Plexus brachialis anaesthesia: Optimising clinical aspects

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2. Synopsis

Brachial plexus blocks are used for analgesia, anaesthesia and in special situations to improve peripheral circulation in the upper extremity. The aim of this thesis is to evaluate the clinical and physiological benefits of the lateral sagittal infraclavicular approach, and modify the use in dedicated areas to improve its analgesic and circulatory benefits and avoid undue harm. We hypothesised that proper modifications of timing and adjuvants of infraclavicular brachial plexus blocks may have a positive impact on postoperative clinical outcome and peripheral circulation.

Lateral sagittal infraclavicular blocks are frequently used to provide anaesthesia and analgesia for volar plate fixations of distal radius fractures. Severe acute postoperative pain and long-lasting pain are common after this type of surgery. Infraclavicular blocks are also used to improve circulation after for example replantation surgery after traumatic amputations and different vascular procedures. Skin microcirculation consists of two different components, the subpapillary blood flow important for thermoregulation, and the nutritive blood flow responsible for oxygenation and nutrition of peripheral cells. The effect of brachial plexus blocks and adrenaline adjuvant on these two different components is not fully explored.

In study 1, we evaluated the preemptive effect of infraclavicular blocks in patients with distal radius fractures scheduled for volar plate surgery. We found a small, but significant, improvement in early postoperative pain with pre-operative (i.e. preemptive) blocks compared with postoperative blocks. Mean (SD) time to first rescue analgesic after emergence from general anaesthesia was 544 (217) min after pre-operative blocks compared with 343 (316) min after postoperative blocks (p=0.015). Pre-operative blocks resulted in reduced postoperative pain scores, fewer patients requiring rescue analgesia during the first 4 hours after surgery, and less analgesic consumption at day seven after surgery. However, a pre-operative block did not attenuate strong pain during block resolution and did not seem to have an impact on the high incidence of minor persistent pain.
In study 2, we compared the effect of single (oral etoricoxib) and double (oral etoricoxib and intravenous dexamethasone) anti-inflammatory prophylaxis in patients with distal radius fractures scheduled for volar plate surgery with brachial plexus anaesthesia. We found that intravenous dexamethasone improved early postoperative analgesia. Median (IQR[range]) worst pain score during the first 24 hours, as assessed by verbal numeric rating scale (0-10), was 4(2-6[0-7]) in the patients receiving both dexamethasone and etoricoxib, compared with 8(5-8[2-10]) in the patients receiving etoricoxib only (p<0.001). Adding intravenous dexamethasone to oral etoricoxib and paracetamol before start of surgery also resulted in increased block duration, shorter duration of moderate-severe pain and reduced rescue analgesic consumption from 8-24 hours after surgery. Perioperative intravenous dexamethasone may also reduce the development of chronic pain.

In study 3, we evaluated the effect of lidocaine infraclavicular blocks with or without adrenaline on peripheral microcirculation using laser Doppler Fluxmetry, capillary video microscopy and temperature measurements. It was a cross-over study in healthy volunteers. We found substantially increased subpapillary blood flow 30 minutes after lidocaine brachial plexus blocks, from median (IQR[range]) 8.5(4.4-13.5[2.9-28.2]) to 162.7(111.0-197.8[9.5-206.7]) arbitrary units with adrenaline (p=0.017), and from 6.9(5.3-28.5[1.8-42.1] to 133.7(16.5-216.7[1.0-445.0] arbitrary units without adrenaline (p=0.036). Nutritive blood flow (functional capillary density), measured at the dorsal side of the hand, decreased in the blocked extremity when adrenaline was used as adjuvant, from median (IQR[range]) 45(36-52[26-59]) to 38(29-41[26-42]) capillaries/mm² (p=0.028), whereas no significant change occurred without adrenaline.

In conclusion, to improve efficacy for management of acute and possibly also long-lasting pain after volar plate surgery, brachial plexus block should be performed preincisional rather than postoperatively and be combined with NSAIDs and intravenous dexamethasone. When used to increase the microcirculation and oxygenation of peripheral cells, the best approach may be to use a block without adrenaline adjuvant.
3. Norsk vitenskapelig sammendrag (Norwegian summary)

Plexus brachialis blokader brukes som smertelindring, bedøvelse og i enkelte situasjoner for å bedre perifer sirkulasjon i overekstremiteten. I denne avhandlingen ønsker vi å se nærmere på kliniske og fysiologiske effekter av lateral sagittal infraklavikulær blokade og justere bruken innen noen områder for å utnytte blokadens analgetiske potensial og sirkulatoriske effekter bedre. Hovedhypotesen vår er at bedre tilpasset bruk av infraklavikulær blokade, både med tanke på tidspunktet den settes på og bruk av tilsetninger, kan forbedre både postoperativt klinisk resultat og perifer sirkulasjon.


I den første studien inkluderte vi pasienter med distale radiusfrakturer planlagt fiksert med volar plate for å se om infraklavikulære blokader har en preemptiv effekt av klinisk betydning. Vi fant en liten, men signifikant, bedring i akutt postoperativ smerte med preoperativ (dvs preemptiv) infraklavikulær plexus brachialis blokade sammenliknet med postoperativ blokade. Gjennomsnittlig (SD) tid til første analgetika ved behov var 544 (217) min etter preoperative blokader sammenliknet med 343 (316) min etter postoperative blokader (p=0.015). Preoperative blokader førte også til lavere postoperativ smerte, til at færre pasienter hadde behov for smertestillende de første 4

I den neste studien sammenlignet vi effekten av dobbel anti-inflammatorisk profylakse (etorikoksib og deksametason) med enkel anti-inflammatorisk profylakse (etorikoksib) hos pasienter med distale radiusfrakturer planlagt fiksert med volar plate. Vi fant at intravenøs deksametason førte til betydelig forlenget effekt av blokaden og mindre postoperative smerter. Median(IQR[range]) høyeste smertescore de første 24 timene målt med en verbal numerisk smerteskala (0-10), var 4(2-6[0-7]) hos pasientene som fikk både etorikoksib og deksametason sammenliknet med 8(5-8[2-10]) hos pasientene som bare fikk etorikoksib (p<0.001). Både varighet av moderat-sterk smerte og bruk av analgetika fra 8-24 timer var betydelig redusert etter en enkelt dose intravenøs deksametason. En perioperativ dose med intravenøs deksametason hadde muligens også en positiv effekt med tanke på å redusere forekomsten av kroniske smerter.

I den tredje studien så vi på hvordan lidokain blokader med og uten adrenalin tilsetning påvirker den subpapillære og nutritive sirkulasjonen ved hjelp av laser Doppler, kapillær videomikroskop og temperatur målinger. Dette var en eksperimentell studie med friske frivillige. Vi fant en betydelig økt subpapillær sirkulasjon de første 30 minuttene etter infraklavikulær blokade med lidokain, fra median(IQR[range]) 8.5 (4.4-13.5[2.9-28.2]) til 162.7(111.0-197.8[9.5-206.7]) arbitrære enheter med adrenalin (p=0.017), og fra 6.9(5.3-28.5[1.8-42.1] til 133.7(16.5-216.7[1.0-445.0] arbitrære enheter uten adrenalin (p=0.036). Den nutritive sirkulasjonen (funksjonell kapillærtetthet), målt på håndens dorsalside, sank i blokkert ekstremitet etter blokader med adrenalin, fra median(IQR[range]) 45(36-52[26-59]) til 38(29-41[26-42]) kapillærer/mm² (p=0.028), mens vi ikke fant noen forskjell uten adrenalin.

Vi konkluderte med at en preoperativ infraklavikulær plexus brachialis blokade kombinert med både etorikoksib og deksametason gir best effekt med tanke på å redusere postoperative smerter etter fiksering av distale radiusfrakturer med volar
plate. Når blokaden brukes for å øke mikrosirkulasjonen og oksygeneringen av perifere celler, kan det være best å benytte en blokade uten adrenalin.

Vi håper resultatene i denne avhandlingen vil være et bidrag til videre forbedring i klinisk bruk av infraklavikulær plexus brachialis blokade.
4. List of original papers

This thesis is based on the following scientific papers:

Paper 1:

Holmberg A, Sauter AR, Klaastad O, Draegni T, Raeder JC: Pre-operative brachial plexus block compared with an identical block performed at the end of surgery: a prospective, double-blind, randomised clinical trial. Anaesthesia 2017; 72: 967-977

Paper 2:

[published online ahead of print, 2020 May 30]. Anaesthesia. 2020;
doi:10.1111/anae.15111

Paper 3:

5. Abbreviations

ASA: American Society of Anesthesiologist

AU: Arbitrary units

AVAs: Arteriovenous anastomosis

CRF: Case Registration Form

CRP: C-reactive protein

FCD: Functional capillary density

HR: Heart rate

Hz: Hertz

IQR: Interquartile range

LDF: Laser Doppler Flow

LSIB: Lateral sagittal infraclavicular nerve block

ms: millisecond

NRS: numerical rating scale

NSAIDs: non-steroidal anti-inflammatory drugs

PONV: Postoperative nausea and vomiting

PRWHE: Patient Rated Wrist and Hand evaluation

SD: standard deviation

US: Ultrasound

USG: Ultrasound guided
VAS: Visual analogue scale

VNRS: Verbal numeric rating scale

VRS: verbal rating scales
6. Introduction

Brachial plexus blocks have undergone several exciting advances and gained increased popularity in the last decades (1). The introduction of ultrasound guidance has improved the success rate, efficacy, ease of performance and safety, resulting in nerve blocks being used more routinely in anaesthesia, analgesia and to improve peripheral circulation. Infraclavicular brachial plexus blocks are widely used for analgesia and anaesthesia of the elbow, forearm and hand and with the intention to improve peripheral circulation. The overall goal of this thesis is to evaluate the clinical and physiological benefits of this method further and modify the use in dedicated areas to improve its benefits, and avoid undue harm. We hypothesised that modifications of timing and adjuvants in brachial plexus block will improve both postoperative clinical outcome and peripheral circulation.

Both acute and long-lasting pain is a major problem after volar plate surgery for distal radius fractures (2). A previous study in this patient group showed superior postoperative analgesia and less chronic pain in patients who received infraclavicular brachial plexus block compared with general anaesthesia during surgery (3). Brachial plexus blocks are therefore used for surgical anaesthesia to enhance patient comfort and recovery after volar plate surgery for distal radius fractures.

A successful infraclavicular brachial plexus block results in a complete block of nociceptive nerve impulses from a surgical field of the distal upper arm, the forearm and the hand. The potential benefits of perioperative regional anaesthesia may extend beyond acute pain relief. It is unclear if the timing of brachial plexus blocks, before or after surgery, affects the incidence of acute and long-lasting pain after surgery. In everyday practice, it is an on-going discussion if we should take the time to perform nerve blocks prior to the operation, or rather wait till after the operation to potentially gain a few extra hours with an effective nerve block. In study 1 we try to explore this area of interest.
One of the main challenges of brachial plexus blocks in acute pain management is the abrupt termination of the analgesic effect after single-injection techniques. This is particularly problematic in ambulatory surgery when the patients are at home when the nerve block wears off. A prolonged analgesic effect of brachial plexus block after surgery may reduce both rebound pain and opioid consumption in the postoperative period (4). This is important in light of the current focus on eliminating unnecessary perioperative use of opioids. In study 2, we try to evaluate the effect of single (etoricoxib) and double (etoricoxib and dexamethasone) anti-inflammatory prophylaxis after volar plate surgery in brachial plexus anaesthesia. We aim to ascertain if the addition of a single dose of intravenous dexamethasone (to oral etoricoxib) can reduce the patient’s total pain burden (both acute and long-lasting pain) and opioid consumption after volar plate surgery.

Sympathetic blocks may play an important role in the treatment of several medical diseases with alterations of skin microcirculation. In our hospital, which is the national unit for reconstructive surgery of the upper extremity, we use brachial plexus blocks to optimise circulation during and after reconstruction surgery due to traumatic amputations. The effect of brachial plexus blocks and adjuvants on the two different but important components of peripheral microcirculation, the sub-papillary blood flow and the nutritive blood flow, is not fully explored. In study 3, we want to investigate skin microcirculation and haemodynamic changes after brachial plexus blocks, with a focus on the use of adrenaline as an adjuvant.

With this PhD thesis focusing on different clinical aspects of infraclavicular plexus block, we hope to add relevant knowledge and understanding and further improve its clinical use.
7. **Background**

7.1 **Brief history**

Brachial plexus blocks have been used as an anaesthetic technique for more than a century. It has gradually developed from open surgical techniques, to percutaneous techniques based on landmarks, further to the use of nerve stimulator to confirm needle placement, and finally to ultrasound-guided techniques. While brachial plexus block previously was associated with a significant failure rate and thus not used routinely in many clinics, the development of the method and the introduction of ultrasound guidance has improved the success rate to make the nerve blocks a reliable and popular form of anaesthesia.

7.1.1 **History of local anaesthetics**

The foundation of all regional anaesthesia was the isolation of cocaine alkaloid from cocoa leaves by Albert Niemann (5). The invention was the basis for his PhD thesis published in 1860. Before that, the properties of cocoa leaves had been utilized for various purposes for millennia. The Incas in the Andes used cocoa leaves for religious, social and medical purposes (6). The Italian explorer, Amerigo Vespucci described local people chewing cocoa leaves when he reached the coast of Venezuela in 1499 (6).

In 1855, the German chemist Friedrich Gaedcke isolated red crystals, “erythroxylum,” from the cocoa leaf, and reported its ability to anaesthetise the tongue (7). The latter was also described by Albert Niemann in his PhD thesis (8). A few years later, in 1884, Carl Koller introduced cocaine as the first effective local anaesthetic (9). The introduction led to revolutionary changes in anaesthesia, even though cocaine was a toxic substance with an addictive potential and had a rather short duration of the local anaesthetic action (10, 11).

After the introduction of cocaine, several attempts were made to develop a more ideal local anaesthetic with fewer side effects. The progress accelerated after Willstätters determination of the chemical structure of cocaine in 1898 (8). Several agents were
developed, including “Stovaine” in 1904, but none of them turned out to be a suitable local anaesthetic (11). The use of additives to improve the effect of local anaesthetics was also investigated. Heinrich Braun was the first to report adrenalin’s ability to prolong the local anaesthetic effect of cocaine in 1903 (12). The first suitable local anaesthetic agent was procaine (Novocaine®), patented by Einhorn in 1904 (8). It quickly became the standard local anaesthesia. However, the anaesthetic effects of procaine were weak, there were major problems with allergic reactions, and high concentrations of adrenaline was required (8).

First after World War II, alternatives to procaine became available. Lidocaine (Xylocaine®) was developed by Nils Löfgren and Bengt Lundquist in 1943 and released both with and without adrenaline adjuvant in January 1948 (13). With an efficient and almost non-toxic local anaesthetic drug available, local and regional anaesthesia rapidly became more popular (8, 13). In the years to follow, the development of local anaesthetics accelerated. HC Marks and MI Rubin developed chloroprocaine in 1949. Bupivacaine and mepivacaine were synthesised by Bo Af Ekenstam and released in 1957 (14). The longer duration of action of bupivacaine made it possible to conduct long acting blocks. Several other local anaesthetics have been developed after bupivacaine, including prilocaine by Löfgren and Tegner in 1969 and articaine by Winther in 1972. Ropivacaine was synthesized in 1957 by Ekenstam, but first introduced into clinical practise in 1996 (14, 15) as a less cardiac toxic alternative to bupivacaine. Levobupivacaine was introduced in 1999, and is considered to be less toxic than bupivacaine with a small increase in sensory block duration (16). Cocaine is the only naturally occurring local anaesthetic substance available today. All others are synthetically derived.

