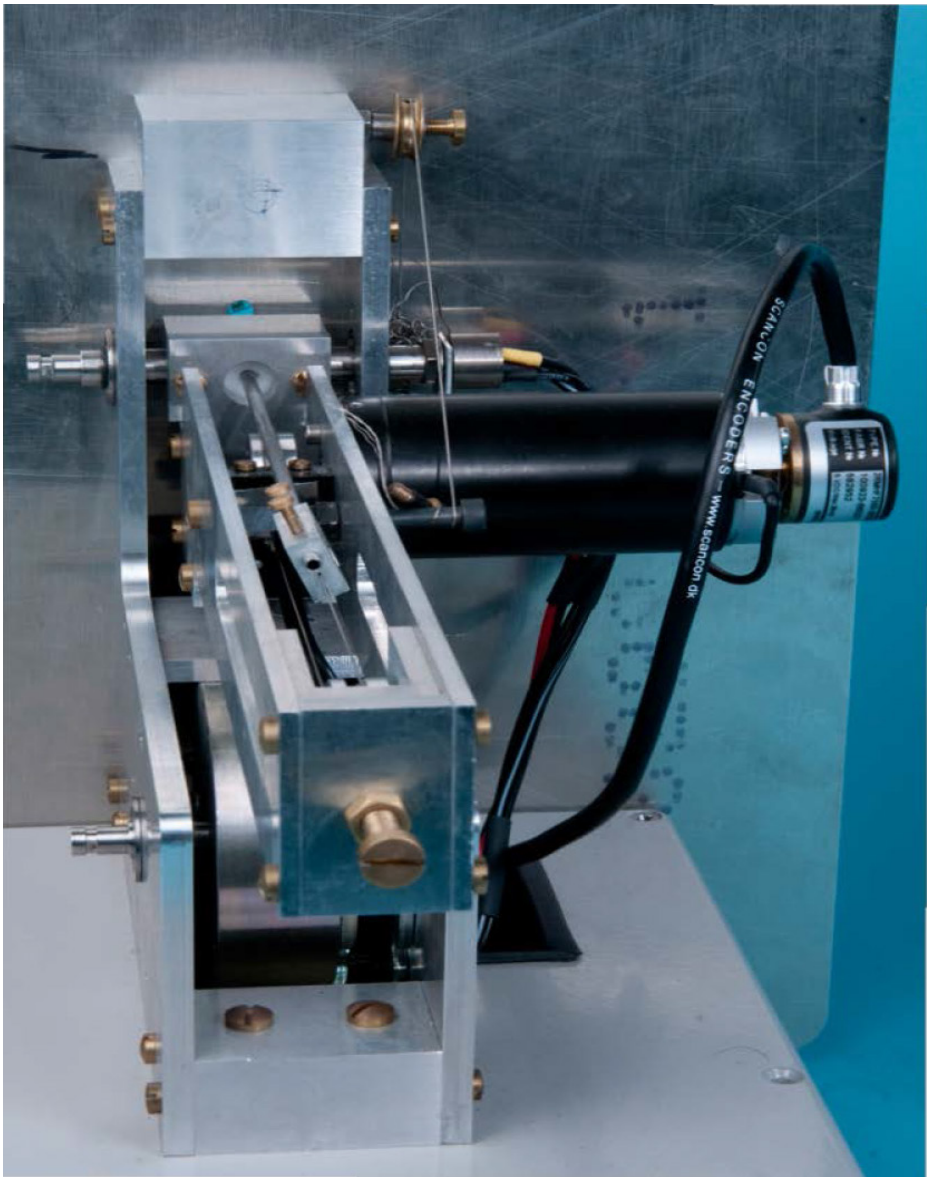

Figure 2. Details of mechanical construction of the simulator, back side of metal plate

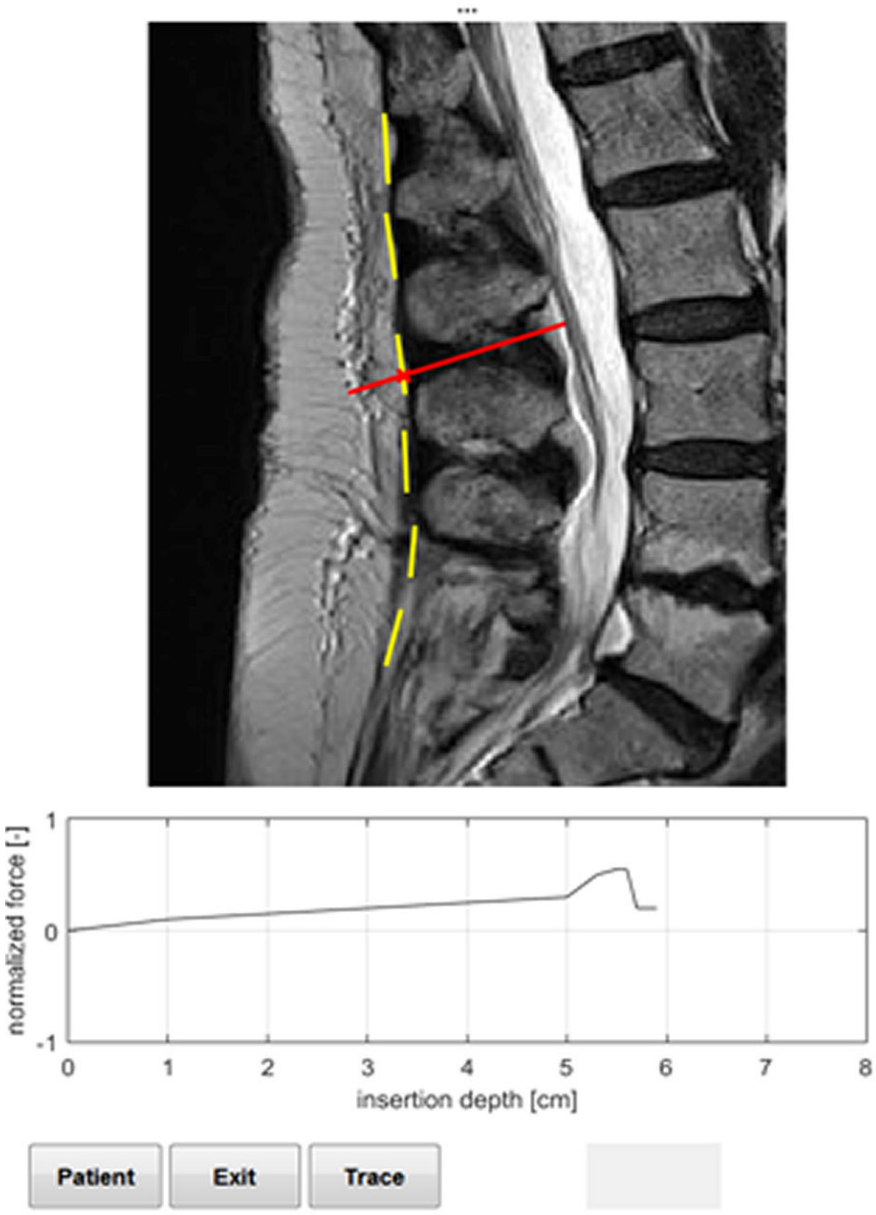

Figure 3. Screen shot of monitor visualizing real time needle advancement during the procedures with visualization aid.

Anesthesiologists, anesthesiology residents and students of our department were included. Their experience in epidural needle placement varied from zero procedures to over a thousand. We divided the participants into two groups based on their experience. Novices were defined as having performed up to 30 epidural punctures, as suggested by the literature.[12-15] The experienced group was defined as those having performed more than 30 epidurals. Participants were asked to position/align the needle in the sagittal plane and then to insert it into the epidural space along a straight line. Upon reaching the epidural space the participants gave oral confirmation and proceeded with the next interspace until completion of the study task. Thus, each participant performed 12 epidural needle placements in total, six with and six without the visual support turned on. Whether the participant started with the visual support turned on or off was decided by computer randomization. We randomized participants to: either performing the epidurals *with simultaneous needle visualization* on MRI or to *first perform the punctures blindly*. In this manner, the value of a pre-scan visualization aid was evaluated. All participants received a standardized introduction to the simulator that included the content and features of the simulator and an explanation of the study questions. Participants were informed that the purpose of this study was to evaluate the simulator and not the participants and that all data were saved anonymously. After performing 12 epidural needle placements, participants completed a form consisting of eleven questions to be answered on a modified Likert Scale.

Those questions addressed the participants' experience with the simulator and its advantage and added value as a teaching device. Participants were asked to provide their age, sex and experience with epidural needle insertions. We registered: number of passes, bone contacts, dura contacts, spinal taps as well as the time for the epidural procedure. The participants received feedback on their performance after completion of the study task and after answering all questions in the form.

All data were analyzed using SPSS® Version 22 (SPSS Inc., Chicago, IL, USA). We tested the simulator for face and construct validity. Face validity was tested by assessing the "realism" of the simulator based on the feedback of the participants, who rated their experience on a Likert scale (strongly disagree=1, strongly agree=5). The consistency of the questionnaire was tested with Cronbach's

alpha score. The simulator's construct validity was evaluated by comparing experienced and inexperienced groups for bone contacts, dura contacts, spinal taps, time taken for epidural needle placement and number of attempts. The correlations were tested by Pearson's chi square test. The influence of the visual aid was assessed by comparing the results with the visualization aid on or off by means of the Wilcoxon signed rank test. The effect of visualization aid prior to performance without visualization was tested by Mann-Whitney U test. A p-value of < 0.05 was considered statistically significant.

Results

Sixty-eight participants were included in the study. The participants were divided in two groups based on their previous experience in epidural needle placement. Forty-eight participants were defined as 'expert group' (more than 30 epidural needle placements) and 20 participants were assigned to the 'novice group'. Demographic data are displayed in table 1.

Table 1 Demographics

Group	novice	experts	Total
Total number (male/female)	20 (11/9)	48 (32/16)	68 (25/43)
Median age (range)	29 (23-35)	37 (29-66)	35 (23-66)

The face validity questionnaire revealed a satisfactory overall score of 3.7(2.0-4.8) on a 5-point scale. The highest scores were given for usefulness of the simulator (4.15 ± 0.83) for hand-eye coordination and intuitivity, while the lowest scores were given for adequacy of the simulator to measure performance and ligamentum flavum resistance (table 2). High marks were also given for the loss of resistance experience with experts grading 4.0 ± 0.9 and novice 3.8 ± 0.9 on average. Scores regarding face validity given by experts and novices did not differ significantly.

Table 2 Rating of the simulator by participants

	Question:	novice		experts		total	
		mean	SD	Mean	SD	mean	SD
1	*The simulator handling is intuitive*	4.2	1.06	3.96	0.71	4.03	0.83
2	*The resistance of the plunger is realistic*	3.55	0.76	3.63	1.04	3.60	0.96
3	*Movement of the needle through the simulated tissue is realistic*	3.5	0.61	3.15	0.99	3.25	0.9
4	*Bone contact with the needle is realistic*	3.45	1.05	3.79	0.77	3.69	0.87
5	*The resistance of the lig.flavum is realistic*	3.05	0.69	3.23	0.93	3.18	0.86
6	*The loss of resistance is realistic*	3.75	0.91	4.04	0.92	3.96	0.92
7	*The simulator looks realistic*	3.6	0.6	3.29	1.07	3.38	0.96
8	*The simulator is useful for training hand-eye coordination*	4.4	0.82	4.04	0.82	4.15	0.83
9	*The simulator is an adequate tool to learn placing epidural catheters*	4.2	0.62	3.9	0.99	3.99	0.91
10	*The simulator is a useful tool for educating anesthesiologists*	4.15	0.81	3.88	0.94	3.96	0.9
11	*The simulator is an adequate tool for measuring performance*	3.15	0.81	2.88	1.18	2.96	1.08

For the questionnaire's consistency and reliability a Cronbach's alpha score of 0.82 was calculated.

Table 3 illustrates no significant difference between the experienced and novice group regarding total bone contacts, number of attempts and procedure time, although there was a slight tendency for an increased total number of attempts in the novice group (p=0.06). However, the novices had significantly more dura contacts (p=0.001) and spinal taps (p=0.04).

Table 3. Effect of experience on different parameters (CI 95%)

Parameter	mean (range)		p-value
	experienced	Novice	
total number of attempts	18.7 (12-42)	22.1 (14-41)	0.06
total bone contacts	6.2 (0-25)	8.7 (2-27)	0.10
total procedure time (s)	425 (150-1684)	440 (207-708)	0.80
total dural contacts	0.4 (0-3)	1.5 (0-6)	0.001
total spinal taps	0.07 (0-2)	0.4 (0-4)	0.04

2-tailed independent samples T test with equal variances assumed

With the visual aid turned on, participants made significantly less bone contacts

(2.8 (0-14) versus 4.3 (0-23)), needed less attempts (8.9 (6-19) versus 10.9 (6-29)) and required less time to finish the task (197s (55-1079) versus 233 (53-605)) when compared to attempts without the visual aid. However, turning visual aid on or off made no statistically significant difference with respect to dura contacts and spinal taps (table 4).

Table 4. Comparison between participants performance with visual aid usage off or on

Parameter	mean (range)		p-value
	Visual aid off	Visual aid on	
total number of attempts	10.9 (6-29)	8.9 (6-19)	0.01
total bone contacts	4.3 (0-23)	2.8 (0-14)	0.02
total procedure time (s)	230 (27-605)	194 (0-1079)	0.02
total dural contacts	0.4 (0-5)	0.3 (0-2)	0.07
total spinal taps	0.12 (0-4)	0.04 (0-2)	0.4

Visualization in the first round led to less attempts and a shorter procedure time (table 5). There was no difference for bone contacts, dura contacts and spinal taps between the groups that practised with the visual aid first compared to those using visual support in the second round.

Table 5. Comparison between participants 'blind' performance before or after training with the visualization aid

Parameter	mean (range)		p-value
	Before visualization training N=36	After visualization training N=32	
total number of attempts	11.9 (7-27)	9.7 (6-29)	0.047
total bone contacts	4.9 (0-23)	3.5 (0-23)	
total procedure time (s)	279 (70-574)	182 (53-605)	0.01
total dural contacts	0.5 (0-5)	0.3 (0-2)	
total spinal taps	0.2 (0-4)	0 (0)	

Discussion

Face validity of our simulator is rated as good but not perfect (3.7 out of 5). In the clinically important measures number of dura contacts or spinal taps, the experienced anesthesiologist performed significantly better than the novices. On the other hand, we found no differences regarding surrogate parameters as number of attempts or bone contacts or total time required. Possibly experienced anesthesiologists were more cautious in the proximity of the epidural space. Turning on the visual aid decreased bone contacts, led to fewer attempts and less time required. The difference in number of dura contacts or spinal taps did not reach significance. Finally, practising with visualization improved the performance time and decreased the number of attempts even after the visualization support was turned off. Although the results generally underline the validity of the simulator and the advantage of visualization, they also raise questions regarding adequate variables to measure good performance.

Overall satisfaction of the participants with the simulator was reasonable to good depending on the item asked. All 11 items were rated as good on the average (> 2.5 of 5 on a Likert Scale) with very good ratings for usefulness for training hand-eye coordination (4.2) and intuitive handling (4.0). On the other hand, the simulation of the ligamentum flavum and movement of the needle through the tissues as well as the appearance of the simulator were rated less favourably. Since resistance to needle movement is not influenced by faster or slower movement of the needle, the handling of the needle feels rather unnatural and might explain the lower marks given on this parameter. Having only two degrees of freedom, our simulator implemented some, but not all features of the real procedure and therefore participants agreed less on the statement that the simulator can be used to measure performance.

There is no unique variable to measure performance of procedures in regional anesthesia. Usually, the ability to perform a block under experienced supervision without help is rendered as 'success' in clinical studies. However, more objective measures are not validated. Therefore, we used 5 different variables to measure success. We defined the avoidance of dura contact and spinal tap as being clinically most important. Since we expected the incidence to be low, we also instituted 3 surrogate variables (number of bone contacts, number of attempts

and time required). Clinical experience was significantly correlated with less dura contacts and spinal taps. Surprisingly this was not the case with other surrogate parameters (table 3). Two other studies using different simulators also failed to demonstrate a correlation between previous experience and bone contacts, procedure time and number of attempts.[5 16] In our study procedure time was not correlated at all, but there was a (not significant) tendency towards a smaller number of attempts and bone contacts by the experienced group. It seems as if experience becomes important during the more crucial part of the procedure. However, this is just one possible interpretation and it might also be possible that the simulator was more realistic when the epidural space was reached.

Compared to clinical practice all participants seemed to require a large amount of time, had more attempts and bone contacts. This may be due to the fact that the simulator was based on tomographic pictures of the lumbar spine taken in the supine position. In the clinical situation the epidural puncture is performed on a flexed vertebral column in the sitting or lateral decubitus position causing the opening of the posterior interlaminar space and thus changing the relationship of osseous and soft tissues.[17 18] This might be the reason for the relatively high number of bone contacts and attempts in both groups. Furthermore, this might have led to equality between groups. However, after reaching the ligamentum flavum the situation seemed to be more realistic and here the performance of experienced group was superior. Thus, regarding the clinically important measures the construct validity was demonstrated, whereas it remains unclear why this did not show up in the less important surrogate parameters.

As expected, after enabling the visual aid, participants made less bone contacts, needed fewer attempts and required less time to finish the task. This is in accordance with data proving the advantage of pre-scan ultrasound imaging on success rate of epidural punctures.[19 20] Mirroring the clinical situation, a pre-scan of the anatomical structures could improve the precision of the simulated puncture. The possible programming of our simulator with different radiologic scans could help future students: first take an ultrasound scan of the patient, upload this into the simulator and practice this specific patient on the simulator before returning to the patient to do the procedure. Such an individualized planning may facilitate or enable otherwise difficult or impossible punctures.

The impact of the visual aid was also observed when participants who had it turned on for their first six attempts then performed the following six attempts without visual support. Hence, it required less time and participants needed fewer attempts, which could be attributed to learning and acquiring proficiency and the benefit of the visual aid as a learning tool. However, the incidence of dura contact and spinal taps remained unaltered.

We could demonstrate face and construct validity of this simulator with only 2 degrees of freedom. Thus, even a low-fidelity simulator is useful in learning epidural punctures. However, we still have a long way to go before we develop a more realistic simulator with more degrees of freedom, more realistic feeling while advancing the needle, incorporation of ultrasound pre-scans into the simulator in order to individualize training and finally the proof that novices could accelerate their learning curve using a simulator, having the "expert" skills when performing their first epidural on a real patient.

In conclusion, the TU-Delft Simulator for Epidural Needle Skills (SENS) has a sufficient face and construct validity for teaching epidural needle placement to anesthesiology residents. We showed the value of real-time visualization and demonstrated that pre-procedure visualization led to a higher precision. This was present even when the following simulations were done without visualization. Development of high-fidelity simulators for epidural punctures based on ultrasound pre-scans might not only abandon the need to train motor skills on a patient, but will also enable or at least facilitate epidural punctures in anatomically difficult situations.