### 7.1.2 History of brachial plexus blocks

Shortly after Carl Koller introduced cocaine as the first effective local anaesthetic in 1884, Halsted and Hall began infiltrating cocaine into the brachial plexus to perform painless operations on the upper limb at the outpatient department of the Roosevelt Hospital in New York (8, 17). In 1911, both Kulenkampff and Hirschel described
different percutaneous techniques of brachial plexus blocks (18). The use of electrical nerve stimulation was first described by Georg Perthes in 1912 (19). Fifty years later, Greenblatt and Denson revived the method by introducing a small battery-operated nerve stimulator (20). This development greatly improved the success rates of brachial plexus blocks and facilitated for reduced volume and dosage of local anaesthetic agents (20, 21). In the years to follow, improvements of local anaesthetics and nerve block equipment, as well as studies on the anatomy, contributed to the development of more effective nerve blocks. Winnie and Collins studied the anatomy of the brachial plexus and suggested an accurate percutaneous location for a single injection subclavian perivascular technique in 1964 (22). In 1989 ultrasound was used for the first time to visualize the local anaesthetic spread during an axillary block procedure (23). In the early nineties, more ultrasound-guided nerve block techniques were performed after Kapral had published the first description of an ultrasonic guidance of the injection cannula in 1994 (24, 25). Advances in ultrasound technology with small and mobile ultrasound units with improved image resolution in an affordable price range made peripheral nerve blocks increasingly popular. The use of ultrasound guidance led to improved success rates and reduced performance time during block procedures.

7.2 Lateral sagittal infraclavicular blocks

The brachial plexus is a network of nerves originating from C5-T1. Various contributions may also come from C4 and T2. The network of nerves begins as spinal nerve roots, which merges to form the three trunks. The trunks then split to form the six divisions, and further reorganises into three cords before they give rise to the five terminal nerve branches (26).
Figure 1: Brachial plexus with roots, trunks, divisions and cords and various approaches for brachial plexus blocks. (Illustration by Jennifer Gentry. Reproduced from Upper extremity regional anesthesia: essentials of our current understanding, 2008. Neal JM, Gerancher JC, Hebl JR et al. Reg Anesth Pain Med. 2009;34(2):134-70, Copyright 2009 by American Society of Regional Anesthesia and Pain Medicine, with permission from BMJ Publishing Group Ltd (26)).

The infraclavicular brachial plexus block was first described by Bazy in 1917 (27). In 1973, P. Prithvi Raj described a new infraclavicular approach using the peripheral nerve stimulator (28), and the technique was further modified by Sims in 1977 (29). Øivind Klaastad at our Department of Anaesthesiology at the Oslo University Hospital optimised the infraclavicular block technique further based on magnetic resonance imaging studies. He described the highly successful clinical method of lateral sagittal infraclavicular block (LSIB) in 2004 (30). LSIB was introduced as a nerve-stimulator guided technique, but ultrasound guidance rapidly became more popular.

When using ultrasound in the infraclavicular region, the lateral, medial and posterior cords may be located as round hyper echoic structures close to the axillary artery. Local anaesthetic spread reaching all three cords, or surrounding the artery from 3 to 11 o´clock (if all the cords cannot be identified), are considered sufficient for a successful LSIB (31). The method is easy to perform, precise and has a low risk for
adverse events or complications (30). Ultrasound guided LSIB has a success rate of at least 95% (32, 33).

![Image 1: Ultrasound image of the brachial plexus in the infraclavicular region. A cannula can be visualised in the 7 o’clock position to the axillary artery. Authors own photo.](image)

Peripheral nerve blocks are considered a safe anaesthetic technique with few complications (34). Persistent postoperative neuropathy due to the nerve block is a serious complication with an overall incidence of approximately 0.22% (35). Complications that can be associated to infraclavicular blocks are vessel puncture, pneumothorax, nerve injury, and local anaesthetic toxicity.

### 7.3 Clinical use of lateral sagittal infraclavicular blocks

The infraclavicular brachial plexus block is widely used to provide analgesia and anaesthesia for the elbow, forearm and hand. It is also used with the intention to improve peripheral circulation after microvascular procedures, reconstruction surgery after traumatic amputation, in treatment of vasospasm induced by Raynaud disease, and in treatment of peripheral embolism (36-39).

Evidence suggests that the use of peripheral nerve blocks as sole anaesthesia technique during a surgical procedure reduces both operating room time and length of hospital
stay (40-42). The patient may be awake during the procedure and not subjected to the potential side effects of general anaesthesia, such as hypotension, cognitive dysfunction and respiratory impairment. Compared with general anaesthesia, regional anaesthesia offers the benefits of better pain protection and less need of opioids postoperatively, with subsequent reduced incidence of nausea or vomiting as well as more rapid mobilisation (43, 44). This allows for earlier discharge of the patient after ambulatory surgery (45).

Peripheral nerve blocks are also used with the intention to improve tissue perfusion after free flap and replantation surgery. Although sparse evidence for improved clinical outcome, there are studies supporting the use after digital replacements, and promising reports for more proximal limb replantation (46-48).

7.4 Local anaesthetics and adjuvants in peripheral nerve blocks

Several different local anaesthetics are available. They typically contain a hydrophilic tertiary amine group linked to a lipophilic ester or amide (49), and are accordingly classified as either ester or amide local anaesthetics (50). Local anaesthetics in the amine group are more commonly used, due to a lower risk of allergic reactions and systemic toxicity (49). The primary mode of local anaesthetic action is by a reversible inhibition of sodium influx in nerve fibres (51). However, local anaesthetics have a wide range of effects, as they inhibit sodium, potassium, and calcium ion channels, alpha-adrenoceptors, and phosphatidylinositol signallling (49). More lipophilic local anaesthetics are more potent as the molecules are more likely to remain in the lipid rich environment of the axonal membrane where the sodium channels are present (49, 50).

The quality of a nerve block depends on the choice of local anaesthetic, the concentration on site, the amount of the nerve exposed to the agent and the characteristics of the nerve. Smaller nerve fibres are easier to block than larger fibres (a shorter length of the axon needs to be blocked to halt the conduction completely).
and myelinated fibres are more easily blocked than unmyelinated (local anaesthetics pool near the axonal membrane) (50). Thin unmyelinated C-fibres are most resistant to local anaesthetics.

The onset-time and duration of the block depends on several factors; the choice of local anaesthetic, how close to the nerve the local anaesthetic is deposited, the volume, concentration and lipid solubility of local anaesthetic, the physical characteristics of the tissue surrounding the nerve, and the actual pH value at the injection site (50).

Adjuvants are commonly added to peripheral nerve blocks to increase a desired effect of the blockade. The most commonly used adjuvants are adrenaline, clonidine, dexmedetomidine, dexamethasone, and buprenorphine. However, only adrenaline has been officially approved for perineural administration (1). In this thesis we seek to further explore the effects of adrenaline on both microcirculation and haemodynamic parameters.

Intravenously administered drugs may also affect nerve blocks. Dexamethasone has been used perineurally as well as intravenously to improve the effects of peripheral nerve blocks (52). The effect of intravenous dexamethasone on infraclavicular brachial plexus blocks used during volar plate surgery is one of the major topics of this thesis.

The characteristics of the local anaesthetics and adjuvants used in this thesis are summarised in the following paragraphs.

**7.4.1 Ropivacaine**

Ropivacaine is a long-acting amide local anaesthetic drug metabolized mainly in the liver by the cytochrome P450 system. It has a lower cardiotoxic potential than bupivacaine (53). High concentrations (5mg/ml and higher) result in a profound motor and sensory blockade and are therefore commonly used in peripheral nerve blocks during surgical procedures. Lower concentrations (2.0 mg/ml and lower) result in a sufficient sensory blockade with a limited motoric effect and are best suited for postoperative pain relive. Onset-time and duration depends on the volume and
concentration as well as site of administration. Ropivacaine has an intrinsic vasoconstrictive property and is little affected by the use of vasoconstrictors as an adjuvant (such as adrenaline).

The onset-time for infraclavicular brachial plexus block with ropivacaine 7.5 mg/ml is about 14 min for sensory block and 20 min for motor block, with a sensory block duration of about 9-11.5 hours, and motor block duration 7-10 hours (54). The minimum effective volume for infraclavicular blocks with ropivacaine 7.5 mg/ml sufficient for surgery distal to the elbow in 95% of the patients has been estimated to 31 ml (55). A high block success rate is also reported with smaller volumes, i.e. 20 ml, in one study (56).

### 7.4.2 Lidocaine

Lidocaine is an amide local anaesthetic drug with intermediate duration of action, mainly metabolised in the liver by the cytochrome P450 system (49). It may be used with or without the addition of adrenaline. Lidocaine induces vasodilatation at high concentrations commonly used in clinical practice and accelerates the transfer of locally injected adrenaline to the blood (57). The use of low concentrations may induce vasoconstriction. Onset-time for brachial plexus blocks (25-30 ml of lidocaine 20 mg/ml with adrenaline 5 µg/ml added) is about 20 min (58). In a Canadian study, the minimum effective volume of lidocaine 15 mg/ml with adrenaline 5 µg/ml for infraclavicular blocks was estimated to be 35 ml (59). High success rates are also reported with smaller volumes, i.e. 16 ml of lidocaine 20 mg/ml in one study (60).

### 7.4.3 Dexamethasone

Dexamethasone is a corticosteroid with predominantly glucocorticoid effects (only minimal mineralocorticoid effects), high potency and long duration of action. The molecules are lipophilic and cross the blood-brain barrier. Dexamethasone is metabolized in the liver and mainly excreted through the urine. It is frequently used to reduce both acute and long-lasting postoperative pain during operations in both general and regional anaesthesia, for example in abdominal surgery, gynaecologic
surgery and spine surgery (61, 62). It has an anti-inflammatory effect by inhibition of prostaglandin synthesis and reduces tissue oedema by decreasing vascular permeability (63). Corticosteroids may also inhibit the initiation of neuropathic pain by reducing spontaneous discharge of the membrane potential in the injured nerve as demonstrated in animal models (63, 64). Improved postoperative analgesic effect when dexamethasone was added to a nonsteroidal anti-inflammatory drug (rofecoxib) is previously shown before breast surgery (65).

Both intravenous and perineural dexamethasone prolong duration and analgesic effect of peripheral nerve blocks (66-69). Interestingly, both intravenous and perineural administration of doses more than 8 mg seem to result in similar prolongation of duration of blocks from ropivacain (66, 68, 70). At lower doses, i.e. 5 mg or less, perineural administration seems to be more effective (68, 71-73). The effect of perineural dexamethasone appears to be dose dependent up to a ceiling of 4 mg to reduce postoperative need of analgesic (1, 71, 74). The mechanism behind this observation is not fully understood (69), but prolonged duration of block may by itself reduce rebound pain scores (4). An earlier study with a single 10 mg dose of intravenous dexamethasone resulted in an increase in interscalene block duration of 8-9 hours (66).

The literature lacks safety data on perineural use of dexamethasone. The benefits over intravenous dexamethasone, which is considered safe and well established, seems marginal (62, 75). When dexamethasone is added to ropivacaine a crystallisation reaction may occur due to the elevated pH of dexamethasone (1, 76). When administering intravenous dexamethasone (0.1 mg/kg) it is important to be aware that it causes an increase in blood glucose levels by 1.5 mmol in both diabetic and non-diabetic patients (1).

Even though there are published several studies on dexamethasone and peripheral nerve blocks the last few years, several questions remain unanswered. The complete mechanisms behind the effects of dexamethasone on peripheral nerve blocks are not fully understood. Whether or not dexamethasone reduces the highest pain score, the
duration of high pain scores, and the development of long-lasting pain after surgery are not fully explored. Neither is the ideal dose of intravenous dexamethasone for optimising the effect of nerve blocks.

### 7.4.4 Adrenaline

Adrenaline is commonly added as an adjuvant to local anaesthetics in peripheral nerve blocks. It is a vasoconstrictor that prolongs block duration, increases the density of the block, serves as a marker of intravascular injection, and reduces the peak plasma level of local anaesthetics by up to 50% with subsequent reduction in toxicity (1, 77, 78). Adrenaline may also affect haemodynamics and microcirculation. Systemic effects of adrenaline include increased heart rate, contractility and arterial blood pressure. Locally, adrenaline causes vasoconstriction in the skin through an alfa-adrenergic effect, whereas binding to beta-adrenergic receptors in arterioles in skeletal muscles induce vasodilation (79).

The recommended dose of adrenaline added in a nerve block is not known, but it has been suggested that doses higher than 5 µg/ml may result in more systemic effects. One study on the effect of adrenaline comparing high and low doses and its hemodynamic effects (blood pressure and heart rate) concluded that low dose adrenaline offered more stable haemodynamics and similar block quality (80). The microcirculation may also be affected by adrenaline adjuvant in brachial plexus blocks, but there is a lack of studies describing how adrenaline adjuvant affects the different parts of the microcirculation.

### 7.5 Pain and peripheral nerve blocks

Pain is a subjective experience and is usually associated with actual or potential tissue damage. The different aspects of pain include: intensity, frequency/temporal characteristics, location, affect, quality, and pain interference (impact on life, emotional impact). A person’s attitude, beliefs and personality have a strong impact on the pain experience (81).
It is common to distinguish between acute pain as pain that resolves quickly and chronic pain as long-lasting pain. Some authors define acute pain to last less than 30 days and chronic pain to be pain lasting more than 3, 6 or 12 months (81). Yet, the distinction between acute and chronic pain can be difficult. Acute pain may also be defined as the normal predicted physiological response to an underlying cause (81). It is sometimes specified to be the initial phase of a nociceptive cascade triggered by tissue injury (81). It may last for less than a month, but can also last for more than 6 months (81). Chronic pain is long-lasting, and may continue even after the tissue injury that caused the initial pain is completely healed. Some patients suffer from chronic pain without any previous injury or damage.

Acute pain may quickly transform into more long-lasting pain. Short periods of acute pain can trigger long-term remodelling and sensitisation, and thus the development of chronic pain (81). Already within the first hours of injury, the biological and physiological foundation for long-term persistent pain may be in place (81).

The actual cause of pain is often a tissue destruction that activates nociceptors and initiates a local inflammatory response. Multiple mediators and immune cells maintain the local inflammation. Sensitised nociceptors at the site of tissue injury are affected by multiple inflammatory mediators, neurotransmitters and growth factors (81). The different pain qualities are associated with different causes, sources and types of pain. Different nociceptors and fibres underlie different pain sensations. The two main types of nociceptors are the myelinated A-delta fibres responsible for localised “sharp,” ”stinging,” and ”shooting” pain, and the unmyelinated C-fibres responsible for less localised dull pain sensations (82). Pharmacological treatment of pain affects both central and peripheral pain mechanisms.

Optimal pain treatment after surgery can improve clinical outcome, while a significant stress response may impair recovery (81). Theoretically, sufficient postoperative pain treatment may also prevent chronic pain by allowing the patients to do exercises important for their recovery.
The local anaesthetics in a nerve block efficiently stop transmission of nociceptive pain provoking impulses from a surgical site (83). However, the potential anti-inflammatory effects on a remote surgical site seem to be minor or moderate (84). This may explain why brachial plexus blocks often result in strong rebound pain when the blocks resolve (2, 85).

7.6 Preemptive and preventive analgesia

*Preemptive analgesia*: The concept of preemptive analgesia is based on the assumption that an anti-nociceptive treatment administered prior to the surgical trauma is more effective than the same treatment administered after the surgical trauma (86). The activation of pain reducing mechanisms before the start of the surgical trauma counteracts central sensitisation (87-89).

*Preventive analgesia*: The concept is simply to provide analgesia before the patients report pain, i.e. prophylactic analgesia as opposed to treating pain upon demand. Preventive encompasses all perioperative efforts to decrease postoperative pain and analgesic consumption (86). It includes placebo treatment and multimodal treatment, and can be given at any time in the perioperative period (both pre-operatively, during the operation and postoperatively) before the patient is expected to report pain.

Both preemptive and preventive analgesia are old concepts in anaesthesia. George Washington Crile (1864-1943) postulated that despite unconsciousness, the tissue trauma of surgery was sending painful signals to the brain and that these signals were being processed (90). In 1887 he used cocaine for regional anaesthesia to reduce nociceptive activity during surgery to prevent shock in his surgical patients (before, during and after the surgical trauma). He recommended a multimodal approach combining drugs, regional blocks and general anaesthesia (86). He found that the site, duration, and intensity of a stimulus made a difference in postoperative outcome and postulated that “the more complete the surgical anaesthesia, the less physiologic disturbance would be observed during recovery” (90).
Today, we know from basic pain physiology that continuous nociceptive stimulation results in an increase in pain sensation, partly as a result of physiological changes in the wounded area (peripheral sensitisation) and partly because of changes in the impulse transmission in the medullary dorsal horn and higher brain areas (central sensitisation). Preventive analgesia is used with the intention to decrease peripheral and central sensitisation as well as hyperalgesia. Regional anaesthesia may reduce long-lasting pain after surgery by decreasing pain sensitisation and by decreasing intraoperative opioid use and subsequently opioid induced hyperalgesia (91). The combination of preemptive analgesia before the surgical trauma and a multimodal analgesic regime (preventive analgesia) is probably the most effective method to reduce postoperative and long-lasting pain after operations (92).

Whether the incidence and severity of postoperative long-lasting pain is reduced by the use of regional anaesthesia is controversial. Some reports have been promising, especially with epidural analgesia and paravertebral blocks, while the documentation for local anaesthesia, ketamine and NSAIDs are uncertain (43, 93-96). However, some studies have shown a significantly improved pain control for a prolonged period of time after the primary effect of the local anaesthesia has vanished (3, 97).

Even more contentious is whether a regional nerve block is more effective in the postoperative phase when performed before the start of surgery compared with after surgery. Some studies and reviews are in favour of pre-operative administration (98, 99), whereas numerous studies could not demonstrate such benefits (100-103). In a study of interscalene brachial plexus block using lidocaine for shoulder surgery, Haltiavaara et al. showed no benefits in applying the block before the start of surgery compared with a postoperative block (104). This study was criticized because lidocaine may be too short acting to have an effect on nociceptive pain mechanisms that occur following the surgical intervention (105). Proximal nerve blocks do not reduce local inflammation or release of potent proteins from damaged cells in the wound area. Release of these substances into the general circulation has an impact on the systemic stress response as well as on cellular processes in the medullary spinal cord, and may potentially result in more pain (92, 101).
In every day practice, there is on-going discussions if we should take the time to perform our nerve blocks prior to the operation, or rather wait until after the operation to potentially get a few hours extra with an effective nerve block. When a brachial plexus block is performed before surgery, nociceptive impulses may be more effectively reduced than by general anaesthesia alone. On the other hand, when the nerve block is performed after surgery, several extra hours of good postoperative analgesia may be expected, compared with a block performed 1-2 hours earlier, before start of surgery.

7.7 Volar plate fixations of distal radius fractures

Radius fractures are one of the most common fractures in humans. An earlier study has estimated that a 50 year old white woman in the US or Northern Europe has a 15% lifetime risk of a radius fracture (106). Volar plate fixations of displaced radius fractures are every-day procedures in orthopaedic surgery. Many patients experience pain after these operations, both severe acute postoperative pain and long-lasting pain (2). Long-lasting pain after volar plate surgery may be a combined result of prolonged pain after the fracture per-se and the pain from the surgical procedure. In a large series of non-operated radius fractures, 9.8% had stiffness after one year and 9.5% had dystrophia or chronic regional pain syndrome (107).

Brachial plexus blocks provide excellent postoperative analgesia in the immediate postoperative period after volar plate surgery. A previous study in this patient group supports the long-term benefits of less persistent pain after surgery during infraclavicular nerve blocks compared with general anaesthesia (3), while others find no such connection (2, 108). On the downside, strong rebound pain at block resolution 12-24 hours postoperatively can be a relevant problem (2, 85, 109).

Good pain treatment may improve postoperative outcome. Therefore, it is important to explore methods to reduce both postoperative pain (including the strong pain at block resolution) and impede the development of long-lasting pain in this large patient group.
7.8 Skin microcirculation of the upper limb

Human microcirculation includes 99% of the blood vessels in adults. It consists of a network of arterioles, capillaries and venules between the arterial and venous part of the circulation (110). 8-10% of the total blood flow in the body can be found in the skin. Temperature regulation is the major task of the cutaneous vascular supply, but the microcirculation is also essential for the transfer of nutrients and oxygen to the tissues according to their needs, elimination of waste products, and to prevent variations of hydrostatic pressure at the level of the capillaries (111, 112).

Skin blood flow is complex with regional variations across the body for the thermoregulatory and nutritional vascular systems. It consists of horizontal vascular plexuses parallel to the skin surface that communicate through arterioles and venules (113). Skin microcirculation consists of two different components which differ in their importance on perfusion of tissue cells: the subpapillary blood flow which is controlled by synchronous opening or closing of arterio-venous anastomosis for thermoregulation, and the superficial nutritive blood flow in papillary capillaries which supplies oxygen and nutrients for epithelial cell proliferation (114). The nutritive blood flow compromises about 20% of the skin blood flow, the rest of the blood flow is functional (113, 115).

Arterio-venous anastomosis are direct connections between small arteries and small veins in the dermis, that bypasses the capillary network (116). They are short vessels with a thick muscular wall, and provide a low-resistance connection between arteries and veins when they are open. They are innervated by the autonomic nervous system and important for temperature regulation in humans. To reduce heat loss and ensure deep cutaneous circulation, they can restrict the blood flow through the superficial plexuses. Humans have numerous arterio-venous anastomosis in the glabrous (non-hairy) skin of the palmar side of the hands, while they are not present in the non-glabrous (hairy) skin on the dorsal side of the hand (116).
Several factors influence the human skin microcirculation, including temperature, arterial pressure, physical and mental activity, age, feeding, menstrual cycle, stress, medication, smoking and different pathological changes (111).

### 7.9 Changes in microcirculation induced by brachial plexus blocks

Both a sympathetic blockade and any systemic uptake of local anaesthetics or adjuvants may induce changes in microcirculation and haemodynamics.

Peripheral nerve blocks decrease the intensity of sympathetic nervous signals transmitted by noradrenaline to blood vessels in the arm, both in muscles and skin. A blockade of vasoconstrictive sympathetic nervous impulses to blood vessels, is expected to increase both local nutritive blood flow to skin and muscle, as well as increase the blood flow through arterio-venous anastomoses (117). A previous study has shown that a block of the sympathetic nerve fibres innervating the arteriovenous anastomosis in the glabrous (non-hairy) skin increases blood flow in the palms and fingers (39). As far as we know, no studies have been done to confirm this theory after brachial plexus blocks.

Laser Doppler was used in several studies to investigate changes in skin perfusion after brachial plexus blocks, all of them reporting alterations in circulations. Laser Doppler measurements have shown arterial vasodilatation, increase in blood flow velocity, and increase in blood flow through the ipsilateral brachial artery after axillary brachial plexus blocks (118). Landsverk et al observed alterations in the oscillatory components of the flowmetry signal in the blocked arm and the contra-lateral arm. However, blood flow was not significantly increased in this study (119). Interestingly, the group measured skin perfusion on the volar side of the hand where arteriovenous anastomoses are not present. Lethipalo and colleagues observed increased skin perfusion in the index finger after interscalene brachial plexus block (120).

Comparing brachial plexus blocks with and without adrenaline, McGregor et al. found a greater increase in blood flow to the arm and a higher temperature rise when adding
adrenaline to an axillary brachial plexus block (121). The authors suggested that these findings were caused by the systemic effect of adrenaline inducing a rise in cardiac output.

The effect of brachial plexus blocks and adrenaline adjuvant on the two different vascular entities of human skin microcirculation, subpapillary blood flow and nutritive blood flow, has not to our knowledge been studied in detail so far.

7.10 Microcirculation and pain

Reduced microcirculation can cause pain and microcirculatory changes may affect pain. Several non-injury pain conditions are due to compromised microcirculation. Pain may increase the risk of vasospasms. A number of pain conditions are treated with techniques to improve microcirculation, for example different types of tendinitis, Raynaud disease, ischemic pain and muscular pain. The analgesic effects of acupuncture are believed partly to be due to increased microcirculation (122, 123).

During an acute inflammatory reaction, several microcirculatory changes occur. First, the arterioles go through a transient vasoconstriction, then a vasodilation that results in increased blood flow. The following increase in vascular permeability leads to reduced blood flow, stasis and interstitial oedema (111).

Vascular disturbances affecting the microcirculation are believed to be part of the mechanism behind complex regional pain syndrome, although the complete pathophysiology behind this syndrome is not fully understood (124). At least two different suggestions of the mechanism behind the pain and oedema are suggested: a high capillary filtration capacity possible due to an imbalance between the sympathetic constrictor tone of post-capillary and pre-capillary vessels, or a local inflammatory reaction causing microcirculatory alterations(125).

Peripheral nerve blocks are believed to only have limited effect in the treatment of ischemic pain, because ischemic pain is mediated by thick A-beta fibres resistant to local anaesthetics (surgical pain are mediated through unmyelinated C-fibres and
myelinated A-delta fibres). However, brachial plexus blocks are known to increase peripheral blood flow. A possible improvement in microcirculation due to brachial plexus blocks can theoretically reduce both inflammatory and ischemic reactions, and subsequently have the potential to reduce pain.
8. Aims and hypothesis

The general aim of this thesis is to evaluate the clinical and physiological benefits of infraclavicular brachial plexus block and modify the use in dedicated areas to improve its benefits and avoid undue harm.

Overall hypothesis of the thesis:

1: Proper modifications of timing and adjuvants of infraclavicular brachial plexus block may have a positive impact on postoperative clinical outcome and peripheral circulation (addressed in papers 1, 2 and 3).

2: Modification of preemptive and preventive non-opioid analgesia will reduce pain intensity, duration of moderate to severe pain, and total opioid requirement postoperatively (addressed in papers 1 and 2).

3: Enforced anti-inflammatory prophylaxis will reduce pain after volar plate surgery. Double prophylaxis with etoricoxib and dexamethasone will result in less pain compared with single prophylaxis with etoricoxib (addressed in paper 2).

4: Brachial plexus block will improve peripheral circulation, including both subpapillary and nutritive blood flow. The addition of adrenaline to a lidocaine infraclavicular brachial plexus block may further modify both local and systemic blood flow (addressed in paper 3).

The specific research questions were as follows:

A) Does a pre-operative infraclavicular brachial plexus block have a significant preemptive effect, resulting in better and more long-lasting postoperative analgesia compared with an identical block performed at the end of surgery? (Study 1)

B) Does a single pre-incisional intravenous dose of dexamethasone reduce both acute and long-lasting postoperative pain after surgery performed under infraclavicular brachial plexus anaesthesia with both paracetamol and etoricoxib as premedication? (Study 2)
C) Do infraclavicular brachial plexus blocks with or without adrenaline added cause alterations in both subpapillary and nutritive blood flow and systemic cardiovascular variables? (Study 3)
9. Materials and methods

9.1 Study designs

To answer our specific research questions, we decided to do two clinical studies on patients and one study in healthy volunteers.

A) Does a pre-operative infraclavicular brachial plexus block have a significant preemptive effect, resulting in better and more long-lasting postoperative analgesia compared with an identical block performed at the end of surgery?

To answer this question we designed an interventional, prospective, double-blind, randomised clinical study with a parallel design comparing two groups (Study 1).

B) Does a single pre-incisional intravenous dose of dexamethasone reduce both acute and long-lasting postoperative pain after surgery performed under infraclavicular brachial plexus anaesthesia with both paracetamol and etoricoxib as premedication?

We aimed to explore if increased inflammatory prophylaxis would reduce acute and long-lasting pain after volar plate surgery, and how dexamethasone influences on the brachial plexus block. To answer these questions, we designed a clinical study with a prospective, double-blind, parallel, randomised design comparing two groups (Study 2).

C) Do infraclavicular brachial plexus blocks with or without adrenaline added cause alterations in both subpapillary and nutritive blood flow and systemic cardiovascular variables?

To answer this, we designed a randomised double-blind study in healthy volunteers. We chose the crossover design to limit the number of volunteers needed (Study 3).
**Table 1: Overview of studies included in this thesis**

<table>
<thead>
<tr>
<th>Study</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study design</strong></td>
<td>Prospective, double-blind, randomised controlled clinical trial.</td>
<td>Prospective, double-blind, randomised controlled clinical trial.</td>
<td>Randomised, double-blind, crossover study in healthy volunteers.</td>
</tr>
<tr>
<td><strong>Study population</strong></td>
<td>52 patients aged 18-70 scheduled for volar plate surgery for distal radius fracture.</td>
<td>53 patients aged 18-65 scheduled for volar plate surgery for distal radius fracture.</td>
<td>12 healthy adult male volunteers.</td>
</tr>
<tr>
<td><strong>Study period</strong></td>
<td>2011-2014</td>
<td>2017-2018</td>
<td>2014</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Infraclavicular brachial plexus block before or after surgery.</td>
<td>Intravenous dexamethasone or placebo at start of surgery.</td>
<td>Lidocaine brachial plexus block with or without adrenaline added.</td>
</tr>
<tr>
<td><strong>Aim</strong></td>
<td>To compare brachial plexus blocks performed before and after surgery with regard to acute and long-lasting postoperative pain after volar plate surgery.</td>
<td>To evaluate the effect of intravenous dexamethasone on brachial plexus block, acute postoperative pain and long-lasting pain after volar plate surgery.</td>
<td>To investigate the effect of adrenaline when added to lidocaine in brachial plexus block on both subpapillary and nutritive blood flow, as well as on general systemic cardiovascular variables.</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>Time until first rescue opioid analgesia after emergence from anaesthesia.</td>
<td>Highest pain score during the first 24 hours after surgery.</td>
<td>Alterations in subpapillary blood flow after adrenaline adjuvant.</td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td>Postoperative pain and analgesic consumption at 30 min, 60 min, 120 min, 4 hours, 8 hours, 24 hours, 7 days and 6 months after surgery. Incidence of postoperative side effects. Overall satisfaction and quality of life measures. Changes in plasma stress mediators.</td>
<td>Postoperative pain and analgesic consumption at 30 min, 60 min, 120 min, 4 hours, 8 hours, 24 hours, 36 hours, 3 days, 7 days, 6 weeks, 6 months and 1 year after surgery. Incidence of postoperative side effects. Overall satisfaction and quality of life measures. Block duration. First time with pain score less than 4 after block resolution. PRWHE score after 6 weeks.</td>
<td>Alterations in nutritive blood flow after adrenaline adjuvant. Changes in systemic cardiovascular variables. Characterise the time course of changes in blood flow to the blocked arm and control arm as well as the characteristics of block with or without adrenaline adjuvant.</td>
</tr>
<tr>
<td><strong>Main data material</strong></td>
<td>VNRS scores</td>
<td>VNRS scores. Analgesic consumption in mg. Likert scale on quality of life measures. Time in hours and minutes.</td>
<td>Laser Doppler measurements. Data from video microscopy. Temperature measurements. Continuous haemodynamic measurements from Nexfin measurement device and HR from a three lead electrocardiogram.</td>
</tr>
</tbody>
</table>
9.2 Study settings

The studies for paper 1 and 2 were conducted at the orthopaedic unit in Storgata, Oslo University Hospital. The orthopaedic unit in Storgata takes care of ambulatory orthopaedic surgery in ASA 1 and 2 patients (also stable ASA 3 patients) and planned surgery in ASA 1 and 2 patients.

The study for paper 3 took place at Oslo University Hospital, Rikshospitalet. The experimental runs were conducted in an operating theatre with controlled air temperature. Some pre- and post-experimental observations were obtained in the department for research and development.

9.3 Study populations

9.3.1 Study 1 and 2

These two studies were clinical studies on healthy adult patients (ASA 1 and 2) able to communicate in a Scandinavian language scheduled for volar plate surgery of distal radius fractures. All patients included had to be able to follow up and cooperate on the study.

Common exclusion criteria for the two studies included pregnancy or current breastfeeding, body mass index under 18 kg/m² or greater than 35 kg/m², and contraindications for: brachial plexus block, ropivacaine or oxycodone. Patients with severe psychiatric disorders, known nerve injury or nerve compression syndrome (e.g. carpal tunnel syndrome) of the upper limb, chronic pain or regular use of non-steroidal anti-inflammatory drugs, steroids, opioids, or other types of analgesics before the radius fracture, were also excluded from the study.

In study 1, we excluded patients with contraindications for general anaesthesia with a laryngeal mask as all patients in this study received general anaesthesia.
In study 2, we excluded patients with contraindications for dexamethasone or etoricoxib, immunocompromised patients and patients with diabetes mellitus due to risk of adverse events. Patients using drugs with sedative effect on a regular basis were also excluded as these drugs may interact with oxycodone, and the patients potentially have a greater risk of developing opioid dependence. We decided only to screen patients scheduled for operation 1-20 days after their fracture trauma to get a reasonably homogenous group of patients.