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Chapter 9

Microbiological and scanning electron microscopic evaluation of epidural catheters

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Abstract

Background

Epidural catheters are frequently colonized by gram-positive bacteria. Although the incidence of associated epidural infections is low, their consequences can be devastating. We investigated bacterial growth on epidural catheters by quantitative bacterial culture and scanning electron microscopy (SEM) in order to explore the patterns of epidural catheter colonization.

Methods

28 patients undergoing major abdominal surgery with thoracic epidurals (treatment ≥72 h) were studied. Before removal of the catheter, the skin surrounding the insertion site was swabbed. The entire catheter was divided into extracorporeal, subcutaneous and tip segments. Skin swabs and catheter segments were quantitatively cultured, bacterial species were identified, and SEM was performed on four selected catheters.

Results

27 of 28 catheters were included. The percentages of positive cultures were: skin swab 29.6%, extracorporeal segments 11.1%, subcutaneous segments 14.8%, and tip segments 33.3%. One patient was diagnosed with catheter-associated infection. *Staphylococcus epidermidis* was cultured from the skin and the catheter extracorporeal, subcutaneous and tip segments. SEM of this catheter showed bacteria-like and intraluminal host cell-like structures. SEM of two other catheters showed intraluminal fibrin networks in their tip segments.

Conclusions

We present the first SEM pictures of an epidural catheter with bacterial infection. Bacterial growth developed from the skin to the tip of this catheter, indicating the skin as primary source of infection. By SEM, catheters with low levels of bacterial growth demonstrated an intraluminal fibrous network which possibly plays a role in catheter obstruction.

Introduction

The use of epidural catheters has a potential risk of infection. The documented incidence of epidural catheter infection is rather low but, such infections can potentially be devastating. The incidence of epidural catheter-associated superficial infections ranges from 5% to 12% and that of associated deeper tissue infections, potentially causing permanent neurological damage, ranges from 1:1,000 – 1:100,000.[1-3] Although not proven, bacterial colonization of epidural catheters may be a source of epidural infection.[4 5] The colonization rate of epidural catheters is higher than of actual infection, varying from 5% to 30%, with coagulase-negative staphylococci (CNS) being the most frequent pathogen.[4-9] There are various proposed routes of epidural catheter colonization. Skin flora may spread along the catheter or its lumen, or become a source of contamination during needle or catheter insertion. Colonization can also occur via hematogenous spread from a distant source or via contaminated infusion fluid or delivery systems.[10] The most common route of colonization is thought to be skin flora migrating along the epidural catheter.[9] Skin disinfection is a standard procedure prior to epidural catheter insertion. However, bacteria residing in the deeper layers of the skin, including hair follicles, cannot be reached by disinfectants.[11] Such resident bacteria recolonize the skin and epidural catheters when the protective skin barrier is breached by needle insertion.

The pattern of bacterial colonization along the epidural catheter has never been investigated in detail. In this observational study, we explored whether bacteria present *on* or *in* the skin are the primary source of colonization of the epidural catheter which progresses along the outer catheter surface towards the tip and from there potentially into its lumen. Therefore, we examined skin swabs, extracorporeal segments, subcutaneous segments and tip segments of epidural catheters from patients receiving anesthesia and analgesia for bacterial growth.

Methods

In this 6-month exploratory prospective study, 28 ASA 1 – 3 patients with thoracic epidural catheters (B.Braun Medical B.V. epidural anesthesia set 18G) *in situ* for at least 72 h were included after approval by the ethics committee

(W14_264#14170320) and after giving informed consent. Initially, catheters of 30 patients were collected, but 2 patients were excluded since they did not fulfill the study criteria (no thoracic epidurals, ≤12 hrs *in situ*). We chose 72 h as a cutoff point to have a higher chance of finding bacterial growth and subsequent infection, since most infections concerning epidural catheters start around the third day.[12 13] Patients 14 and 9 were treated with epidural therapy for 69 and 70 hrs respectively, instead of the intended 72 hrs treatment duration. Since this marginal time difference does not significantly change the level of bacterial colonization, we have decided to include their data. All included patients underwent abdominal surgery, except patient 8, who underwent thoracic surgery. The catheters were placed according to a standardized local protocol based on the guideline by the Association of Anaesthetists of Great Britain & Ireland (AAGBI).[14] The epidurals were inserted in the operating room under sterile conditions. The anesthesiologist prepared for a sterile procedure: hand disinfection, sterile gown, face mask, head covered with operative head gear and sterile gloves. Patient was positioned by assistant who was also wearing a face mask and head gear. After twice disinfecting the skin with 0.5% chlorhexidine in 70% alcohol, and waiting for it to dry, the sterile tray with epidural set was unpacked, and the dorsal side of patient was draped with sterile plastic surgical draping. The epidural catheter was inserted at the level appropriate for the operative procedure (T4-T8) but not tunneled. Fixation was done using StatLock® Stabilization Device covered by a Tegaderm® transparent surgical dressing and bacterial filter connected to the epidural catheter. Intravenous antibiotic prophylaxis (cefazolin, metronidazole) was administered after epidural catheter placement and prior to incision. Standard postoperative epidural analgesia was given by means of patient-controlled epidural analgesia with sterile pharmaceutically-prepared bupivacaine 0.125% or bupivacaine 0.125% combined with 1 µg/ml sufentanil. Epidural therapy was ended by the acute pain service after at least 72 hrs, if postoperative pain remained below 4 (Numeric Rating Scale) after discontinuation of epidural infusion. Catheters were removed according to the study protocol: first a skin swab was taken surrounding the point of insertion. This was followed by skin disinfection with 0.5% chlorhexidine in 70% alcohol to reduce the incidence of contamination of skin flora during withdrawal and subsequent removal of the catheter. Directly after catheter removal, the catheter was cut with sterile scissors in two segments: the proximal segment (extracorporeal and subcutaneous) and the distal segment (tip). The segments and skin swab were transported to the

microbiology research laboratory in sterile tubes.

Microbiological methods: The subcutaneous and tip catheter segments were cut in 0.5 cm segments under sterile conditions to assess a possible gradient of bacterial growth along the catheter (Figure 1). The catheter segments were labeled as follows: EC1 for the extracorporeal segment (outside the patient), SC1, SC2, SC3 for the subcutaneous segments and T1, T2, T3 for the tip segments (Figure 1). The skin swab was labeled as SkSw1 (Figure 1). The segments were used for either quantitative bacterial culture, scanning electron microscopy (SEM) or were stored frozen (-80 °C) for later evaluation (Figure 1). Bacteria of the catheter segments were retrieved by the sonication method as previously described, with minor adaptations.[15] In brief, catheter segments were sonicated for 30 sec in 500 µl sterile 0.9% NaCl at 35 kHz in a sonicator water bath (Elma, Transsonic 460) followed by vortexing for 10 sec. Sixty microliter aliquots of the sonicate fluid (1:8.3 of total sonicate fluid) were plated on blood agar plates in duplicate and incubated either aerobically or anaerobically at 37°C for 48 hrs up to 96 hrs. In addition, ten-fold dilution series of the sonicate fluids were made and incubated under the same circumstances as described above to allow precise enumeration in case of bacterial growth above the countable range. If bacterial growth was observed, colonies were counted and distinguished based on colony morphology. Bacterial growth was quantified in colony forming units (CFU) per catheter segment based on the numbers of CFU recovered and the respective dilution. Bacterial growth on the skin is expressed in CFU per swab. We defined a bacterial culture as positive if we found ≥1 CFU on the agar plates. The lower detection limit of bacterial quantification was <8.3 CFU and the upper detection limit was ≥4165 CFU. The species of retrieved bacteria were identified using Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF; Microflex LT, Bruker Daltonic).[16] Finally, we performed SEM on four selected catheters: a control catheter (not inserted in a patient), a non-colonized catheter (patient 14), a catheter with low levels of bacterial growth (patient 29) and a catheter of a patient with clinical infection (patient 5). Catheter segments for SEM were fixated in 4% formaldehyde. To ensure fixation of the lumen of the catheter segments, they were placed under vacuum for 30 sec. Fixated catheter segments were prepared for SEM according to standardized protocols. Catheter segments were imaged using a Zeiss Sigma-300 FE scanning electron microscope.

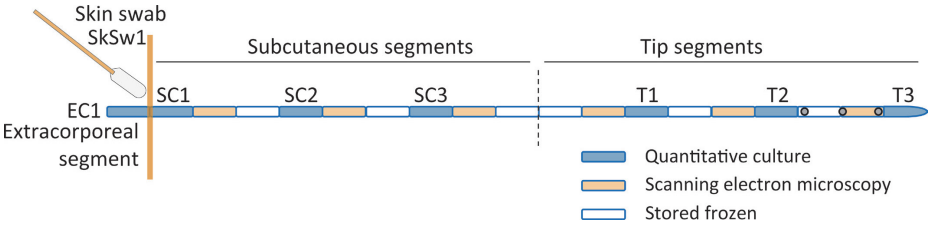

Figure 1. Schematic overview of epidural catheter segments and skin swab used for quantitative bacterial culture (blue segments) or scanning electron microscopy (orange segments). EC1, Extracorporeal segment; SkSw1, Skin swab; SC1, SC2, SC3, Subcutaneous segments, from superficial (SC1) to deep (SC3); T1, T2, T3, Tip segments (T3 is end of epidural catheter).

Results

Of the catheters collected from the 28 patients included in the study, 27 catheters were investigated. One catheter was excluded from analysis due to non-adherence to the protocol. One patient, patient 5, had signs of local infection (redness of skin, tenderness and pus around the insertion site). The catheter tip segment of this patient was cultured by the microbiology diagnostic laboratory using the standardized roll plate method[17] instead of the sonication method used in the microbiology research laboratory.