9.3.2 Study 3

To get a homogenous group with as little risk for adverse events as possible, the study was conducted on healthy volunteers (ASA 1-2) aged 18 – 60, with body mass index 18-35 kg/m², and without known nerve injury or nerve compression syndrome of the upper limb, diabetes mellitus, known reduced immune response or any contraindications to lidocaine or adrenaline. We only included males, because women’s menstrual cycle affects microcirculation (126). As smoking, feeding, and medication may influence on microcirculation, all volunteers were non-smoking, had fasted at least 6 hours, and were instructed not to consume coffee, black tea or garlic 12 hours prior to the experiments and no medication the last seven days before the experiments (111).

9.4 Study procedures.

9.4.1 Inclusion

Study 1:

According to the presence of the first author (or Ketil Spook the first few months of the study), patients scheduled for volar plate fixations at the orthopaedic unit in Storgata were screened for eligibility to participate in the study during the period from November 2011 to December 2014. One-hundred-and-twenty-three patients were assessed for eligibility to participate, 71 were not included (42 did not meet the inclusion criteria, 26 refused to participate, three were not included due to pre-
operative logistic problems). Fifty-two patients were included and randomised after oral and written informed consent. One patient was not studied after randomisation due to change of operation technique to percutaneous pinning instead of volar plate surgery. For five patients, data on the primary outcome was not complete. Forty-six patients were analysed for the primary outcome.

Study 2:

Patients aged 18-65 years scheduled for volar plate fixations at the orthopaedic unit in Storgata were screened for eligibility to participate during the period from January 2017 to April 2018. A total of 162 patients were screened, 109 of them were not included (31 did not meet the inclusion criteria, 66 due to our exclusion criteria, five refused to participate, six due to no study doctor present for inclusion, and one due to a pre-operative logistic problem). A total of 53 patients were included and randomised after oral and written informed consent. Six patients dropped out after inclusion for different reasons. One patient was not able to answer any of our questions after discharge from hospital on the day of surgery or the day after. Another had the operation postponed after inclusion. Unfortunately, no study doctor was present during the block procedure on the day of the operation, hence the patient was excluded from the study. One patient had the operation technique changed to percutaneous pinning instead of volar plate surgery. In three patients, the surgeon discovered antebrachii fractures after inclusion. Hence, they did not fill the inclusion criteria. These three patients were followed up and received postoperative care according to the protocol, but were excluded from the published data to present clean material with only volar plate surgery for distal radius fractures. Forty-seven patients were analysed for the primary outcome, 23 in the dexamethasone group and 24 in the placebo group.

Study 3:

The twelve volunteers participating in this study were recruited by poster advertisements and included after oral and written informed consent. The experimental runs took place in March and April 2014. Due to the crossover design in the study, all volunteers received two brachial plexus blocks with a two weeks washout period
between the blocks. An incorrect group allocation occurred in one volunteer who mistakenly received a block without adrenaline twice. We therefore had no paired data from this participant, and excluded the dataset from the analysis.

### 9.4.2 Brachial plexus blocks

To diminish the risk of complications after brachial plexus blocks, all the blocks were performed by doctors well experienced with ultrasound guided infraclavicular blocks. The blocks were performed under aseptic conditions with standard monitoring (electrocardiogram, pulse oximetry and non-invasive blood pressure) and an intravenous line established.

Lateral sagittal infraclavicular brachial plexus blocks were performed ultrasound-guided in a standardised way in all three studies (31, 33). A 22-gauge, 80mm SonoPlex® Stim cannula (Pajunk® GmbH, Geisingen, Germany) was placed under ultrasound guidance, in-plane in a central position to the plexus, cranio-posterior and close to the axillary artery under sterile conditions (31). Start of block was defined as the time when the injecting needle was withdrawn (‘needle out’).

In study 1, Anne Holmberg and Ketil Spook performed all blocks, using a SonoSite S-Nerve ultrasound unit (SonoSite, Bothell, WA, USA) with a C11, 5–8 MHz, broadband curved array probe. Because the patients received the blocks under general anaesthesia, nerve stimulation and injection pressure monitoring were used in addition to ultrasound to minimise the risk of intraneural injection. A volume of 0.5 ml/kg ropivacaine 0.75% was injected.

In study 2, all blocks were performed by one of the authors (Anne Holmberg, Anders Nordby, Fredrik Ottesen, Allan Gulestøl or Johan Ræder) using a SonoSite Edge 2 ultrasound unit (SonoSite, Bothell, WA, USA) with a C11x, 5–8 MHz, broadband curved array probe or a HFL38, 13-6 MHz linear probe. All patients were awake during the block procedure. They received 0.4 ml/kg ropivacaine 0.75%, with a minimum volume of 25 ml and a maximum volume of 40 ml.
In study 3, Axel Sauter performed all blocks using a Phillips HD 11 XE ultrasound unit (Philips Medical Systems, Bothell, WA, USA) with a C8-5, 5-8 MHz, curved linear transducer. All patients were awake during the block procedure. A volume of 0.4 ml/kg lidocaine 1.5% was injected, either with or without adrenaline 5 µg/ml.

We chose different local anaesthetic solutions in the clinical and experimental studies. In study 1 and 2 we used ropivacaine because we wanted a long lasting agent, and because it is the most frequently used local anaesthetic solution for volar plate surgery in our hospital. In the study on microcirculation (Study 3), we chose lidocaine to get a short-acting agent with low toxicity when performing infraclavicular blocks in volunteers.

### 9.4.3 Block assessment

We used the same block assessment and definition of block success in all three studies. Sensory testing included the musculocutaneous, radial, median, ulnar, and medial antebrachial cutaneous nerve. The blocks were assessed by temperature testing, repeatedly touching the skin on predefined positions in the sensory area of the nerves. A sensory block was considered successful when the participant had either no sensation for cold or touch (anaesthesia) or no sensation for cold (analgesia). Motor testing included the musculocutaneous, radial, median and ulnar nerve. A motor block was considered successful when the subjects had less than 50% of normal muscle power as estimated by the examiner.

The blocks were assessed at predefined times in all studies. In study 1 (where the patients got their blocks under general anaesthesia before or after surgery), the blocks were assessed at 30 min and 2 hours after surgery. In study 2, the blocks were assessed preoperatively 30 min after the block procedure and 30 min after surgery. In study 3, the effect of the blocks was assessed after all measurements were completed, about 60 min after local anaesthetics injection.

In study 1, we used time to first analgesic to estimate sensory block duration. In study 2 and 3, we designed a simple test the participants could easily perform themselves at
home. They were asked to report the first time they were able to hold a cup (or another object) and lift it to the face area with the blocked extremity. Hence in study 2, where our aim was to evaluate pain, we used the duration of motor blockade as a surrogate for the endpoint of interest, nociceptive blockade.

### 9.4.4 Perioperative procedures study 1 and 2

#### Study 1

All patients received paracetamol 2 g as oral premedication.

Standard monitoring during surgery included ECG, pulse oximetry, non-invasive blood pressure and capnography. Surgery was performed under general anaesthesia with propofol and remifentanil target controlled infusions (127-129). Propofol target controlled infusion was kept at an effect site target of 2.0-2.5 µg/ml, adjusted to maintain a bispectral index (BIS monitor XP 2000, SW 3.12, Aspect Medical Systems, Natick, MA, USA) of between 45 and 55. The remifentanil target controlled infusion was adjusted to maintain the systolic blood pressure between 85 and 120 mmHg. The patients’ lungs were ventilated through a laryngeal mask whilst maintaining normocarbia.

Blood samples for plasma leukocyte counts, blood sugar, C-reactive protein (CRP) and cortisol levels were taken after induction of anaesthesia, just after surgery, and two hours after emergence from general anaesthesia.

In case of post operative nausea or vomiting (PONV), Metoclopramide 10 mg intravenously was given, supplemented by rescue ondansetron 4 mg intravenously when needed.

#### Study 2

The patients were tested for pressure pain threshold (defined as when a non-painful increasing pressure stimulus turned into a painful pressure sensation) with a pressure algometer (Algometer type II, Sonomedic production AB, Sollentuna, Sweden) before premedication and block procedure.
All patients received paracetamol 2 g and etoricoxib 120 mg (i.e. 90 mg if weight under 70 kg) as oral premedication.

The dexamethasone group received 4 ml of dexamethasone 4 mg/ml slowly intravenously (DexaGalen®, Galen Pharma GmbH, Kiel, Germany), a total of 16 mg, at start of surgery. Patients in the placebo Group received 4 ml of NaCl 0.9% (Natriumklorid 9 mg/ml, Fresenius Kabi, Halden, Norway).

Surgery was performed in brachial plexus block with or without intravenous sedation, either propofol target control infusion (Schnider effect site model) (130) or midazolam bolus with maintenance of non-assisted spontaneous ventilation, at the discretion of the anaesthesiologist. In case of pain, either from tourniquet or from the operation site, intravenous oxycodone (OxyNorm®) was given.

9.4.5 Surgical procedure study 1 and 2

The surgical procedure was performed through a standardised flexor radialis carpi-approach while using a tourniquet. Pronator quadratus was detached from radial and distal origin. After reduction, the fracture was fixed by a volar locking plate. The tourniquet was released, and surgical haemostasis performed. The wound was covered with soft dressing. The fractures were considered stable after surgery and early mobilization was allowed.

9.4.6 Postoperative analgesic procedures study 1 and 2

Study 1

In the post-anaesthesia care unit, the patients were given rapid release oxycodone (OxyNorm®) 1 mg intravenously or 5 mg orally if a rescue analgesic was required due to patient request or a numeric rating scale score above 3.

After discharge, all patients received a standardised per oral multimodal analgesic regime, according to verbal and written instructions. Paracetamol 1 g x 4 was prescribed as long as they felt pain from surgery. Controlled release oxycodone (OxyContin®) 20 mg was prescribed as further baseline medication every 12 hours,
three doses in total (10 mg if weight less than 70 kg or age above 60 years). First dose of controlled release oxycodone was given in the evening after the operation if pain was present, otherwise it was introduced the next morning. Oral rapid release oxycodone (OxyNorm®) 5 mg was taken as needed on top of baseline medication during the first 48 hours. If pain medication was needed beyond day two, oral paracetamol was recommended as a first line drug, on demand combined with codeine.

**Study 2**

After discharge, all patients received a standardised per oral multimodal analgesic regime, according to verbal and written instructions. Paracetamol 1 g x 4 was prescribed as long as they felt pain from surgery. Etoricoxib (Arcoxia®) 120 mg x 1 was given on postoperative day 1 and 2, (90 mg if weight was less than 70 kg).

Controlled release oxycodone (OxyContin®) 20 mg was prescribed as further baseline medication every 12 hours, three doses in total (15 mg if weight less than 70 kg). The first dose was given 8 hours after brachial plexus block. Oral rapid release oxycodone (OxyNorm®) 5 mg was taken as needed on top of baseline medication during the first 48 hours. If pain medication was needed beyond day two, oral paracetamol was recommended as a first line drug, on demand combined with tramadol or codeine.

**9.4.7 Randomisation and blinding**

The patients in study 1 and 2 were randomly allocated to two groups using a computer-generated list of random numbers. Codes for two group allocations were made and placed in sealed envelopes before the start of the study by a person not involved with the patient handling. In study 3, the sequence of blocks, i.e. if adrenaline was added in the first or the second session, was randomised by computer-generated codes and packed in sealed envelopes by a person not involved in the experiments.

**Study 1:**

The doctor performing the block opened the envelope after induction of anaesthesia. Patients in the pre-operative block group received an ultrasound-guided lateral sagittal infraclavicular brachial plexus block just after induction of general anaesthesia, 20 min
before application of an upper arm tourniquet and the start of surgery. Patients allocated to the postoperative block group received an identical block just after the end of the surgical procedure. These patients were then kept anaesthetised for 20 min before emergence of anaesthesia (and removal of the laryngeal mask), in order to allow the brachial plexus block to be effective, and ensure blinding of the postoperative observation personnel. No one present in the operating theatre took part in postoperative care or observations of the patients.

**Study 2:**

To ensure double blinding for all data, two nurses not involved in the patient handling opened the sealed envelopes after patient inclusion and prepared syringes with dexamethasone or NaCl. The syringes were then handed over to the anaesthetic nurse, who injected the content slowly (to avoid perineal irritation) before application of the tourniquet. The patients, all investigators and all hospital staff involved in the patients were blinded to group allocation.

**Study 3:**

An investigator not taking part in the conduction of the experiments opened the sealed envelopes and prepared two 20 ml syringes containing the local anaesthetic solution (lidocaine with or without adrenaline). The volunteers and all investigators present at the experimental sessions were blinded to group allocation. All nerve blocks were tested by a doctor (Øivind Klaastad) who was blinded to group allocation and not present during the experimental runs.

**9.4.8 Follow up after discharge**

In the first two studies, the patients were followed up at different time intervals up to one year after the operation (6 months in study 1, 12 months in study 2).

We decided to use phone-calls for our follow up at 8 hours, 3 days, 7 days, 6 months and 12 months. At discharge from hospital, all patients received a folder containing general information about the study and all the questions we were to ask during the phone calls so they could prepare. Before every scheduled phone interview, we sent a
text message to agree on an appropriate time. When we did not reach the patients as agreed, we would try to contact them again at least twice and specified their opportunity to leave the study. At 6 weeks after the operation, the patients had a scheduled appointment with the surgeon. The patients got the choice of handing in a questionnaire at that appointment, or participating in a phone interview. To try to ensure the questions were asked equally to all patients, two investigators conducted almost all the phone interviews.

In study 3, all patients were called the day after the experimental runs to make sure the block had completely resolved, to get the time of block resolution (some volunteers went home with a remaining block), to register adverse events, and to answer questions they might have had about the study.

9.4.9 Data registration and security

All data in our studies were handled according to the Norwegian laws and guidelines for research. The data in all studies was registered in a paper Case Registration Form (CRF) and stored in ring binders securely stored in locked cabinets. The de-identified data was then entered into an Access CRF database, further analysed by IBM SPSS (SPSS Inc., Chicago, IL, USA) (different versions for the different studies), and stored on a secured platform in Oslo University hospital, separately from identifiable personal patient information. The data was only accessible for the main investigators of the studies.

9.5 Outcomes

All outcomes in all studies were predefined.

9.5.1 Study 1

Our primary aim was to evaluate whether a pre-operative infraclavicular brachial plexus block has a significant preemptive effect, resulting in better and/or more long-lasting postoperative analgesia compared with an identical block performed at the end of volar plate surgery.
The primary outcome was time until first rescue opioid analgesia after emergence from anaesthesia. Secondary outcomes were postoperative pain scores (VNRS) and analgesic consumption at 30 min, 60 min, 120 min, 4 hours, 8 hours, 24 hours, 7 days and 6 months after emergence of anaesthesia. Other secondary outcomes were incidence of postoperative side effects (nausea, vomiting, sedation and pruritus), overall satisfaction and quality of life measures (sleep quality, working capacity, impact on social life and cognitive function) as well as changes in plasma stress mediators (white cell count, glucose, CRP and cortisol levels). Unfortunately, we were not able to look at changes in lactate levels due to lack of analysis facilities on site.

9.5.2 Study 2

Our primary aim was to evaluate the effect of double anti-inflammatory prophylaxis with oral etoricoxib and intravenous dexamethasone compared with single prophylaxis with oral etoricoxib on acute postoperative pain and long-lasting pain after volar plate surgery in brachial plexus anaesthesia.

The primary outcome was the difference between the two groups (dexamethasone group and placebo group) in highest pain score (VNRS) during the first 24 hours after surgery. Major secondary outcomes were: difference in highest pain scores during the first 36 hours after surgery, postoperative pain scores (VNRS) and analgesic consumption at 30 min, 60 min, 120 min, 4 hours, 8 hours, 24 hours, 36 hours, 3 days, 7 days, 6 weeks, 6 months and one year after end of surgery. Other secondary outcomes were differences between the two groups in block duration, differences between the two groups to first time with VNRS score less than 4 after block resolution, incidence of postoperative side effects (nausea, vomiting, sedation and itching) as well as overall satisfaction and quality of life measures (sleep quality, working capacity, impact on social life). Cognitive function (Likert scale) was evaluated as memory and concentration problems may be a consequence of long lasting pain). We looked at differences in PRWHE (Patient Rated Wrist and Hand evaluation) score after six weeks. We also asked about pain frequency, activities causing pain, and some questions about different qualities of pain that could indicate
development of neuropathic pain.