Of the 27 cultured catheters, 10 (37%) catheters had some level of bacterial growth on the subcutaneous and/or tip segment. The majority of the patients had no bacterial growth (0 CFU) on any segment of the catheter or on the skin (Table 1). The number of patients (4) with subcutaneous segments positive for bacterial growth (≥ 1 CFU) was lower than the number of patients (9) showing positive bacterial growth on the tip of the catheters (Table 1).

Table 1. Patients with bacterial growth on epidural catheters and skin

	Extracorporeal segment	Skin swab	Subcutaneous segment	Tip segment
Patients, n (%)				
0 CFU	24 (88.9%)	19 (70.4%)	23 (85.2%)	18 (66.7%)
≥ 1 CFU	3 (11.1%)	8 (29.6%)	4 (14.8%)	9 (33.3%)

CFU, colony forming units.

Positive bacterial growth is indicated by ≥ 1 CFU, and no bacterial growth as 0 CFU, n=27.

All positive cultures of the subcutaneous and tip segment exhibited low numbers of bacteria, no distinct bacterial growth pattern and corresponding patients had no signs of infection, with the exception of patient 5 (Table 2). Moreover, patients with positive cultures of the subcutaneous or tip segment did not always have positive cultures of the extracorporeal segment or the skin swab (Table 2), indicating no direct correlation between skin colonization and catheter colonization in these patients. In patient 5, a clinically relevant skin infection was diagnosed 96 hrs after insertion of the epidural catheter. The catheter of this patient was removed immediately, and the patient was monitored closely for 48 h. In contrast to the other catheters, which were cultured in the experimental laboratory, this epidural catheter was cultured in the clinical laboratory because of this clinically relevant infection. Clinical treatment of patient 5 consisted of 2 days of "watchful waiting" with no antibiotic therapy, as there were no signs of aggravating local or systemic infection. During this period, the patient developed no further signs of systemic or neuraxial infection. The bacterial growth levels decreased from skin to tip and culture of skin swab and epidural catheter revealed a monoculture of *S. epidermidis*.

The bacterial species isolated from the epidural catheters are shown in Table 3. The most frequently isolated bacteria were coagulase-negative staphylococci (CNS) and *Micrococcus luteus*, both part of the normal skin flora. The bacterial population present on the subcutaneous and tip segment mostly consisted of a monoculture whereas the population retrieved from the extracorporeal segment and the skin swab mostly consisted of mixed bacterial species.

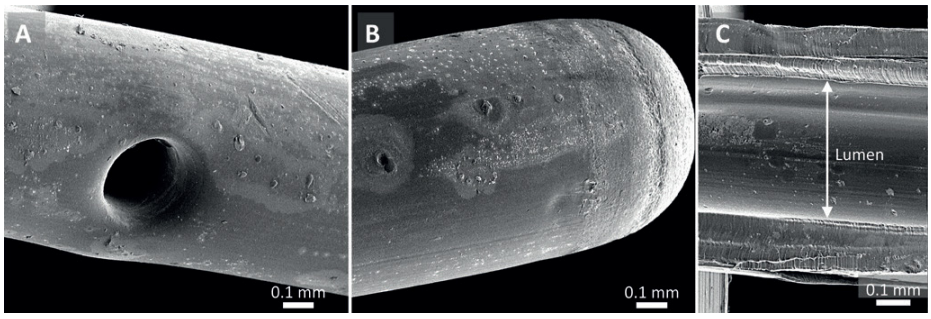

Figure 2. Scanning electron microscope images of sterile epidural catheter, not inserted in patient. (A) Outer surface of catheter with side hole. (B) Outer surface of the tip. (C) Cross-section of catheter showing catheter wall and lumen. White bar indicates scale.

Table 2. Pattern of bacterial growth on epidural catheters

Patient no.	Numbers of CFU cultured from Extracorporeal segment	Skin swab	Subcutaneous segment			Tip segment			Duration of epidural, h
	EC1	SkSw1	SC1	SC2	SC3	T1	T2	T3	
2	316.5	0	0	0	0	0	0	0	173
8	0	16.66	0	0	0	0	0	0	76.5
11	0	≥4165	0	0	0	0	0	0	73.5
12	0	3332	0	0	0	0	0	0	101
14	1532.7	0	0	0	0	0	0	0	69
18	0	≥4165	0	0	0	0	0	0	74
17	0	0	<8.3	0	0	0	0	0	99
1	0	≥4165	0	0	<8.3	16.7	0	0	77
13	0	≥4165	0	0	0	25.0	0	0	80
27	0	0	0	0	0	0	<8.3	0	73
29	0	≥4165	0	<8.3	0	0	0	<8.3	72
7	0	0	0	0	0	0	0	<8.3	76
9	0	0	0	0	0	0	0	<8.3	70
4	0	0	0	0	0	0	41.7	0	96
3	0	0	0	0	0	0	0	25.0	73
5*	≥4165	≥4165	1774.3	158.3	91.6	Diagnosed as positive and evaluated in clinical lab			96

Abbreviations: CFU, colony forming units; EC1, extracorporeal catheter segment; SkSw1, skin swab; SC1-SC2-SC3, subcutaneous catheter segments, from superficial (SC1) to deep (SC3); T1-T2-T3, catheter tip segments, T3 is the utmost tip in epidural space; h, hours. Values indicate numbers of CFU or *in situ* duration (h). No growth is indicated as 0 CFU. Lower detection limit 8.3 CFU. Upper detection limit 4165 CFU. *Patient with superficial infection. The average duration of epidural therapy in non-colonized patients was 95 hrs (range 72 - 171 h) (data not shown). **Note:** Many diagnostic microbiology laboratories define at least 100 CFU in quantitative studies as a threshold indicating colonization.

SEM examination of sterile epidural catheters revealed smooth areas but also irregularities on the outer surface and lumen of the catheter (Figure 2). SEM of the infected catheter showed biological deposits on the outer surface with spherical structures resembling staphylococci (Figure 3A, 3B, 3C). In the lumen of this infected catheter adherent host cell-like structures were observed (Figure 3D). The extensions emerging from these structures resemble the pseudopodia of immune cells (e.g. macrophages) (Figure 3E). Analysis of the catheters with

low levels of bacterial growth revealed biological deposits on the outer surface of the catheter (Figure 4A). The lumen of the tip segments of this catheter revealed a network of fibrin-like fibers with erythrocytes and blebs (Figure 4B, 4C, 4D, 4E). Interestingly, this was not the case in the corresponding subcutaneous or extracorporeal segments. Similar intraluminal structures were observed in a non-colonized catheter (data not shown).

Table 3. Bacterial species cultured from epidural catheters and skin swabs

	Extracorporeal segment	Skin swab	Subcutaneous segment	Tip segment
Patients positive for bacterial growth, n				
CNS[1]	2	4	1	1
Micrococcus luteus	0	0	1	5
Propionibacterium acnes	0	3	0	0
Streptococcus spp.[2]	1	0	0	1
Bacillus spp.[3]	0	1	1	1
Kocuria rhizophila	0	0	0	2
Neisseria spp.[4]	1	0	0	0
Rhodotorula mucilaginosa	1	0	0	0
Actinomyces oris	1	0	0	0
Unknown	1	3	1	0

[1]CNS = coagulase-negative staphylococci which include *S. epidermidis, S. saccharolyticus, S. capitis, S. warneri.* [2]*Streptococcus* spp.: *S. salivarius, S. mitis.* [3]*Bacillus* spp.: *B. simplex*, *B. horneckiae*, *B. licheniformis.* [4]*Neisseria* spp.: *N. perflava, N. flavescens.*

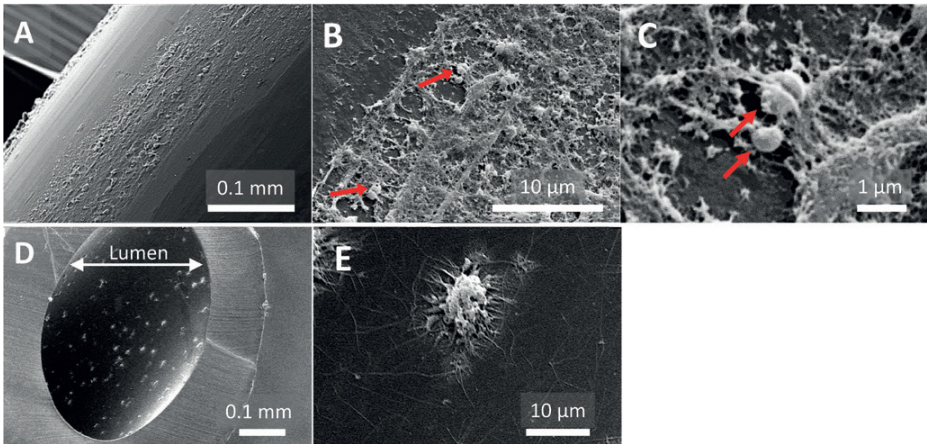

Figure 3. Scanning electron microscope images of subcutaneous segments of infected epidural catheter (patient 5). Outer surface of catheter with (A) low, (B) medium or (C) high magnification; The surface of the catheter is partially covered with biological deposits with staphylococci-like spheres, indicated by red arrows. Side view of catheter lumen with adherent cell-like structures in (D) low and (E) medium magnification. Pseudopodia are emerging from the cell-like structures. White bar indicates scale.