9.5.3 Study 3

The aim of this exploratory study was to investigate if infraclavicular brachial plexus blocks with or without adrenaline adjuvant cause alterations in subpapillary and nutritive blood flow and systemic cardiovascular variables.

Our primary outcome was differences in subpapillary blood flow between lidocaine infraclavicular blocks with or without adrenaline added, measured by laser Doppler. Other major outcomes were differences in nutritive blood flow measured with capillary video microscopy, temperature differences and differences in systemic cardiovascular variables after lidocaine brachial plexus blocks with or without adrenaline. We also wanted to characterise the time course of changes in blood flow to the blocked arm and control arm as well as the characteristics of block with or without adrenaline adjuvant.

9.6 Outcome measures

9.6.1 Pain

We used several methods for evaluating pain in our studies. We used a 0-10 verbal numeric rating scale (VNRS) to evaluate pain intensity (for both acute and long-lasting postoperative pain). We registered both pain at rest and during movement at predefined points in time. We also asked for recall rating of average and worst pain scores over different time periods. A Likert scale with five categorical ratings (no pain, mild pain, moderate pain, strong pain and very strong pain) was used in addition to VNRS score on some endpoints.

Both total analgesic consumption and rescue opioid consumption were recorded first week after the operation as well as last week before every follow up, and used it as an indicator of pain in our studies. We also registered time to rescue opioid consumption and duration of moderate to severe pain (VNRS score above 3).
To evaluate pain impact, we used a Likert scale with five categories (no impact, minor impact, medium impact, high impact and very high impact). To evaluate different pain qualities, we used dichotomous scales (yes-no).

9.6.2 Microcirculation

In study 3, we used a combination of laser Doppler measurements, capillary video microscopy and temperature measurements to evaluate skin microcirculation. All methods are discussed in depth in the methodological considerations chapter of this thesis.

Laser Doppler measurements

Laser Doppler Fluxmetry (LDF) (MBF3D, Moor Instruments, Devon, UK) was used to measure continuous subpapillary skin blood flow from the left and right hypothenar. During the measurements, a low-energy monochromatic laser beam is reflected from red blood cells 1 – 2 mm below the skin surface (131). By analysing the spectrum of the reflected light, the concentration of moving blood cells and their average velocity can be calculated. This permits measurement of blood flow mainly in the subpapillary vessels (including the arteriovenous anastomoses) where the blood flow is primarily serving a temperature-regulating purpose (114).

The laser Doppler probes were fixed to the skin with double-sided tape. The noise-limiting filter of the instrument was set at its highest level (21 kHz), and the emitted wavelength was 820 mm. The flux output signal was filtered with a time constant of 0.1 second and sent to the recording computer. The sampling frequency was 2 Hz.

Capillary video microscopy

Capillary video microscopy with a few micrometres penetration depth was used to assess the nutritive circulation of the skin (132). This permits direct assessments of both the functional density and the flow velocity of visible capillaries (110). Functional capillary density (FCD) is a dynamic measurement (measured in videos because all capillaries cannot be clearly seen in a static image) that indicates the quality of tissue perfusion (133, 134).
Capillary video microscopy was performed twice with a handheld digital microscope (GT700 UV, Firefly, Belmont, MA, USA), first after 20 minutes of acclimatisation and again 30 minutes after the brachial plexus block, by one of the investigators (Anne Holmberg). Baby skin care oil (Sebamed®, Boppard, Germany) was applied on the skin before examination. The microscope was then placed between the first and second metacarp on the dorsal side of both hands. The hand of the extremity to be blocked was examined first. Five video sequences were recorded for each examination, each video lasting 15 seconds. The recorded sequences were subsequently analysed using the software QuickTime Player 10.4 for MAC (Apple Inc., Cupertino, CA, USA) on a ME32C colour display unit (Samsung electronics, Surrey, UK). Xscope software for MAC (the Iconfactory, Greensboro, NC, USA) was used to create a grid dividing the screen into 16 equal squares. Capillaries were counted in the four central squares. When artefact occurred in any of the selected squares, four alternative adjacent squares were randomly chosen. Average numbers from the capillary counts of two investigators (Anne Holmberg and Axel Sauter) were used for analyses of functional capillary density (average number of counted papillary loops per mm$^2$).

A third investigator (Torjus Wester) with broad experience in capillary flow assessment examined the flow velocity. The flow was classified into five different categories: 0) No flow; 1) Sluggish flow; 2) Continuous low flow; 3) Continuous high flow; 4) Brisk flow (135).

**Temperature measurements**

We attached thermocouples to the digital pulp of finger 1, 2, 4, and 5 on both hands, excluding the middle finger with the blood pressure cuff. The temperatures were continuously sampled at 1-minute intervals with a multi-channel Hydra Series II data logger (Fluke, Everett, WA, USA) and transferred for storage to a recording computer. The mean temperature of the four fingers on each hand was calculated for each time bin of 1 minute, and the median response from all subjects was calculated.
9.6.3 Non-invasive continuous haemodynamic measurements

In study 3, heart rate (HR) was calculated over each R-R interval of a three lead electrocardiogram (ECG). Blood pressure was recorded continuously and non-invasively by the volume clamp method through a finger pneumonic cuff placed on the third finger of both hands, using two Nexfin measurement devices (Nexfin®, BMEYE B.V., Amsterdam, the Netherlands) (136). The measurements were performed on both sides to have comparable situations on the blocked extremity and on the control arm. Only the recording from the dominant hand, which was not used for plexus block, was reported. During the experiments, both hands were placed on the arm boards of the operation table at the height of the right atrium. The instantaneous blood pressure curve was transferred to a recording computer where beat-to-beat mean arterial pressure (MAP) was calculated by integration over each RR-interval.

The automatic self-calibration of the Nexfin disturbed minor parts of the recordings. After the experiments, the MAP values measured during these calibration periods (3-5 heart beats) were replaced by values obtained by interpolation from the MAP values on the beats immediately before and after calibration. This was done with a custom-made computer program coded in MATLAB (MathWorks inc, Natick, MD, USA).

In order to calculate an average time course of the cardiovascular responses to the brachial block, the median value from all subjects was calculated in each separate time bin of 0.1 second for the cardiovascular variables.

9.6.4 Other outcomes

For the evaluation of postoperative sedation, nausea, vomiting and itching we used a five rating categorical scale (non, little, medium, much, very much). Categorical scales were also used to evaluate amount of sleep, sleep quality and functional capacity. Amount of sleep was categorised as less than usual, usual or more than usual. Sleep quality was categorised as OK, pain/uneasy and nightmares. Functional ability was categorised as in bed, able to sit up, and up and going.
Dichotomous scales (yes-no) were used for different measures for work ability and use of analgesics.

9.7 Statistical analyses

To avoid errors in our data material, two investigators checked all access case registration forms and excel files for accuracy before transferring them to SPSS.

In our datasets, there are both continuous and categorical variables. The VNRS scores are not truly continuous, but a discrete variable given numerical values with many levels. It is therefore treated as continuous in our analysis. We analysed our continuous data using both parametric and non-parametric methods. P-values smaller than 0.05 were considered statistically significant in all studies.

The data was checked for normal distribution and independent samples t test were used for two group comparison for the parametric data in study 1. This includes the primary outcome (time to first rescue analgesic) and some of the secondary outcomes (duration of surgery and general anaesthesia, dosis of ropivacaine, propofol, remifentanil and oxycodone). This data was presented as median (SD).

Mann-Whitney U test was used for two group comparison of the non-parametric data in study 1 and 2. Because of the relatively small sample size we decided to treat all our postoperative pain scores as non-parametric. In study 2, we used non-parametric methods on all other outcomes as well. As a result of the small sample size in study 3, Wilcoxon rank-sum test for paired samples was used for all continuous data. We presented the median values with interquartile range and range.

For categorical data, Pearson chi-squared test was used in all our studies, and Fisher exact test when any of the expected scores was under 5. Pearson Chi-squared test with Yates’s continuity correction was used to evaluate block success in study 3.
10. Results

10.1 Study 1

The aim of this double-blind study was to evaluate whether preventive analgesia with a pre-operative ultrasound-guided infraclavicular brachial plexus block results in better postoperative analgesia compared with an identical postoperative block. We hypothesised that time to first rescue analgesia would be longer in patients receiving block before surgery compared with after.

Time to first rescue analgesic after emergence from general anaesthesia was significantly longer in the pre-operative block group (Table 2). Postoperative pain was stronger and more patients needed rescue analgesia during the first four hours after surgery in the postoperative block group (Table 2). More patients in the postoperative group still used analgesics at day seven (Table 2), but there were no significant differences in opioid consumption. Pain at block resolution was described as very strong in 27 (63%) of the patients (groups pooled). After 6 months, 26 patients (76%) had episodes of mild pain, with no significant differences in pain scores between the two groups.

We conclude that a pre-operative ultrasound-guided infraclavicular block provides longer and better analgesia in the acute postoperative period when compared with an identical postoperative block in patients undergoing volar plate hand surgery.
### Table 2: Major outcomes in study 1. Patients receiving pre-operative compared with postoperative brachial plexus blocks. Verbal Numeric Rating scale (VNRS) 0-10. Values are median (IQR[range]), number (proportion) or mean (SD).

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Pre-operative group</th>
<th>Postoperative group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain at rest</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>24/26</td>
<td>2.0(0.0-3.8[0.0-8.0])</td>
<td>1.5(1.0-2.3[0.0-6.0])</td>
<td>0.606</td>
</tr>
<tr>
<td>30 min</td>
<td>25/26</td>
<td>0.0(0.0-0.0[0.0-8.0])</td>
<td>0.0(0.0-6.0[0.0-8.0])</td>
<td>0.001</td>
</tr>
<tr>
<td>1 hour</td>
<td>24/26</td>
<td>0.0 (0.0-0.0[0.0-6.0])</td>
<td>0.0(0.0-4.0[0.0-7.0])</td>
<td>0.003</td>
</tr>
<tr>
<td>2 hours</td>
<td>25/25</td>
<td>0.0 (0.0-0.0[0.0-4.0])</td>
<td>0.0 (0.0-2.0[0.0-3.0])</td>
<td>0.030</td>
</tr>
<tr>
<td>4 hours</td>
<td>25/25</td>
<td>0.0 (0.0-0.0[0.0-2.0])</td>
<td>0.0 (0.0-1.0[0.0-3.0])</td>
<td>0.031</td>
</tr>
<tr>
<td>Number (%) with VNRS above 3 first 4 hours</td>
<td>25/26</td>
<td>1(4%)</td>
<td>10 (39%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Number (%) with need of analgesics first 4 hours</td>
<td>24/25</td>
<td>2 (8%)</td>
<td>11 (44%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Mean (SD) time (min) to first opioid rescue</td>
<td>22/24</td>
<td>544 (217)</td>
<td>343 (216)</td>
<td>0.015</td>
</tr>
<tr>
<td><strong>Worst pain score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-24 hours</td>
<td>25/26</td>
<td>8.0 (5.0-9.0[0.0-10.0])</td>
<td>8.0 (6.3-9.0[0.0-10.0])</td>
<td>0.787</td>
</tr>
<tr>
<td>Day 1-7</td>
<td>23/24</td>
<td>5.0 (3.0-7.0[0.0-10.0])</td>
<td>5.0 (3.0-6.8 [0.0-9.0])</td>
<td>0.592</td>
</tr>
<tr>
<td>Number (%) with need of analgesics after 7 days</td>
<td>22/24</td>
<td>8 (36%)</td>
<td>16 (67%)</td>
<td>0.040</td>
</tr>
<tr>
<td><strong>6 months:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (%) of patients with pain</td>
<td>17/17</td>
<td>15 (88%)</td>
<td>11 (65%)</td>
<td>0.225</td>
</tr>
<tr>
<td>Average pain last week</td>
<td>15/12</td>
<td>2.0 (1.0-3.0[0.0-5.0])</td>
<td>1.0(0.0-1.8[0.0-4.0])</td>
<td>0.053</td>
</tr>
<tr>
<td>Worst pain last week</td>
<td>15/12</td>
<td>4.0(2.0-5.0[0.0-6.0])</td>
<td>3.0 (1.3-4.8[0.0-5.0])</td>
<td>0.457</td>
</tr>
</tbody>
</table>

### 10.2 Study 2

The aim of this double-blind study was to evaluate the effect of a single intravenous dose of dexamethasone on acute and chronic pain. The primary endpoint was highest pain score first 24 hours after surgery.

The worst pain score during the first 24 hours after surgery was significantly lower in the patients receiving intravenous dexamethasone compared with the control group (Table 3). Also average pain score and rescue opioid consumption (5(0-10[0-35]) mg versus 10(5-15[0-50]) mg (p=0.037)) were lower in the dexamethasone group from 8-24 hours after surgery. Brachial plexus block duration was 69% longer in the
dexamethasone group (Table 3). Two patients (9%) in the dexamethasone group compared with 12 (50%) in the placebo group experienced worst pain score of 8-10 during the first 36 hours (p=0.002). After three and seven days there were no significant differences in pain scores or opioid consumption. At six months, 27 patients (57%) reported episodes of pain at the site of surgery, with lower average pain score in the dexamethasone group, but no significant differences between the two groups in worst pain score in the last week (Table 3). At one year, 10 patients (42%) in the placebo group reported long-lasting pain, (i.e. VNRS pain score above 0, last week at one year) compared to 2 (10%) in the dexamethasone group (p=0.015). Among them, five patients (42%) had experienced pain score above 3 in the last week.

We conclude that intravenous dexamethasone improves postoperative analgesia when added to etoricoxib, and may also be hypothesised to improve clinical outcome after 6 and 12 months.
**Table 3:** Major outcomes in study 2. Patients receiving dexamethasone compared with placebo during hand surgery. Verbal Numeric Rating scale (VNRS) 0-10. Values are median (IQR[range]) or number (proportion).

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Dexamethasone group</th>
<th>Placebo group</th>
<th>P -value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average pain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-24 hours</td>
<td>22/24</td>
<td>2[1-4][0-5])</td>
<td>5[3-6][0-8])</td>
<td>0.001</td>
</tr>
<tr>
<td>24-36 hours</td>
<td>20/23</td>
<td>3[1-4][0-5])</td>
<td>1[0-2][0-4])</td>
<td>0.035</td>
</tr>
<tr>
<td>36-72 hours</td>
<td>23/24</td>
<td>2[1-2][0-4])</td>
<td>1[1-2][0-4])</td>
<td>0.292</td>
</tr>
<tr>
<td>day 3-7</td>
<td>23/23</td>
<td>1[1-2][0-5])</td>
<td>1[1-2][0-5])</td>
<td>0.706</td>
</tr>
<tr>
<td><strong>Worst pain score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-24 hours</td>
<td>23/24</td>
<td>4[2-6][0-7])</td>
<td>8[5-8][2-10])</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-36 hours</td>
<td>19/23</td>
<td>4[2-6][0-9])</td>
<td>3[1-4][0-7])</td>
<td>0.176</td>
</tr>
<tr>
<td>8-36 hours</td>
<td>23/24</td>
<td>5[3-7][0-9])</td>
<td>8[5-8][2-10])</td>
<td>0.005</td>
</tr>
<tr>
<td>36-72 hours</td>
<td>23/23</td>
<td>4[2-5][0-7])</td>
<td>2-5[0-7])</td>
<td>0.363</td>
</tr>
<tr>
<td>day 3-7</td>
<td>23/24</td>
<td>4[2-5][0-8])</td>
<td>3[2-4][0-7])</td>
<td>0.764</td>
</tr>
<tr>
<td>first week in total</td>
<td>23/24</td>
<td>6[4-7][0-9])</td>
<td>8[5-8][2-10])</td>
<td>0.024</td>
</tr>
<tr>
<td><strong>Duration of brachial plexus block (hours)</strong></td>
<td>23/24</td>
<td>21.5[19.1-23.4[12.9-</td>
<td>12.7[11.9-15.3[7.4-</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Time from block resolution to first pain less than VNRS 4 (hours)</strong></td>
<td>23/20</td>
<td>0.9[0-3.3[-0.8-6.8])</td>
<td>6.6[1.3-11.0[-8.0-</td>
<td>0.001</td>
</tr>
<tr>
<td>6 months:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (% of patients with pain at rest</td>
<td>23/24</td>
<td>1[4%]</td>
<td>4[17%]</td>
<td>0.348</td>
</tr>
<tr>
<td>Pain score above 0 last week</td>
<td>23/24</td>
<td>11[48%]</td>
<td>16[67%]</td>
<td>0.192</td>
</tr>
<tr>
<td>Average pain last week</td>
<td>23/24</td>
<td>0[0-0[0-1])</td>
<td>0[0-1[0-3])</td>
<td>0.036</td>
</tr>
<tr>
<td>Worst pain last week</td>
<td>23/24</td>
<td>2[0-3[0-7])</td>
<td>3[0-5[0-7])</td>
<td>0.218</td>
</tr>
<tr>
<td>12 months:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (% of patients with pain at rest</td>
<td>21/24</td>
<td>0[0%]</td>
<td>5[21%]</td>
<td>0.051</td>
</tr>
<tr>
<td>Pain score above 0 last week</td>
<td>21/24</td>
<td>2[10%]</td>
<td>10[42%]</td>
<td>0.015</td>
</tr>
<tr>
<td>Average pain last week</td>
<td>21/24</td>
<td>0[0-0[0-1])</td>
<td>0[0-1[0-4])</td>
<td>0.056</td>
</tr>
<tr>
<td>Worst pain last week</td>
<td>21/24</td>
<td>0[0-0[0-4])</td>
<td>0[0-2[0-7])</td>
<td>0.018</td>
</tr>
</tbody>
</table>

* Time to first time after the block the patient succeeded in holding an object and lifting it to the facial area with the blocked extremity
** For those who never had VNRS 4, length of block

**10.3 Study 1 and 2 combined**

There were small differences in the inclusion criteria and the postoperative pain regimes in study 1 and 2, thus the results of the two studies cannot be directly compared. However, a comparison may be done as a hypothesis for future studies.
Comparing the two studies, preventive anti-inflammatory prophylaxis with etoricoxib may reduce postoperative opioid consumption (Table 4). The addition of dexamethasone does not seem to reduce opioid consumption further, but seems to reduce postoperative pain scores (Table 4). Dexamethasone may also reduce pain after 6 months.