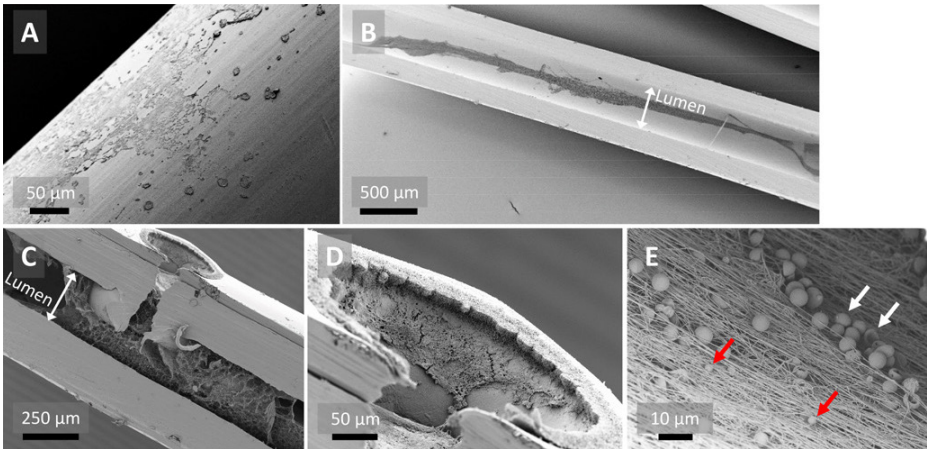

Figure 4. Scanning electron microscope images of tip segments of epidural catheter with low levels of bacterial growth (patient 29). (A) Outer surface of catheter with biological deposits. (B) Cross-section of catheter segment showing intraluminal fibrin-like fibers stretching in the length of the catheter. (C) Cross-section of catheter with side hole showing intraluminal fibrous network and clot. Fibers seem to progress from side hole to intraluminal space. (D) Higher magnification of side hole, showing organized layer of cell-

like structures lining the border and interior of the side hole. (E) Higher magnification of fibrin-like fibers with erythrocytes and blebs embedded in the fibrous network, indicated by white and red arrows respectively. Black bars indicate scale.

Discussion

Bacterial colonization of the skin is often suggested as a potential source of infection of epidural catheters. In this exploratory study we show a pattern of colonization decreasing from the skin to catheter tip in one patient with a clinical relevant infection. SEM of this catheter revealed biological deposits with staphylococcal-like structures and intraluminal immune-cell-like structures. Catheters with low levels of bacterial growth had no distinct bacterial growth pattern. Interestingly, SEM revealed a dense intraluminal fibrous network in these non-infected catheters.

A third (33%) of the patients had some level of growth on the epidural catheter tip segments, which corresponds with data from the literature.[7] In contrast to the patient with clinical infection, bacterial growth on the skin of patients without clinical infection was not a predictor for bacterial growth on the catheter tip. The low numbers of bacteria cultured from the tip segments may have been contamination occurring during catheter removal or processing. The catheters with low-levels of bacterial colonization, along with significant skin colonization, showed little consistency of bacterial species between that on the skin and that affecting the catheter, indicating bacteria from distant sources. Further studies are needed to evaluate whether high skin colonization may be a predictor for catheter colonization in case of longer catheter duration.

In the absence of a standardized definition, relevant bacterial growth on epidural catheters tips, also designated as bacterial colonization, is often defined according to the criteria used for central venous catheter (CVC) tips. Depending on the culture method, reference cut-offs of ≥15 CFU (semi-quantitative) or ≥100 CFU (quantitative) are used to define bacterial colonization and these are associated with clinical infection in CVC.[17 18] For epidural catheters this relation between bacterial colonization and infection is uncertain when using these cut-offs.[4 7 8] We defined a bacterial culture as positive if we found ≥1 CFU on the catheter

segment or skin. If we would apply the reference cut-off to our data, only the case of infection would reach this cut-off, and all patients without infection symptoms would not. This indicates that the cut-off used for relevant bacterial growth on CVC tips may also give a good estimation of relevant bacterial growth on epidural catheter tips, but this should be investigated in a more extensive study.

Biological deposits on the surface of catheters are a common phenomenon with CVCs. Upon blood contact, the catheter surface is coated with host-derived proteins (e.g. fibrin) to which bacteria can attach and form a biofilm.[19] A comparable process may occur with epidural catheters when blood ends up on the catheter tip during catheter insertion. Immunohistochemistry could reveal whether the biological deposits observed on the catheter surfaces are host-derived or bacteria-biofilm-derived. Interestingly, the observed intraluminal fibrin-like fibers seemed to enter from the side holes into the lumen and became less in density as they progressed to the subcutaneous catheter segments. This phenomenon of an intraluminal fibrous network (clot) in epidural catheters has never been shown before and might be one cause of catheter obstruction.
The main limitation of our study is the small number of patients and catheters investigated. However, this was an exploratory study to investigate and image the pattern of bacterial colonization on the full length of epidural catheters rather than only investigating catheter tips. The inspected catheters displayed some interesting new findings, such as suspicion of biofilm formation, host cell invasion and fibrin clot formation inside the catheter tip which have never been demonstrated before.

In conclusion, our data indicate that the level of bacterial colonization on epidural catheters is low and only in the case of clinical infection the skin seems the primary source of bacterial colonization. Our data also suggest that an intraluminal fibrous network develops from the side holes into the lumen and possibly plays a role in catheter obstruction.

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Chapter 10

Summary of Thesis 'Safety and quality aspects of regional anesthesia'

Aim of this thesis was to investigate various aspects of currently used methods in the practice of regional anesthesia (RA). Effectivity, and specific safety aspects of techniques was the focus of research.

We provide an overview and discuss recent developments, how implementation of RA can reduce perioperative opioid use. The global opioid crisis adds an important reason to the urgency of using RA techniques. A transitional pain service can aid in further reducing opioid use, and might also help to shorten the duration of hospital stay. Safety in RA is influenced by several factors: a pre-procedural checklist to ascertain the correct side of block and procedure, proper hygiene measures during the performance of the block (probe cover, ultrasound machine cover, disinfection, single use ultrasound gel), recommended technique and dosing while watchful for local anesthetic systemic toxicity (LAST), use of safety connectors (NR fit), and use of simulators during teaching and learning procedures. Proper use of ultrasound guidance in performing nerve blocks reduces incidence of LAST, pneumothorax and intravascular injection of local anesthetic during the procedure. Surgery performed under RA can prevent aerosol formation, inherent to airway management in general anesthesia, and is therefore useful during the Corona pandemic. A phenomenon described after the block wears off, characterized by disproportionately high (higher than in patients without block) pain, is called 'rebound pain'. Timely use of multimodal analgesia aids in reducing rebound pain (chapter 2).

The first comparative analysis of this thesis focuses on patient controlled epidural analgesia (PCEA) and continuous epidural analgesia (CEA). We set out to investigate whether PCEA is superior to CEA in non-obstetric surgery. Our hypothesis, based on evidence in the obstetric population, was that employment of PCEA compared to CEA would lead to reduced pain scores in rest and movement. In a systematic review of the literature we analyzed data from ten randomized controlled trials and one cohort study, including a total of 1,687 patients. Three studies found reduced pain scores during use of PCEA. Seven studies showed a reduction of epidural medication during PCEA. One study showed a reduction of systemic rescue analgesics and side effects of RA. PCEA offered comparable or better patient satisfaction than CEA in some studies. Two studies found that PCEA can reduce epidural top-ups. Overall, the included studies did not show a meaningful clinical important difference between PCEA

and CEA. Thus, the current evidence demonstrates only marginal advantages of PCEA in adult patients undergoing non-obstetric surgery (chapter 3).

PCEA is a refinement of CEA: In PCEA, a basal epidural infusion of the local anesthetic (often containing an opioid as additive) is supplemented by an on-demand bolus by the patient. Based on the previously available evidence from obstetric analgesia, we implemented PCEA in our hospital where CEA was the standard of care. Two years after implementation we retrospectively analysed the data to answer the following questions: 1. Does PCEA reduce the number of top-ups by a physician? 2. Is there a reduction of side effects and workload when using PCEA? 3. Is there a reduced duration of epidural pain treatment by using PCEA? We compared two cohorts of patients, one of them receiving CEA as standard care, and the other receiving PCEA, for a period of nine months. Both groups had comparable pain scores, measured by a numeric rating scale (NRS). We found that PCEA significantly reduced the number of patients requiring top-ups, resulting in a calculated difference in workload by staff in the PCEA patients. We could not demonstrate a reduced duration of epidural analgesic treatment between groups. Thus, our main conclusion was that PCEA leads to reduction in number of top-ups with non-significant clinical improvement of routine pain management (chapter 4).

The optimal treatment of postoperative pain is influenced by the anatomical location of surgery. Where epidural analgesia has been the treatment of choice for many decades, other forms of RA have gained popularity in recent years. The procedure-specific pain management (PROSPECT) collaboration is formed by anesthesiologists and surgeons. They develop recommendations and guidelines for analgesic treatment based on evidence pertaining to the procedure in question.[1 2] There are currently no PROSPECT recommendations relevant to talar and calcaneal fractures. Hallux valgus surgery guidelines include ankle block for the procedure, followed by rescue opioids in the postoperative period. The open reduction and internal fixation (ORIF) of calcaneal and talar fractures is currently treated by intravenous opioid (patient-controlled analgesia=PCA) or peripheral nerve block, similar to the PROSPECT guidelines for hallux valgus surgery.[3] Our hypothesis was that a continuous nerve block would reduce pain scores more effectively, and improve recovery as well as reduce the duration of hospital stay, compared to systemic analgesics (PCA- by opioid pump). We therefore

retrospectively analyzed patients in our hospital who had undergone ORIF repair of talar and calcaneal fractures, over a three-year period. Forty patients had received a continuous nerve block (catheter technique) whereas 47 patients had received PCA with morphine. Pain scores were comparable in both groups. Side effects, length of hospital stay, and incidence of wound infections were comparable. However, patients receiving PCA used a 30-fold higher morphine dose during treatment. Our conclusion was that even if nerve block did not lead to lower pain scores, there may be an advantage in the reduced use of opioids. Our sample size was too small to demonstrate advantages secondary to the reduced morphine use (chapter 5).