Table 4: Comparison of the results in study 1 and 2 with regard to the effect of no anti-inflammatory prophylaxis, single anti-inflammatory prophylaxis (etoricoxib) and double anti-inflammatory prophylaxis (etoricoxib and dexamethasone).

<table>
<thead>
<tr>
<th></th>
<th>Paracetamol (Study 1)</th>
<th>Paracetamol and etoricoxib (Study 2)</th>
<th>Paracetamol, etoricoxib and dexamethasone (Study 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain at rest (VNRS)</td>
<td>Median (range)</td>
<td>Mean</td>
<td>Median (range)</td>
</tr>
<tr>
<td>8 hours</td>
<td>0(0-5)</td>
<td>0.3</td>
<td>0(0-9)</td>
</tr>
<tr>
<td>24 hours</td>
<td>3(0-6)</td>
<td>3.1</td>
<td>2(0-6)</td>
</tr>
<tr>
<td>1 week</td>
<td>1(0-5)</td>
<td>1.3</td>
<td>1(0-4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Worst pain score (VNRS)</th>
<th>Median (range)</th>
<th>Mean (range)</th>
<th>Median (range)</th>
<th>Mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-24 hours</td>
<td>8(0-10)</td>
<td>6.6</td>
<td>7.5(2-10)</td>
<td>6.7</td>
</tr>
<tr>
<td>24 hours-7 days</td>
<td>5.5(0-10)</td>
<td>5.4</td>
<td>3.5(0-7)</td>
<td>3.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rescue oxycodone (mg)</th>
<th>Median (range)</th>
<th>Mean (range)</th>
<th>Median (range)</th>
<th>Mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First 24 hours</td>
<td>20(0-82)</td>
<td>21.9</td>
<td>10(0-50)</td>
<td>12.5</td>
</tr>
<tr>
<td>First week</td>
<td>25(0-220)</td>
<td>31.6</td>
<td>15(0-50)</td>
<td>17.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>At 6 months (VNRS)</th>
<th>Median (range)</th>
<th>Mean (range)</th>
<th>Median (range)</th>
<th>Mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worst pain last week</td>
<td>3(0-5)</td>
<td>2.9</td>
<td>3(0-7)</td>
<td>2.8</td>
</tr>
<tr>
<td>Average pain last week</td>
<td>0(0-4)</td>
<td>1.1</td>
<td>0(0-3)</td>
<td>0.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Do you ever feel pain or a different feeling in the operated arm? (% yes)</th>
<th>Median (range)</th>
<th>Mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol (Study 1)</td>
<td>75,8%</td>
<td>75%</td>
</tr>
<tr>
<td>Paracetamol and etoricoxib (Study 2)</td>
<td></td>
<td>78,3%</td>
</tr>
</tbody>
</table>

10.4 Study 3

In this study we evaluated the effect of adrenaline when added to lidocaine in infraclavicular brachial plexus blocks on human skin microcirculation (nutritive and subpapillary blood flow) and systemic cardiovascular variables.
Subpapillary blood flow, measured by laser Doppler, increased substantially 30 minutes after brachial plexus blocks, both with and without adrenaline adjuvant (Table 5). There was no statistically significant difference in blood flow between blocks with and without adrenaline in the blocked extremity.

Nutritive blood flow (i.e. functional capillary density, capillaries/mm², measured at the dorsal side of the hand) decreased in the blocked extremity when adrenaline was used as adjuvant, whereas no significant change occurred without adrenaline (Table 5).

Finger skin temperature increased by median 44% (data pooled) with no significant difference between the groups. No significant changes were found in the systemic cardiovascular variables with or without adrenaline (Table 5).

We conclude that lidocaine infraclavicular brachial plexus blocks cause an increase in skin subpapillary blood flow. The addition of adrenaline results in denser and more long-lasting blocks, but decreases the nutritive blood flow to the skin.

Table 5: Major outcomes in study 3. Comparison of measurements before and 30 minutes after infraclavicular plexus block in the blocked extremity. Lidocaine with and without adrenaline as an additive was used for the blocks. Values are median (IQR [range]).

<table>
<thead>
<tr>
<th>Adrenaline</th>
<th>N</th>
<th>Before block</th>
<th>30 min after block</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood flow (AU)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>8</td>
<td>8.5(4.4-13.5[2.9-28.2])</td>
<td>162.7(111.0-197.8[9.5-206.7])</td>
<td>0.017</td>
</tr>
<tr>
<td>no</td>
<td>8</td>
<td>6.9(5.3-28.5[1.8-42.1])</td>
<td>133.7(16.5-216.7[1.0-445.0])</td>
<td>0.036</td>
</tr>
<tr>
<td>FCD (Capillaries/mm²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>10</td>
<td>45(36-52[26-59])</td>
<td>38(29-41[26-42])</td>
<td>0.028</td>
</tr>
<tr>
<td>no</td>
<td>11</td>
<td>39(35-49[29-51])</td>
<td>40(33-44[30-56])</td>
<td>0.594</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>11</td>
<td>22.1(21.5-22.9[20.5-25.4])</td>
<td>34.1(33.6-34.6[25.9-35.1])</td>
<td>0.003</td>
</tr>
<tr>
<td>no</td>
<td>11</td>
<td>22.4(21.5-25.7[20.8-29.6])</td>
<td>33.9(31.4-34.5[20.8-34.8])</td>
<td>0.004</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>8</td>
<td>56.2(48.4-64.7[43.5-77.1])</td>
<td>62.6(55.6-70.9[51.5-72.6])</td>
<td>0.263</td>
</tr>
<tr>
<td>no</td>
<td>8</td>
<td>52.9(49.9-59.7[46.8-79.0])</td>
<td>63.5(54.1-68.7[50.7-70.0])</td>
<td>0.208</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>8</td>
<td>95.8(91.8-111.8[91.3-122.0])</td>
<td>101.6(88.0-114.6[70.3-125.2])</td>
<td>0.779</td>
</tr>
<tr>
<td>no</td>
<td>8</td>
<td>90.1(76.7-96.6[71.4-102.7])</td>
<td>90.7(89.8-101.0[72.4-124.2])</td>
<td>0.161</td>
</tr>
</tbody>
</table>
11. Ethical considerations and approvals

The studies were reviewed and approved by the Regional Committee for Medical Research Ethics of South Eastern Norway with the permission numbers 2011/476a (study 1), 2016/500 (Study 2) and 2012/2189b (study 3). Study 2 and study 3 were also approved by the Norwegian Medicines Agency, and registered in the EU Clinical Trials Register, EudraCT number 2016-000684-16 (study 2) and 2012-005651-17 (study 3). Study 1 and 2 were reported to the international Clinical Trials registry of planned studies, identifier number NCT01740141 (study 1) and NCT03011905 (study 2). All studies were conducted in adherence to guidelines for Good Clinical Practice and all manuscripts adhere to the CONSORT guidelines.

All participants in the three studies signed a written informed consent prior to inclusion after thorough oral and written information. They were also informed about the possibility to withdraw from participation at any time before, during or after the study. The participants in all the studies received an ultrasound guided infraclavicular brachial plexus block (175). All participants were healthy (ASA 1-2) with no increased risk for nerve damage because of cardiovascular disease, diabetes or pre-existing neurological disorders. The risk for serious complications after peripheral nerve blocks is considered to be low (34).

Study 1 and 2 were clinical studies on patients. The patients received no benefits from taking part in the studies apart from the frequent phone calls (which could be considered both a benefit or a hassle) and the possibility to contact a study doctor whenever needed.

**Study 1:**

The patients received brachial plexus block during general anaesthesia. This might have put them at increased risk for nerve injury because they would not be able to feel pain in case of the needle touching the nerve cords. To avoid nerve damage, we therefore used triple monitoring with ultrasound, injection pressure monitors (to keep injection pressure under 15 psi) and electrical nerve stimulation (no motor response on
a current setting of 0.5 mA, 0.1 ms impulse duration, and a frequency of 2 Hz, if motor response was elicited with 0.5 mA or below, the needle was withdrawn until the response disappeared) (176).

**Study 2:**

Brachial plexus block is the standard anaesthetic method for all patients scheduled for volar plate surgery in our hospital, thus the patients in the study received standard anaesthesia for the surgery. Half of the patients in the study received dexamethasone. Dexamethasone is a well-known medication licenced for intravenous use. Although not licenced to treat pain in Norway, it is frequently used to reduce pain after for example abdominal, gynaecological and spine surgery, and considered to be safe in the doses used in our study (61, 62). The patients randomised to the dexamethasone group could possibly receive better pain treatment than standard treatment in our department, as we did not use dexamethasone for volar plate surgery before or during the study.

**Study 3:**

All medication used in this study were registered in Norway and used within approved indication. Even though brachial plexus block is considered safe and the risk of serious complications are low, the use of brachial plexus block in volunteers needs an ethnical consideration. A possible damage to a nerve in a healthy volunteer would not be acceptable. We used healthy volunteers to get a homogenous group with as little risk for adverse events as possible. This enabled us to diminish confounders caused by factors like pre-existing conditions influencing on human microcirculation, and tissue damage as well as aberrant anatomy in patients. It also made it possible to standardise the conditions during the experimental runs to avoid disturbance to our measurements.

We used the crossover design to limit the amount of volunteers needed. To avoid nerve damage, Axel Sauter, who is extremely experienced, performed all blocks in the healthy volunteers. The three cords were localised using ultrasound, and the needle was approached in safe distance from the cords. The volunteers did not get any sedation, to be able to report to us if they felt any discomfort or signs of intraneural placement of the needle during the procedure.
The volunteers got a gift card for entering the study. The value of the gift card was supposed to be large enough to compensate for all the hours used during the experimental runs as well as the time they had an anaesthetised arm after the experiments. Still, we did not want the compensation to be too large, not to make the compensation the main reason for attending the experiments.

All volunteers got thorough information about how to take care of the blocked extremity after they left the study site to avoid any damage to the arm. They were asked to contact us if they had any questions or worries after the experiments. In addition, we contacted all participants on the day after the experiments to make sure the blocks had worn off and they felt their normal state.
12. Methodological considerations

When conducting a study, it is important to plan how to evaluate the different measures or methods in advance. The validity, reliability and utility have to be considered (82). The validity of a method refers to the appropriateness, meaningfulness and usefulness of a measure for a specific purpose (i.e. if the method measures what is supposed to be measured). The reliability of a method refers to the extent to which the score from a test is free from measurement errors, in other words how precise the data is. The utility of a measure is a more practical issue. Although it would be interesting, it is impossible to design a study measuring pain in all possible activities a person could engage in, and few patients would participate in a study where they would have to report pain every hour for several weeks (82).

There will always be errors in measurements (i.e. deviations of the true values), no matter how careful one is. It is common to distinguish between random errors and systematic errors. Random errors are unknown and unpredictable, and cannot be eliminated from an experiment. By increasing the sample size, the effect of random errors can be minimised. Systematic errors influence the accuracy of the data and include selection bias, information bias and confounding. They can often be avoided.

When measuring physical data it is important to consider several sources of measurement errors. In our three studies, we may have biological variation between individuals, day-to-day variation within an individual, observer variation, laboratory variation, instrument variation, and measurement uncertainty. We tried to adjust our methods to limit these variations. All investigators were well trained in the methods used. The measurements were recorded under controlled conditions. We used multiple measures for some of our endpoints. I will discuss these aspects further in the following sections.
12.1 Study design

All our studies were randomised and double-blinded. The randomisation ensures a fair starting point while the double-blinding prevents observers to be biased during the trial period.

The randomisation is important in order to get two similar and comparable groups with limited systematic errors. It minimises allocation bias (i.e. differences in how the participants are allocated to treatment) and balances the groups with respect to both known and unknown confounding factors (137). A good randomisation and an adequate sample size limits confounders, resulting in reduced need to adjust for them in the analysis. Significant differences between groups regarding possible confounders in a randomised study are due to chance or flawed randomisation.

Despite randomisation, we detected a few variations in our baseline characteristics in the two clinical studies. There may also be undetected confounders in our materials. A larger sample size could possibly have reduced variations between the study groups in our materials. However, we do not believe the baseline variations have influenced our major conclusions. This is further discussed in the “main strengths and limitations” section under the relevant study.

A double-blinded design removes subjective expectations regarding the effect (138). In a clinical study, the investigators may wish to show a treatment effect. The participants may be more likely to report pain if they know they are in the placebo group. We used double-blinded design in all our studies to minimise detection bias.

In study 3, we used a cross-over design to allow for a smaller sample size. The cross-over design may reduce the variance in the data compared to analysing two separate groups. The variation within an individual is usually smaller than between individuals (parallel groups).

All our studies were mainly quantitative, but studies 1 and 2 also have a few qualitative aspects. To better explore the patients’ experiences during the operation and the postoperative period, as well as how the fractures actually affected their
everyday life, both in short-term and long-term, a qualitative design might have been an interesting addition to our quantitative studies. However, as the main purpose of this thesis was to find out if specific modifications of brachial plexus block had clear-cut objective effects, we concluded that a quantitative approach would be most appropriate.

12.2 Study populations

Study 1 and 2 were conducted on patients scheduled for volar plate surgery after distal radius fractures. This surgery is relatively standardised and infraclavicular blocks are frequently used for this procedure. The patient group is large and quite homogenous. Both strong pain in the postoperative period and long-lasting pain after the injury or operation are common after this type of surgery. Thus, we thought it was highly relevant to evaluate measures to reduce pain in this patient group.

In study 1 and 2, we aimed for wide inclusion criteria to cover the relevant population. At the same time, we wanted to limit the possibility for complications from the interventions among our study patients. Therefore, patients with increased risk of complications were excluded. Overall, we think the included population reflects the relevant target population and thus ensures a high external validity of the studies.

In our study on microcirculation, we decided to use volunteers instead of patients because several factors may influence on the human microcirculation including the pathological condition for which the patients are to have surgery. Several factors are mentioned under “Evaluation of human skin microcirculation”. These factors are easier to control in an interventional setting in healthy volunteers than in patients before and during an operation. The equipment used to measure microcirculation in our study might also have been in conflict with the surgical field.

A challenge with our selection of relatively young, healthy male volunteers is that they may not be representable for the patient groups where brachial plexus blocks are used to improve microcirculation. These patients will often have conditions that impact their microcirculation. Thus, the external validity of the study is questionable.
12.3 Outcome measures

12.3.1 Block duration

To estimate block duration, we had to find a surrogate for frequent sensory and motor testing of the nerve blocks, since most of our participants were at home at block resolution. We used different criteria in the three different studies.

In study 1, we used time to first analgesic to estimate the duration of sensory block. A challenge with this definition may be if the patients do not need analgesics or try to avoid analgesics after the operation. However, as all patients in this study experienced significant pain and need for extra analgesia after the operation, we consider this definition to represent a reliable clinical surrogate of block duration.

This definition was not used in study 2 and 3 because several patients in study 2 did not experience pain requiring rescue analgesics, and the volunteers in study 3 did not use analgesics at all. Instead, they were asked to report the first time after the block when they were able to perform a simple test, to hold a cup (or another object) and lift it to the mouth with the blocked arm.

Hence, in study 2, we used the duration of motor blockade as a surrogate for the endpoint of interest, nociceptive blockade. It could be argued that our test of motor blockade will result in an overestimation of block duration as patients may hesitate to try this manoeuvre shortly after block resolution. However, the patients were instructed to check this frequently when they started to feel the nerve block wear off, and if pain should be the cause of delayed registration of block resolution, this should be more evident in the control group. Also in this study, occurrence and start of any pain may be considered as an adjunctive, surrogate measure of block duration, applicable in the majority of cases.

In study 3 where we used a short acting local anaesthetic in the blocks, we could have asked the volunteers to stay in the hospital until the block wore off and performed frequent testing to get a better estimate of block duration. Because block duration was
not an important endpoint in this study, we chose not to spend the volunteers’ time and resources on this.

12.3.2 Pain

General considerations

The main aim of study 1 and 2 was to evaluate pain. Unfortunately, a complete objective method for measuring pain does not exist, as pain is a subjective experience based on nociception in the postoperative setting. The subjective experience of pain includes several different aspects: intensity, temporal characteristics (i.e. variability, frequency and duration), location, quality, affect (i.e. general unpleasantness, fear, anger, sadness, frustration, hopelessness), impact (i.e. impact on life, emotional impact), and pain interference (i.e. how the pain interferes with day-to-day functioning). When evaluating pain in clinical studies, it is important to decide which aspects to focus on, and to have an opinion on factors that may influence the different aspects. It is essential to balance the investigator’s need for a thorough assessment against the need for minimal assessment burden for the patient (82). It is also important to be aware of factors that may influence the patient’s response when asked about pain. This includes the setting (i.e. if the patient is in hospital, at home, alone or among other people), the person administering the measure, the patients experiences and feelings (i.e. upset or fatigued), cultural factors, the patients pain expectations, and motivational factors (i.e. to get more medication) (82).

Methods for evaluating pain

There are several methods for evaluating pain in clinical trials. A high number of different pain scales and pain questionnaires exist. I will discuss a few that could have been relevant in our studies.

Visual analogue scales (VAS), numerical rating scales (NRS) and categorical verbal rating scales are all pain scales used for evaluating pain intensity. They are considered equivalent, adequately valid and reliable to assess pain, and to be sensitive to detect treatment effects (139, 140). For both VAS and 0-10 NRS, score changes between 30-
35% appear to indicate a meaningful change in pain to patients across patient populations (82, 140).

Comparing the three, VAS has shown higher failure rates than NRS and categorical verbal rating scales (82). This may be because it is more abstract, it uses an instrument (i.e. a ruler, written paper etc.) and because increased age and opioid intake is associated with greater difficulty completing VAS measures (82, 140). Categorical verbal rating scales may have advantages for some patient groups. For example, children or patients with cognitive impairment may find it easier to differentiate between some categorical levels than the 11 levels of pain on a NRS scale (140).

NRS score 0-10 is the most commonly used scoring system in clinical studies to evaluate pain intensity. When used for verbal reporting of the patient, it is often called VNRS (Verbal Numeric Rating Scale). It has a high validity and reliability and is easy to understand for most healthy patients. It does not require any instruments or paperwork to perform, and it can be easily reported over the phone or on a questionnaire. The optimal clinical cut points between mild, moderate and severe pain are not clear-cut (141), but a common differentiation is to use the following: A NRS score of 1-3 indicates mild pain, a score of 4-6 implies moderate pain, whereas a score of 7-10 indicates severe pain (142). A 0-10 scale is considered precise enough to detect treatment effects and to show changes over time (82). Recall ratings of pain scores over a period of time may also be used. An earlier study has shown that recall ratings are valid indicators of pain which reflects average pain well (143). However, when recording pain scores it is important to differentiate on what the patient is questioned about: Pain just now or pain during a defined period? Worst pain or average pain? Pain at rest or pain during provocation or movement?

We have used a combination of different VNRS ratings, as the relevance may be for more than one modality such as resting pain which is important for sleep and rest, provocation pain which is important for mobilisation and physiotherapy.

The use of pain intensity as the only outcome measure has been questioned because treating pain strictly based on pain intensity scales (e.g. any value of 4 or higher)
might overestimate treatment requirements of the individual patients (144). This is especially important in light of the opioid crisis. However, patients in a study should not be subjected to undue pain and extra suffering just for the purpose of demonstrating pain differences. Then, the use of rescue analgesia may conceal differences, which would otherwise have been evident.

Thus, rescue opioid consumption and total opioid consumption are often used as an indirect measure of pain in clinical studies. The use of analgesic consumption for evaluating analgesic efficiency of an intervention is criticised for being an uncertain method with a very large variability found between patients (145). There is often a large spread in total doses of rescue opioids with a skewed distribution. However, as patient comfort has an ethical priority in clinical studies, differences between treatment groups in opioid rescue medication may be more sensitive than differences in measured pain.

The other aspects of pain (apart from pain intensity 0-10) may be more complicated to evaluate. There are a lot of different validated pain questionnaires available.

The McGill Pain Questionnaire (MPQ), a multiple item scale consisting of 78 words describing pain, is used to assess pain quality and pain affect (146). It also exists in a short form (SF-MPQ). The draw back with this questionnaire is that it does not allow for evaluating the effect of a treatment on specific pain qualities. The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) questionnaire can be used to distinguish neuropathic from nociceptive pain (147). The questionnaire requires a clinician to examine the patient and is often considered difficult to administer. There is also a Self-report LANSS including 5 pain quality items and a sensory test that can be self administered by the patient. Pain Quality Assessment Scale (PQAS) is a 21-item scoring system intended to be comprehensive enough to capture the majority of a patient’s pain experience, yet brief enough to minimise assessment burden (148). Brief Pain inventory Pain interference scale (BPI) is used to assess pain interference (i.e. the extent to which pain has interfered with general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life)(149).
Overall evaluation of our pain measurements

The major outcomes in both our pain studies were related to pain intensity. In addition, we wanted to do a brief evaluation on the temporal characteristics of the pain, pain interference and pain quality for long-lasting pain.

We chose to use VNRS (verbal numeric rating scale) 0-10 because it is easy to apply, associated with good compliance and can be administered through telephone interviews. Categorical scales, total time with moderate-severe pain, rescue- and total analgesic consumption were used to add to the total evaluation of pain.

A challenge with the VNRS scale is that a rating of for example 3 out of 10 will rarely be exactly the same in two different patients. The Mankoski pain scale (with numbers and corresponding descriptions of pain) seeks to ensure equal understanding of the numerical pain values of patients and investigators, and might have been an alternative, but more cumbersome option in our studies (150).

We could have used diary-based measures to get more information about pain impact and pain quality. We chose to use categorical scales because they require less effort from both the patients and the investigators, and diary-based methods may result in more missing data. The use of existing questionnaires, could have evaluated the different aspects of long lasting pain better and added interesting aspects to the studies. However, it might have made the study more complicated and time consuming for the participants, resulting in fewer patients agreeing to take part in or completing the studies.

In retrospect, we could have asked the important questions: Do you have bothersome pain? Are you satisfied with the postoperative pain treatment? These questions may be considered more important than the actual pain intensity on a 0-10 VNRS scale.

Another issue we should have considered is the fact that increased activity may be accompanied by increased pain. A number of our patients reported highest pain score in the last week during push-ups in the gym after 6 months and 1 year. The total pain
burden for these patients was probably low, even though they reported a high worst pain score.

The strengths about the way in which we assessed pain in our studies are the use of well-established pain scales for our main outcomes combined with multiple other pain and quality of life measures. This made it possible to cover several different aspects of pain and get a fairly good impression of the patients’ total situation without a too high assessment burden for the patients.

12.3.3 Microcirculation

General considerations

When evaluating skin microcirculation, it is important to consider factors that may have an impact on the microcirculation and the measurement methods. This includes the position of the subject, temperature, arterial pressure, physical and mental activity, stress, age, gender, menstrual cycle, feeding, medication, smoking, black tea, coffee, garlic, alcohol, inflammatory reactions, and different pathological changes (111, 115). During our experiments, we tried to eliminate as many as possible of these factors. We kept a constant room temperature of 21 degrees Celsius, played soothing music in the room during the experiments to try to make the volunteers as relaxed and comfortable as possible, and made sure the volunteers rested for at least 20 min before the measurements.

There are several ways to investigate skin microcirculation, but unfortunately there is not a perfect method available. The optimal method for evaluating skin microcirculation would be a non-invasive, safe, easy, exact, fast and reproducible method that does not affect skin blood flow. The output data should preferably be in an absolute variable with easy data analysis (preferably automatic) to simplify the interpretation of the data (151). New technologies and technical improvements of existing methods have given us more reliable measurement tools over the years. Several different non-invasive methods are used to evaluate the skin microcirculation of the upper extremity. Some of them provide indirect measures of the
microcirculation (i.e. assess tissue oxygenation as a surrogate for microcirculatory function), other methods are direct measurements of the microcirculation (152).

**Methods for evaluating skin microcirculation**

Available methods include laser Doppler flowmetry, Doppler ultrasonography with or without intravenous contrast, different capillary microscopy techniques (i.e. traditional capillaroscopy, fluorescence capillaroscopy, videocapillaroscopy and orthogonal polarisation spectral imaging), transcutaneous oximetry, temperature measurements, thermography, photoplethysmography, and laser speckle contrast imaging.

We chose to use a combination of laser Doppler measurements, capillary video microscopy and temperature measurements because we had experience with the methods as well as equipment and local expertise available.

Laser Doppler fluxmetry has been available since the 1970s and is frequently used to evaluate microcirculation (116). It determines dynamic changes in skin microcirculation and enables a real-time, sensitive, continuous, reproducible, non-invasive and easy to apply assessment of blood flow, uninfluenced by the underlying blood flow in skeletal muscles (115, 153). It is a semi quantitative assessment of microvascular blood cell flow (flux) expressed in arbitrary units (AU). During normal conditions, about 85% of the laser Doppler signals originates from the deeper layers (subpapillary blood flow), whereas about 15% originates from the superficial layers (nutritive blood flow) (114). In pathological conditions with reduced capillary density, even more than 85% of the laser Doppler signal may originate from the deeper part of microcirculation (114). Disadvantages of the method includes its sensitivity to motion artefacts and unstable test conditions, the way the anatomical positioning of the probe influences the laser Doppler flux signal, and the lack of absolute perfusion values measured (115, 151). Another downside is the large amount of raw data to be processed (151).

Capillary video microscopy provides direct visualisation of the microcirculation and is a reliable method used to assess the nutritive circulation of the skin (151, 154). Compared with traditional capillary microscopy, capillary video microscopy provides
better magnifying power, and the possibility of storing pictures and off-line analysis (110). Disadvantages with this method is its sensitivity to motion (results in movement artefacts) and pressure (may disturb blood flow), the operator dependent output, and the time consuming off-line analysis (151). A real time automatic digital image analysis would probably be better. An entirely automated system for analysing microcirculation videos to reduce human interaction and computation time is developed, but not yet commonly used (133).

Temperature measurement provides an indirect measure of tissue perfusion. The skin temperature reflects the status of the underlying circulation, and changes in temperature reflect changes in the underlying thermoregulatory microcirculation.

There are other methods we also considered using which could have added interesting information to our experiments. Doppler ultrasonography is a promising and highly available non-invasive method (most ultrasound machines have ultrasound Doppler functions) (111). A major disadvantage with the method is variability from one examiner to another, especially among beginners. As we did not have experience in using the method on evaluating microcirculation, we chose not to use it. We also highly considered using the simple, non-invasive and indirect method of transcutaneous oxygen measurement. The method provides information on the body’s ability to deliver oxygen to the tissues through assessment of the amount of oxygen that diffuses from the capillaries through the epidermis to the electrode (110). It does not require expertise, is not complicated and almost free for examiner-dependent errors. Unfortunately, we had no equipment available and a budget not allowing us to procure this equipment.

**Overall evaluation of our microcirculatory measurements**

A major strength about the way we assessed microcirculation in our study is the combination of laser Doppler flowmetry, capillary microscopy and temperature measurements. This made it possible to examine both the nutritive and the deeper subpapillary microcirculation, which differ in their importance on perfusion on tissue
cells. The use of both direct and indirect measurements is also an advantage with our combination of methods.

We used both laser Doppler and capillary microscopy, which are both sensitive to motion (results in motion artefacts). Therefore, we cannot exclude motion artefacts in our data, even though our volunteers were relaxed in the supine position. Disturbed vessel blood flow might also have affected our capillary microscopy measurements because the method is sensitive to pressure. To get as reliable results as possible, the operator used a gentle touch with the microscope and recorded 5 video sequences for each examination.

Due to limited precision of the instruments and a small sample size in study 3, there may be random errors in our data. We may also have some systematic errors due to insufficient calibration of equipment (although all equipment was calibrated) and environmental factors during the experiments. Because we used multiple analysing methods and analysed differences (due to the paired measurements), this should not be a major source of errors. In addition, a few volunteers were not included in the some of the analysis in study 3 due to technical errors or functional failures with the equipment during the recordings. This might have resulted in loss of power in the study.

12.3.4 Non-invasive haemodynamic measurements

The volume clamp method used in this study is a fairly reliable method based on photoplethysmographic technology (155, 156). The method may overestimate brachial pulse pressure in young healthy subjects as our volunteers, and is contraindicated in patients with severe finger hypoperfusion (157). As we looked at changes in haemodynamics, small inaccuracies in the absolute values should not represent a problem.
12.4 Statistical analysis

12.4.1 General considerations

We present p-values for most of our comparisons in addition to the standard deviation, the interquartile range and range, or the number and proportion. The p-value is the probability of the observed result or a more extreme result to occur assuming that the 0-hypothesis is true. P-values and confidence intervals are different ways of presenting the same information and are seen as measures of how trustworthy the claimed effect of a study-measure is (158). The p-value is a continuous measure, the smaller the p-value is, the more evidence we have against the 0-hypothesis (158). A significance level of 0.05 (or 0.01) is often chosen as a cut off level for rejecting the 0-hypothesis.

The use of hypothesis testing and p-values have been widely criticised the last few years due to misuse and misinterpretation (159-161).

The interpretation of a p-value depends on the analysing process. A statistically significant result does not always imply a clinically significant result. It is possible to obtain small p-values for unimportant differences and large p-values for large differences depending on the sample size and variance in the material. The difference between a “statistically significant” p-value of 0.049 and a “non-significant” p-value of 0.051 is minor. Hence, it is important to report the observed effect size in addition to p-value (158). Some authors suggest to interpret p-values as continuous indices against the 0-hypothesis, or to report the probability for no real effect in addition to the p-value (160, 162).

12.4.2 Analysis of continuous data

A continuous variable is a measurable scale variable. It is numeric and can take any value between two numbers. The intervals between the values are equally spaced.

Standard deviation is a measure of reliability. By indicating the spread for continuous data, it estimates the amount of variability in the population (163). Standard error is a measure of the amount of variability in the sample mean, depending on both the
The confidence interval is a range of plausible values for the population mean, given the sample mean and its standard error. A 95% confidence interval can be estimated as 1.96 x the standard error on either side of the mean (163). The interquartile range indicates the spread of the middle 50% of the distribution. The range is the difference between the largest and smallest values in the sample.