When calcaneal fractures are operated, there is a choice of additional analgesic techniques. Historically, the anesthesiologist and surgeon have both performed local infiltrative anesthesia, without aid of an ultrasound machine. Anatomical landmarks can be used to perform a block for postoperative analgesia. The advantage of the use of an ultrasound guided peripheral nerve block is to perform blocks of structures which are not easily seen without dissection, such as the sciatic nerve in the popliteal fossa. As there was no published evidence available at the time of our research, we chose to test our hypothesis: Are Ultrasound guided popliteal blocks by the anesthesiologist superior compared to ankle blocks performed by the surgeon during operative treatment of intra-articular calcaneal fractures? To this effect, we performed a retrospective analysis of all adult patients who had undergone surgery of a calcaneal fracture in a 5-year period. We compared the postoperative pain scores as one of the most important parameters, using the NRS. The NRS was scored preoperatively and postoperatively. Thirty-three patients received a popliteal block by the anesthesiologist and 50 patients received an ankle block by the surgeon. The NRS scores and cumulative amount of morphine did not differ between groups. Our conclusion was that both blocks are comparable in the treatment of postoperative pain in calcaneal fracture surgery (chapter 6).

Epidural anesthesia and analgesia is commonly used in hepato-pancreatico-biliary (HPB) surgery. To reduce potential complications associated with the anatomical location of the epidural technique (lesion to the spinal cord due to abscess or hematoma or direct traumatic puncture), new RA techniques, such as myofascial blocks are being validated. Fascial plane blocks are more frequently

used but there is still a lack of large trials proving efficiency.[4 5] Another method for pain treatment is the employment of a catheter, placed by the surgeon, in the proximity of the surgical wound during the operation. Wound catheters are a novel method of analgesia employed during HPB procedures.[6] The safety of injecting the local anesthetic via these wound catheters is yet unknown. In a randomized controlled trial comparing wound catheters and epidural analgesia for HPB surgery, there was a case suggestive of local anesthetic toxicity during the bolus administration of local anesthetic through the needle.[6] We performed an exploratory study regarding safety aspects of wound catheters in HPB surgery. 20 patients were included in the study. A bolus of 30 ml bupivacaine 0.25% through the wound catheter was compared with a total bolus of 10 ml of bupivacaine via the epidural catheter. We measured plasma levels of bupivacaine after a pre-peritoneal bolus (wound catheter group) and compared that to bupivacaine plasma levels after an epidural bolus injection. Plasma levels in the patients with wound catheters were higher than those in patients with epidurals, but were well below the toxicity limit of bupivacaine. Intraoperative use of opioids was lower in the epidural group, indicating that the subfascial bolus of local anesthetic at the start of the operation does not totally compensate for the lack of epidural analgesia during the operation (chapter 7).

The past decades have seen a reduction of use of the epidural anesthesia and analgesia due to various reasons. Technological developments have created possibilities with ultrasound, enabling imaging, so that peripheral anatomical structures can be visualized. This has resulted in alternatives for pain treatment with negligible risk of spinal cord damage. Exposure to perform epidural anesthesia and analgesia for novices is decreasing. Nevertheless, there are indications where epidural analgesia is the treatment of choice: peri-partum, open thoracotomies, and major abdominal surgery. Real-time imaging is not possible during the performance of an epidural puncture, and epidural analgesia needs specific needling skills. Therefore, to practice placement of epidural catheters on a simulator is valuable for novices to learn the technique. We were offered the opportunity to test a simulator developed by the TU Delft and performed a validation study including 68 participants: 48 experts (more than 30 epidural experience) and 20 novices (<30 epidurals) participated. This simulator is the only one with a simulated magnetic resonance imaging (MRI) guidance: the needle advances real-time inside an MRI spine image. Each participant

performed 12 punctures, of which half with MRI guidance. Our conclusions were that the look and feel of the simulator was rated as good by the participants. Experienced anesthesiologists performed better than novices regarding dura contacts and spinal taps. Prior visualisation on the simulator with MRI images improved performance by all participants. However, the commercial application of this prototype is not yet available. Further research is needed to determine the effect of training with this specific simulator in clinical practice (chapter 8).
The final chapter of this thesis concerns a safety issue that can evolve in the clinical course of the patient and is not easily visible to the clinical anaesthesiologist who spends most of the time providing care on the operating rooms. During the postoperative phase, epidural catheters can be colonized by bacteria, leading to local and systemic infection in patients. Even when using protective masks and sterile surgical gowns and gloves during placement, there is a chance of colonization of the epidural catheter from the deep skin flora of the patient. Colonization of the catheter can be followed by an infection, eventually leading to epidural abscess formation. Therefore, we performed an explorative study including 28 patients with thoracic epidural catheters for an intended treatment of at least 72 hours. We used scanning electron microscopy to examine possible patterns of bacterial colonization on the catheter after catheter removal. We found that 33% had some level of bacterial growth on the tip segments of the epidural catheter. In a patient with a clinically relevant infection, we showed that colonization decreased from skin to tip of epidural catheter. Upon SEM, biological deposits with staphylococcal and immune cell-like structures were seen inside the lumen of the catheters. Other catheters showed a dense intra-luminous fibrous network. The network develops from the side holes into the lumen and may possibly play a role in catheter obstruction (Chapter 9). Further research is needed to determine the exact nature of the fibrous network and its possible role in preventing infection by immobilisation of bacteria and immune cells.

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Chapter 11

General discussion and future perspectives

Epidural anesthesia is still an important tool for pain management in perioperative care, but can be refined further to reduce working failures. Current evidence concerning comparison of PCEA and CEA in non-obstetric surgery is of medium quality, and is lacking high-quality trials. The absence of evidence showing a significant benefit for PCEA does not imply that PCEA is not superior to CEA, but that we were unable to find sufficient support for our original hypothesis, namely that the implementation of PCEA would lead to lower pain scores and higher patient satisfaction. Studies concerning failure of epidural anesthesia frequently lack uniformity of outcome measure, and therefore quote frequencies of failure rates varying between 13-41% due to: varying definitions, different periods of observation, and other causes including insufficient analgesia and catheter dislodgement. Multimodal analgesia or multidimensional pain assessment were not standard in most studies, which could have influenced the outcome of pain treatment.[1] In the future we need to investigate the benefits of PCEA in a more homogenous group of patients undergoing the same type of surgery, implementing multimodal analgesia, with a multidimensional assessment of pain such as the quality of recovery score, with daily follow-up by a 24 hour pain service available for the full postoperative period including the surgical wards.[2]

Our studies regarding fractures of the talus and calcaneus could not show an advantage in pain scores measured by NRS in patients with a nerve block, when comparing continuous nerve block with intravenous morphine. The observation period did not include multidimensional pain assessment, and there was no follow-up for a longer period after discharge from hospital. Therefore, it is possible that we missed differences between groups in persistent post-surgical pain. A future study should include longer term follow-up (up to 90 days) and multidimensional assessment.

When comparing the single shot ankle block with popliteal block for analgesia in calcaneal fractures, it is possible that the speed of block performed by the surgeon offers logistic advantages, and additionally, does not require ultrasound. Larger trials and longer follow-up periods including the assessment of possible chronification of pain should be the topic of future research to establish optimal pathways of pain treatment in the respective patients.

We performed an explorative study regarding local anesthetic toxicity during bolus injection through wound catheter and epidural catheter, and found plasma levels of bupivacaine to be well below toxic levels in all patients. Local anesthetic systemic toxicity is estimated to be around 3 episodes per 10000 peripheral nerve blocks, with seizures being a symptom of central nervous system toxicity.[3] The chance of such an episode being found in our sample size is not very high, even when accounting for a 10 fold higher chance in the wound catheter group compared to the epidural group. With patients under general anesthesia, cardiac instability will be detected earlier than central nervous system toxicity. The value of our research lies in establishing a baseline, showing that in our population the plasma levels of the wound catheter patients are about twice as high as in the epidural patients. As the implementation of preperitoneal wound catheters increases, implementation of proper techniques should be mandatory (e.g., check needle position and aspiration before injection, slow injection in aliquots of 5ml). It would be preferable to place a catheter in the pre-peritoneal space for injection of local anesthetics, instead of injecting a bolus of the drug through the needle, in order to reduce the chance for perforation of blood vessels. Further, measurement of plasma levels should be performed in the postoperative phase in patients with wound catheters, so that an indication can be formed about average plasma levels of local anesthetics with these newly introduced regional anesthesia plane blocks.

In future studies the true value of simulation should be established by training novices on the epidural simulator, followed by assessment of the novice when performing an epidural puncture on real patients, after the simulation is scored as satisfactory. Unfortunately, simulation of epidural puncture is not available in most practices, and is until today not mandatory before performing an epidural puncture in patients. Unfortunately, the implementation of the TU Delft epidural simulator is not yet possible because of its unavailability in commercial form.

Lastly, our research of colonization of epidural catheters revealed a fibrinous network with entrapped immune cells and bacteria on the removed catheters. As it may be a mechanism explaining secondary failure of epidural catheters through fibrinous deposits, future research should be conducted including the regular flushing of epidural catheters with a bolus of saline, or alternatively comparing the effect of mandatory automated hourly intermittent epidural bolus

of 10ml with the standard constant rate of 10ml/hr. As most patients receive antibiotic prophylaxis perioperatively, the effect of giving this prophylactic dose before placement of the epidural catheter on bacterial colonization should be a topic of research. The ongoing research concerning regional anesthesia has helped to increase safety and efficacy of this kind of anesthesia in the past and will likely do so also in the future.

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Chapter 12

Nederlandse samenvatting van proefschrift 'Veiligheids- en kwaliteitsaspecten van regionale anesthesie'

Het doel van het in dit proefschrift gepubliceerde onderzoek was om verschillende aspecten van de tegenwoordig gebruikte methoden met betrekking tot regionale anesthesie te onderzoeken, waaronder/met name effectiviteit en veiligheid.

Wij geven een overzicht en er worden recente ontwikkelingen besproken. Het toepassen van regionale anesthesie (RA) kan bijdragen aan het verminderen van de behoefte aan opioïden rondom operaties. De huidige opioïden crisis maakt dit tot een belangrijk voordeel. Een transitionele pijn service draagt verder bij tot het verminderen van het gebruik van opioïden en ook ziekenhuisopnameduur. Veiligheid bij RA wordt beïnvloed door een aantal factoren: een checklist ter controle van de juiste zijde van de patiënt voor het blok en ingreep, hygiëne tijdens het uitvoeren van het echo geleid zenuwblok (bescherming van de echokop, echo apparaat, desinfectie, eenmalig gebruiken van echo gel), de juiste techniek en dosis - waarbij altijd alertheid is vereist op lokaal anesthetica systemische toxiciteit (LAST) - veiligheids connectoren (Nrfit), en het gebruik van simulatieonderwijs voorafgaand aan klinische toepassing. Het juiste gebruik van echo geleiding bij zenuwblokken draagt bij aan het verminderen van LAST, pneumothorax en intravasculaire injectie van lokaal anestheticum tijdens een aantal procedures. Ingrepen onder RA voorkomen mogelijk aerosolvorming, inherent aan luchtweg-management onder algehele anesthesie, en zijn daarom mogelijk nuttig tijdens de Coronapandemie. Een fenomeen dat kan optreden na het uitwerken van het zenuwblok is de verergering van hevige pijn, bekend als ‘rebound pain’. Tijdig toepassen van multimodale pijnstilling terwijl de zenuwblokkade nog werkt draagt bij aan het verminderen van ‘rebound pain’. (Hoofdstuk 2)

Het eerste vergelijkende onderzoek betreft patiënt gecontroleerde epidurale analgesie (PCEA) en continue epidurale analgesie (CEA). Ons doel was om te onderzoeken of PCEA beter is dan CEA bij niet-obstetrische chirurgie. Onze hypothese, gebaseerd op eerder bewijs uit obstetrische populatie, was dat het inzetten van PCEA, vergeleken met CEA, zou leiden tot lagere pijn scores in rust en bij beweging. In een systematische review van de literatuur analyseerden wij data uit tien gerandomiseerde gecontroleerde trials en een cohortstudie, met een totaal van 1687 patiënten. Drie studies toonden verminderde pijn scores gedurende PCEA gebruik. Een studie toonde een vermindering van systemische analgetica en bijwerkingen van regionale anesthesie. Twee studies vonden

dat PCEA leidde tot minder epidurale 'top-ups'. In zijn algemeenheid lieten de geïncludeerde studies geen klinisch belangrijk verschil van betekenis zien tussen PCEA en CEA. Aldus laat de huidige literatuur alleen marginale voordelen van PCEA zien bij volwassen patiënten die niet-obstetrische chirurgie ondergaan (Hoofdstuk 3)

PCEA is een verfijning van CEA: In PCEA wordt naast een constante epidurale toediening van lokaal anesthetica (vaak met een opioïde als additivum) ook nog een door de patiënt geïnitieerde bolus toegediend van hetzelfde mengsel indien nodig. Uitgaande van het beschikbare bewijs uit de obstetrische analgesie, implementeerden wij PCEA in ons ziekenhuis, waar tot dan toe CEA als norm werd gezien. Twee jaar na dato analyseerden wij data in een retrospectieven studie om de volgende vragen te beantwoorden: 1. vermindert PCEA gebruik het aantal 'top-ups' door een dokter? 2. Zijn er minder bijwerkingen en werkdruk als gevolg van PCEA gebruik? 3. Wordt de duur van de epidurale pijnbehandeling verkort als gevolg van PCEA? Gedurende 9 maanden vergeleken wij twee patiëntcohorten: een cohort kreeg CEA als standaard zorg en het andere cohort kreeg PCEA. Beide groepen hadden vergelijkbare pijnscores, gemeten met de numeric rating scale (NRS). Wij ontdekten dat PCEA leidde tot een significante vermindering van het aantal patiënten dat top-ups nodig had. Wij konden een vermindering in epidurale behandelduur niet aantonen in een van de twee groepen. Aldus was onze conclusie dat PCEA leidt tot vermindering van het aantal top-ups, met een niet significante klinische verbetering van de pijnbestrijding (Hoofdstuk 4).

De optimale behandeling van postoperatieve pijn wordt mede bepaald door de anatomische locatie van een chirurgische ingreep. Terwijl epidurale analgesie gedurende tientallen jaren de voorkeursbehandeling is geweest, zijn andere vormen van RA sinds een aantal jaren in opkomst. Een samenwerking tussen chirurgen en anesthesiologen heeft geresulteerd in het 'procedure specifieke samenwerkingsverband (PROSPECT)' gericht op het ontwikkelen van richtlijnen voor pijnbehandeling, gebaseerd op bewijs relevant voor de ingreep.[1 2] Er zijn geen PROSPECT richtlijnen betreffende talus en calcaneus fracturen. Hallux valgus chirurgie richtlijnen bevelen een enkel blok aan voor de ingreep, gevolgd door 'rescue' opioïden postoperatief. De open reductie en interne fixatie (ORIF) van calcaneus en talus fracturen wordt momenteel behandeld met een combinatie van intraveneus opioïde (patiënt gecontroleerde analgesie=PCA) of

'single shot' perifere zenuw blokkade, analoog aan de PROSPECT richtlijnen voor hallux valgus chirurgie.[3] Onze hypothese was dat een continu zenuwblok de pijnscores sterker zou veminderen, en tevens het herstel kan bevorderen en de opnameduur kan verkorten, vergeleken met systemische analgetica (PCA met opioïden). Hiertoe analyseerden wij retrospectief de patiënten in ons ziekenhuis die ORIF-behandeling van talus en calcaneus fracturen hadden ondergaan in een periode van drie jaar. Veertig patiënten hadden een een continue zenuwblok gekregen (katheter techniek), terwijl 47 patiënten PCA-morfine hadden gehad. Pijnscores waren vergelijkbaar in beide groepen. Bijwerkingen, opnameduur en de incidentie van wondinfecties waren ook vergelijkbaar. Echter, patiënten met een PCA hadden een 30-voud hogere morfine dosering gedurende de behandeling. Onze conclusie was dat hoewel de zenuwblokken de pijnscores niet verminderden, er toch een voordeel kan zijn in het verminderen van opiaat gebruik. Het geïncludeerde aantal patiënten in onze studie was te klein om voordelen aan te tonen die met dit verminderde gebruik samenhangen. (Hoofdstuk 5).

Als calcaneus fracturen worden geopereerd, is er een keuze uit aanvullende analgetische technieken. Historisch hebben zowel de anesthesioloog als de chirurg lokaal infiltratie anesthesie uitgevoerd, zonder echoapparatuur. Anatomische oriëntatiepunten kunnen gebruikt worden om een blok uit te voeren voor de postoperatieve pijnbestrijding. Het voordeel van het gebruik van een echogeleid perifeer zenuwblok is dat het mogelijk is om structuren te identificeren die anders niet zichtbaar zijn zonder uitgebreide chirurgische dissectie, zoals de nervus ischiadicus in de fossa poplitea. Wij hebben de volgende vraag geprobeerd te beantwoorden: zijn echogeleide fossa poplitea zenuwblokken door de anesthesioloog beter dan de enkelbloks die door de chirurg worden uitgevoerd gedurende de behandeling? Teneinde dit te onderzoeken deden wij een retrospectieve analyse van alle volwassen patiënten die chirurgie hadden ondergaan gedurende een vijfjaarlijkse periode. Wij vergeleken de postoperatieve pijnscores als een van de belangrijkste parameters, met de NRS als meetinstrument. De NRS werd pre en postoperatief gescoord. Drieëndertig patiënten kregen een poplitea blok door de anesthesioloog en 50 patiënten een enkel blok door de chirurg. De NRS-scores en het cumulatieve morfine gebruik verschilde niet tussen beide groepen. Onze conclusie was dat beide blokken vergelijkbaar zijn bij de behandeling van postoperatieve pijn

samenhangend met calcaneusfractuurchirurgie. (Hoofdstuk 6)

Epidurale analgesie wordt regelmatig gebruikt in hepato-pancreatico-biliaire (HPB) chirurgie. Teneinde de potentiele complicaties te verminderen, die inherent zijn aan de anatomische locatie van de epidurale techniek (myelum laesie door abces of hematoom of directe traumatische punctie), worden nieuwe anesthesie technieken, zoals myofasciale blokken, gevalideerd. Fascia blokken worden steeds vaker gebruikt, echter zijn er nog geen grote studies die hun efficiëntie bewijzen.[4 5] Een andere methode is het gebruik van een katheter, die door de chirurg wordt geplaatst, in de nabijheid van de chirurgische wond gedurende de operatie. Wondkatheters zijn een nieuwe vorm van analgesie die gebruikt wordt tijdens HPB-procedures.[6] De veiligheid van het inspuiten van lokaal anestheticum via deze wondkatheters is onbekend. In een gerandomiseerde gecontroleerde trial betreffende wond katheters en epidurale analgesie voor HPB-chirurgie, was er een geval die symptomen vertoonde passend bij lokaal anesthetica toxiciteit tijdens het geven van de bolus door de naald. Wij deden een exploratieve studie betreffende veiligheidsaspecten van wondkatheters in HPB-chirurgie. 20 patiënten werden geïncludeerd in de studie. Een bolus van 30ml bupivacaine 0,25% door de wondkatheter werd vergeleken met een bolus van 10 ml bupivacaine via de epiduraalkatheter. Wij maten plasmaspiegels van bupivacaine na een pre peritoneale bolus (wond catheter groep) en vergeleken dat met bupivacaine plasmaspiegels na een epidurale bolusinjectie. Plasmaspiegels in de patiënten met wond katheters waren hoger dan die in patiënten met epiduralen, maar fors onder de toxiciteitslimiet van bupivacaine. Intraoperatief gebruik van opioïden was lager in de epidurale groep, een teken dat de subfasciale bolus aan het begin van de operatie het gebrek aan epidurale analgesie niet geheel compenseert. (Hoofdstuk 7)

De afgelopen tientallen jaren was er een afname in het gebruik van epidurale analgesie door diverse oorzaken. Technologische ontwikkelingen hebben mogelijkheden met echografie ontsloten, waardoor perifere anatomische structuren te visualiseren zijn. Dit heeft geresulteerd in alternatieve mogelijkheden voor pijnbehandeling met een verwaarloosbare kans op myelumschade. Echter, de mogelijkheid voor onervaren dokters, om de epidurale technieken te leren neemt hierdoor ook gestaag af. Er blijven nochtans indicaties waar een epiduraal in ons centrum de eerste keus behandeling is: peri-partum, open thoracotomieën

en grote buik chirurgie. Actuele bewegende 'live' beeldvorming is (nog) niet mogelijk tijdens het uitvoeren van een epidurale punctie, en epidurale analgesie gaat gepaard met specifieke naaldvaardigheden. Daarom is het oefenen op een simulator van de plaatsing van epidurale katheters waardevol, om de techniek te leren. Wij kregen de gelegenheid om een simulator te testen die door de TU Delft was ontwikkeld, en hebben een validatie studie uitgevoerd met inclusie van 68 deelnemers: 48 experts (meer dan 30 epiduralen ervaring) en 20 beginners (<30 epiduralen) namen deel. Deze simulator is de enige met een gesimuleerde magnetische resonantie imaging (MRI) geleiding. De naald beweegt binnen een beeld van een MRI-wervelkolom. Elke deelnemer deed 12 puncties, waarvan de helft met MRI-geleiding. Onze conclusies waren dat het uiterlijk en gevoel van de simulator als 'goed' werden gescoord door de deelnemers. Ervaren anesthesiologen presteerden beter dan beginners ten aanzien van dura contacten en spinal taps. Voorgaande visualisatie op de simulator met MRI-beelden verbeterde prestaties door alle deelnemers. Evenwel, er is nog geen commerciële versie van de simulator beschikbaar. Verder onderzoek is nodig om het effect van training met deze simulator in de praktijk te beoordelen. (Hoofdstuk 8)

Het laatste hoofdstuk van dit proefschrift betreft een veiligheidsvraagstuk dat kan ontstaan gedurende het klinisch beloop van een patiënt die zich onttrekt aan het zicht van de anesthesioloog, die voornamelijk zorg verleent op de operatiekamers. Gedurende de postoperatieve fase kunnen epidurale katheters worden gekoloniseerd door bacteriën, en leiden tot lokale en systemische infectie bij patiënten. Zelfs met het gebruik van mondmaskers, steriele jassen en handschoenen gedurende het plaatsen van de epidurale katheter, is er kans op kolonisatie van de epidurale katheter vanuit de diepe huid flora van de patiënt. Kolonisatie kan worden gevolgd door een infectie, wat uiteindelijk kan leiden tot een epiduraal abces. Daartoe verrichtten wij een exploratieve studie met inclusie van 28 patiënten met thoracale epidurale katheters met een verwachte behandelduur van minimaal 72 uur. Wij gebruikten scanning electronen microscopie (SEM) om mogelijke patronen van bacteriële kolonisatie op de katheter te onderzoeken na het verwijderen ervan. Wij ontdekten dat bij 33% enige mate van bacteriele groei was op de tip van de katheter. Bij een patiënt met een klinisch relevante infectie was zichtbaar dat kolonisatie afnam van de huid naar tip van de katheter. Bij het verrichten van SEM waren biologische afzettingen zichtbaar met stafylokokken en immuuncel achtige structuren in het

lumen van de katheters. Andere katheters lieten een dicht intra-luminaal fibreus netwerk zien. Dit netwerk ontstaat vanuit de zij openingen naar het lumen en speelt een mogelijke rol bij katheter obstructie (Hoofdstuk 9). Verder onderzoek is nodig om de exacte samenstelling te determineren van het fibreus netwerk en de mogelijke rol bij het voorkomen van infectie door de immobilisatie van bacteriën en immuun cellen.

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Appendices

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Publications

Portfolio

Curriculum Vitae

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Publications

1. Intraoperative Fluid Restriction in Pancreatic Surgery: A Double Blinded Randomised Controlled Trial.
   van Samkar G, Eshuis WJ, Bennink RJ, van Gulik TM, Dijkgraaf MG, Preckel B, de Hert S, Gouma DJ, Hollmann MW, Busch OR.
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2. Value of scintigraphy for assessing delayed gastric emptying after pancreatic surgery.
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   World J Surg. 2013 Dec;37(12):2911-7.

3. Effects of prolonged pneumoperitoneum on hepatic perfusion during laparoscopy.
   Hoekstra LT, Ruys AT, Milstein DM, van **Samkar G**, van Berge Henegouwen MI, Heger M, Verheij J, van Gulik TM.
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4. Early postoperative hyperglycemia is associated with postoperative complications after pancreatoduodenectomy.
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   Ann Surg. 2011 Apr;253(4):739-44

5. Lethal complication after abdominal wall reduction.
   van Samkar G, van der Hoeven J, Hollmann MW, Goslings JC.
   J Plast Reconstr Aesthet Surg. 2009 Oct;62(10):e387-90

Portfolio

Name PhD student:	G. van Samkar
PhD period:	2014 - 2021
PhD supervisors:	prof. dr. dr. M.W. Hollmann, prof. dr. B. Preckel
Co-supervisors:	dr. dr. M.F. Stevens, dr. H. Hermanns

1. PhD training

	Year	**Workload (Hours/ECTS)**
General courses		
GCP (good clinical practice)	2014	0.9
GCP (good clinical practice)	2019	0.9
Specific courses		
ATACC trauma	2015	1
CRM	2015	1
EDRA exam part 1	2014	1
EDRA exam part 2	2016	1
Teach the teacher	2016	1
ALS	2016	1
ESRA instructor	2017	1
Seminars, workshops and master classes		
ESRA ultrasound	2014, 2015	2
DARA	2014-2019	5
ESRA anatomy course Austria	2013	1
ESA workshop ultrasound	2016	1
ESRA cadaver workshop	2013	1
ESRA instructor	2017	1
Presentations		
PGA New York poster presentation	2010	0.5
ESRA meeting Sevilla poster	2014	0.5
ESRA meeting Maastricht oral	2016	0.5
ESA meeting London oral	2016	0.5
DARA meeting oral	2016, 2018	1

Conferences

DARA	2014-2019	5
ESRA	2014- 2019	6
ESA	2017, 18	2
PGA	2020	1
ESAIC	2020	1
SAMBA	2020	1

2. Teaching

Supervisor science thesis (wetenschaps stage)

Jaji Gosschalk	2006	1
Sharon Stoker	2007	1
Angelique Tam	2008	1
Babette van Beem	2008	1
Bas de Wit	2008	1
Henriette Julien	2008	1
Marike Lemmers	2008	1
Lisanne Oudhoff	2009	1
Miriam Braakhekke	2009	1

3. Parameters of Esteem

Awards and Prizes

Second prize ESRA poster presentation	2014
Third prize DARA oral presentation	2018

Curriculum Vitae

Ganapathy van Samkar was born on the 28th of November 1958, in Daulatabad, India, as Ganapathy Sankaranarayanan (name change by Royal Decree to "van Samkar" in 1992). After being raised by his grandparents until his seventh year in India, he joined his parents in Leiden, the Netherlands, in 1965. He learnt the Dutch language, and attended the Dutch Lorentzschool in Leiden for three years. He attended the English international school in the Hague and finally graduated at the Atheneum of the Rijnlands Lyceum in Oegstgeest in 1976. He studied medicine at the Rijksuniversiteit Leiden, where he graduated in 1983. He served as a medical officer in the Royal Dutch Army until 1984, after which he gained experience as a resident in general surgery in the Laurentius Ziekenhuis in Roermond. His interest in anesthesia developed during his residency in chronic pain treatment in Leiden, in 1985. Anesthesia training continued until he was registered as a specialist in 1992. He worked as a consultant in Spaarne Ziekenhuis Heemstede, Zuiderziekenhuis Rotterdam and Lievensberg Ziekenhuis Bergen op Zoom before finally joining the anesthesiology staff at the AMC University Hospital in Amsterdam in 1999. His initial footsteps in research were guided by the late Dr. Mohan Kedaria, his mentor at the time. The arrival of Prof. dr. Markus Hollmann marked an exciting new period: the start of research. After initial research concerning fluid restriction in pancreatic surgery, the focus shifted to local anesthesia and ultrasound. The completion of this thesis marks a new chapter.

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