**Parametric methods**

The two-sample t-test is one of the most frequently applied tests in statistics used to compare mean outcomes of continuous data in two separate treatment groups (164). It is based on the assumptions that all observations are independent, the data is normally distributed, and variance or standard deviations are equal in the groups. For matched samples, the paired t-test is widely used requiring the difference for each pair is normally distributed (164).

**Non-parametric methods**

When the data is not normally distributed, the standard parametric methods described above should normally not be used. Non-parametric methods are often used, although data transformation often can make the data suitable for parametric methods (log transformation for data skewed to the right, and square transformation for data skewed to the left). While parametric tests are based on the observed values, most non-parametric tests are based on rank-sums.

The Wilcoxon rank sum test and the Mann-Whitney U test are used for comparing two independent samples and are less sensitive to outliers than the two-sample t-test (165). The two tests give exactly the same results, but use slightly different test statistics. They are based on the assumptions of independence within and between groups, as well as the same distribution in both groups. The tests rank all values as if they were from the same group. The sums of the ranks are assumed approximately normally distributed, so normal approximation can be used for the tests.
The Sign test and the Wilcoxon signed rank test are commonly used for non-parametric paired measurements (two outcomes measured on the same individual under different treatment) (165, 166). Both tests assume independent observations. The Sign test has no assumptions about the distribution. The Wilcoxon signed rank test assumes symmetrical distributions, and also takes the strength of the difference into account, not just if they are positive or negative. It is slightly harder to get significant results using the Sign test, because of lesser assumptions.

12.4.3 Analysis of categorical data

A categorical variable is a countable variable with two or more categories. There is no intrinsic order on the levels of the categories. Examples are house colour or gender.

To analyse categorical data, the Pearson chi-squared test for independence may be used. It is valid provided all the expected values are at least 5 (167). When chi-squared tests are applied on larger tables (than the 2x2 table), the test is valid when less than 20% of the numbers are under 5, and none of the expected numbers are less than 1. The Pearson chi-square test is known to be more precise in studies with high numbers of expected counts. The Pearson chi-squared test with Yates’s continuity correction is sometimes used to prevent overestimation of statistical significance in small datasets (when any of the expected values are less than 5). The method is criticized because it tends to overcorrect and may result in type 2 errors (168). The use of Fisher exact test is recommended when the expected numbers are less than 5 or the sample size is small. This test is also sometimes criticized for being too conservative (168). To get less conservative results, the use of a mid-p adjustment method (by subtracting half of the point probability from the p-values) could be preferable (169, 170).

12.4.4 Sample size calculations

Conclusions in scientific studies depend on the sample size. It is important to estimate the sample size when planning a new study. The sample size has to be large enough to detect an effect. A large sample size will equally distribute all factors (confounders) in the treatment groups (except the treatment influencing the outcome). A small sample
size reduces the chance of getting significant results as well as the generalisability of the study.

When calculating sample sizes, it is essential to consider the minimum effect of interest, and make sure it is clinically relevant. It is also important to decide on a level of significance and power. With a significance level of 5%, there is a 5% chance of discovering difference when there really is no difference between the groups. The power of the study is the probability to find a difference between the groups if there really is a difference.

There are two main errors when testing hypothesis. Type 1 error is to conclude there is a difference, when in reality there is not (false positive, reject a true 0-hypothesis) (158). It correlates with the significance level. Type 2 error is not to discover a true effect (false negative, fail to reject a false 0-hypothesis). A higher power makes type 2 errors less likely.

The smaller the effect size is, the more data is needed to get a high power. Continuous measurements yield more power than categorical, and may reduce the required sample size. Use of paired measurements is another option to reduce the required sample size. The power and sample size have to be weighted against whether the participants entail a risk, how many participants it is possible to include in a given time, the cost of including participants, and the total workload with the study.

In our studies, we calculated our sample sizes based on the primary outcomes. In study 1 and 2 (in patients), we decided on a power of 0.95, to also make a negative result valid. The studies were not powered to find statistically significant differences after 6 and 12 months. To find differences in long-lasting pain, we would have needed a much higher number of patients. In study 3, we decided on a lower power of 0.80 (the usual minimum for a study with “good” power), because of the potential hassle and risk for the volunteers.
Due to the small sample sizes in our studies, we may have some random errors caused by random variation in the two study groups. Type 2 errors are a problem with small sample sizes.

### 12.4.5 Overall evaluation of the statistical methods

We had one main outcome in each study, and several secondary outcomes. A challenge with several outcomes is the fact that more tests increase the risk of finding chance associations \((171)\). With a \(p\)-value of 0.05, one in 20 tests will appear to be significant when it is really coincidental \((172)\). Corrections for multiple analyses with \(p\)-value adjustments reduce the risk for type 1 errors, but results in greatly reduced significance values and increase the chance for type 2 errors \((171, 172)\). The Bonferroni method is the classical method of adjusting \(p\)-values by dividing the \(p\)-value with the number of tests performed. This correction is criticised for being too conservative. We did not adjust for multiple testing in our studies, but each study had one predefined primary outcome with quite large effect size. Our secondary outcomes were also predefined and related to the primary aim of the studies. Because we evaluated several secondary outcomes, we may have statistical significance by chance on some of the variables with a low level of significance (i.e. 0.01-0.05 range). However, our major conclusions build on the primary outcomes and the combination of several predefined secondary outcomes. It is therefore unlikely that a potential type 2 error in some of the secondary outcomes has affected our main conclusions.

We could probably have used more parametric methods in our analysis, but chose to use mainly non-parametric tests. A concern is that this may have resulted in too conservative results and subsequently type 2 errors. The parametric t-test is robust for moderate departures from normality. Because of our randomised design with a similar number of observations in each group, most distributions not extremely skewed, and few extreme observations, the t-test could be considered valid \((173)\). It is difficult to balance the risk reporting a non-existent difference and the risk of not reporting a true difference. Weighting the two, we decided rather to be too conservative than too positive in our conclusions.
Relative risk and odds ratio may be used to compare outcome between two groups. We could have used odds ratio to compare the risk of several events in our studies, like presence of pain and back at work after 6 and 12 months. We used frequency distributions and Pearson chi squared/Fisher Exact tests because we think it presented the results satisfactorily and some readers might find them easier to comprehend.

Our pain scores were mainly treated as continuous variables, but for some analysis we categorized the VNRS scores before analysing them. This includes number of patients with pain scores less than 4 and number of patients experiencing worst pain scores 8-10 in the first 36 hours. The categorization of continuous variables is disputed and raises two important questions: how many categories do we want and where should we put the cut off between the categories. The categorization can lead to loss of information and may increase the risk of a false positive result (type 1 error). We used the categorization in addition to presenting the analysis of the continuous variables, with similar results. The categorization has therefore not changed the major conclusions of the papers, but rather served to simplify the interpretations of the results.

A few patients were not studied after being included in the studies. This decision was taken before unblinding due to reasons accounted for in the inclusion section in this thesis. Most questionable is probably the exclusion of the three patients due to antebrachii fractures in study 2. This can be considered a violation to the intention-to-treat principle which implies all patients should be analysed in their original group as if they have received the planned intervention and regardless of their adherence to the entry criteria (174). It may also violate the principles of randomisation. Another strategy is per-protocol analysis which implies analysis of only those patients who strictly adheres to the protocol and estimates the true efficacy of an intervention (174). A concern about per-protocol analysis is that they may cause selection biases because of the reasons for the exclusion of the patients. We chose to exclude the patients from the published data to present clean material with only volar plate surgery for distal radius fractures. The number of excluded patients in our material was low compared to the total number of patients. In addition, we performed control analysis on all major
outcomes with these patients included, with no major differences from the published results. We therefore consider a possible bias created by exclusion of patients not to be relevant. All other patients in the materials were analysed according to their original group, regardless of how they followed up the study, according to the intention-to-treat concept. This was to maintain comparability between the groups, to try to eliminate bias and to reflect clinical practise (174).

Overall, we think the statistical analyses used in our studies were adequate to answer our research questions satisfactorily. Our sample sizes in study 1 and 2 were estimated to detect differences in acute pain, but too small to achieve appropriate statistical power for long-lasting pain. Hence our findings should be corroborated with new studies. The latter also applies to the results from study 3 considering its exploratory nature. We could have defended using more parametric methods instead of non-parametric methods, and chi-squared tests instead of exact tests, but chose to be more conservative and therefore may have type 2 errors in our materials. We also could have corrected for multiple outcomes in our analysis in all studies, but chose to look at the effect sizes and build our major conclusions on the combination of several outcomes.
13. Discussion of results

Table 6: Summary of articles in this thesis

<table>
<thead>
<tr>
<th>Study 1</th>
<th>Study 2</th>
<th>Study 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aim</strong></td>
<td>To compare brachial plexus blocks performed before and after surgery with regard to acute and long-lasting postoperative pain after volar plate surgery.</td>
<td>To evaluate the effect of intravenous dexamethasone on brachial plexus block and acute and long-lasting postoperative pain after volar plate surgery.</td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td>52 patients scheduled for volar plate surgery were included in a randomised controlled clinical trial.</td>
<td>53 patients scheduled for volar plate surgery were included in a randomised controlled clinical trial.</td>
</tr>
<tr>
<td><strong>Main findings</strong></td>
<td>Optimal efficacy for management of acute postoperative pain is more likely to be obtained with pre-operative rather than postoperative nerve blockade.</td>
<td>Intravenous dexamethasone increases duration of brachial plexus blocks and improves postoperative analgesia when added to etoricoxib. It may also improve clinical outcome after 6 and 12 months.</td>
</tr>
<tr>
<td><strong>Main strengths</strong></td>
<td>The randomised double-blinded design. High success rates of blocks.</td>
<td>The randomised double-blinded design. Uniform patient population. High success rates of blocks. Low dropout range at 6 and 12 months.</td>
</tr>
<tr>
<td><strong>Main limitations</strong></td>
<td>We did not classify type of radius fracture or register if the patients had associated soft tissue injuries. High dropout range at 6 months. The blocks in the postoperative group might still have been developing at emergence of anaesthesia 20 min after blocks procedure.</td>
<td>The use of motor blockade to estimate block duration. Our sample size was determined to find differences in worst pain score first 24 hours after surgery, the sample size was too small to achieve appropriate statistical power for long-lasting pain.</td>
</tr>
</tbody>
</table>
13.1 General discussion

13.1.1 Study 1

The specific aim of this study was to explore the preemptive effect of infraclavicular brachial plexus blocks. We investigated if a pre-operative infraclavicular brachial plexus block results in better and more long-lasting postoperative analgesia compared with an identical block performed at the end of surgery. We concluded that optimal efficacy for management of acute postoperative pain is more likely to be obtained with pre-operative rather than postoperative nerve blockade. Pre-operative blocks resulted in less pain during the first postoperative hours and less analgesic consumption 1 week after surgery, but had no impact on the high incidence of mild long-lasting pain.

The preemptive effect of infraclavicular brachial plexus blocks demonstrated in this study is important, and to our knowledge not previously demonstrated after peripheral nerve blocks. Time to first rescue analgesic after emergence from general anaesthesia was significantly longer in the pre-operative block group. The patients in the pre-operative block group also reported significantly less pain and rescue analgesic consumption first 4 hours after surgery. In addition, fewer patients in this group used paracetamol analgesics after one week. The latter supports that the effect of a pre-operative block significantly outlasts the duration of the block per se. To perform the nerve blocks pre-operatively rather than postoperatively is simple, it does not require extra resources and is easy to incorporate in a clinical setting to improve perioperative treatment. Also, when blocks are used for upper extremity surgery, the clinical routine is to apply them pre-operatively for the benefit of per-operative anaesthetic effect without the need for general anaesthesia.

Another important effect of pre-operative nerve blocks is the reduced need of opioids during surgery. Per-operative use of remifentanil may cause hyperalgesia, which is related to the dose and duration of administration (177, 178). The patients in the postoperative group received substantially more remifentanil during surgery that the pre-operative block group in this study. Opioid induced hyperalgesia could partly explain the differences in initial postoperative pain. But the difference after 7 days is
difficult to explain by less hyperalgesia, and is probably due to improved analgesia in the pre-operative block group.

A pre-operative infraclavicular block could potentially result in less surgical trauma for the patients due to more relaxation in their forearm muscles, permitting improved access to the fracture and less need for dissection and trauma to the neighbouring muscles. However, we registered a similar decrease in systemic serum stress response parameters (i.e. cortisol, leucocyte count, C-reactive protein and glucose values) in the two groups during surgery, as well as a similar increase 2 hours postoperatively. Thus, we assume the surgical trauma in the two groups to be similar.

In this study we demonstrated severe pain at block resolution approximately 10 hours postoperative in the majority of our patients, with no significant difference between the two groups. The abrupt termination of the analgesic effect of single-injection techniques is one of the main challenges of brachial plexus blocks in acute pain management. Rebound pain after peripheral nerve blocks are demonstrated in several other studies (2, 4, 85, 109, 179, 180). Severe pain at block resolution is particularly problematic in ambulatory surgery, like volar plate fixations, because it can cause considerable discomfort and fear in the patients and may increase the need for unplanned medical assistance after discharge (109).

The patients in the study were instructed to take analgesics as soon as they started to feel mild pain after surgery. Because peripheral nerve blocks resolve rather quickly, this might have been too late to achieve adequate effect of the analgesics before complete emergence of the blocks. The patients in this study did not receive any anti-inflammatory protection or multimodal analgesic regimen perioperatively. Thus, once the analgesic effects on the antinociceptive afferent nerves disappeared, the patients could have been in a state of strong local and central sensitisation from systemic inflammatory mediators. The local anaesthetics in an infraclavicular brachial plexus block efficiently stops transmission of nociceptive pain provoking impulses from a surgical site (83), but the potential anti-inflammatory effect on a remote surgical site seems to be minor or moderate (84). Further, when a tourniquet is applied during
surgery, there is no access of systemic analgesics to the surgical site, and there is a local build-up of acidity stimulating peripheral nociceptors (181). When the tourniquet is released at end of surgery, potent circulating mediators from the arm and wound areas are expected to be released into general circulation.

In this study, 76% reported episodes of mild pain 6 months after surgery with no significant difference between the two groups. Long-lasting mild pain has also been demonstrated after volar plate surgery in other studies (182, 183). Unfortunately, we do not know how many patients had bothersome pain in everyday life, or during which activities they experienced the worst pain scores after 6 months. However, pain at 6 months did have an impact on work ability for about half of our patients and on social life for about 20% of the patients, while it did not influence quality of sleep or cognitive function for the majority of the patients.

13.1.2 Study 2

With this study, we wanted to address the problem with severe pain at block resolution demonstrated in the first study. Our specific aim was to explore the effect of a single pre-incisional intravenous dose of dexamethasone on acute and long-lasting postoperative pain. In contrast to the first study, all patients in this study received anti-inflammatory prophylaxis with etoricoxib, which was supposed to be circulating in the area of surgery before application of tourniquet and start of surgery.

We found that adding intravenous dexamethasone to oral etoricoxib and paracetamol before start of volar plate hand surgery resulted in more long-lasting brachial plexus blocks, less pain upon block resolution, and shorter duration of moderate-severe pain. Further, at six months after surgery, average pain scores were lower and we found less need for adjustments at work in the dexamethasone group. At one year after surgery, less patients in the dexamethasone group experienced long-lasting pain, 2 versus 10 patients in the placebo group.

The increased block duration in the dexamethasone group in this study is important and in agreement with earlier publications (66-69). The possible more pronounced
prolongation in our study might be explained by a higher dose of dexamethasone. From a clinical point of view there is considerable benefit for the patient not to wake up during the first night after surgery with strong postoperative pain, but rather have the experience of a dimishing block and need of rescue medication while being awake the next morning.

Our primary endpoint in this study was worst pain score first 24 hours after surgery. The increase in block duration after intravenous dexamethasone to median 21.5 hours could make the value of this endpoint discussable. However, median block duration after end of surgery was 19 hours, and only three blocks lasted longer than 24 hours after surgery. Additionally, we found a similar reduction in worst pain score first 36 hours after surgery. Retrospectively, this could probably have been a better primary endpoint. Possibly more important than the reduction in worst pain score first 36 hours after surgery, is the considerably reduced duration of moderate-severe pain (VNRS above 3) with pre-incisional dexamethasone.

An interesting result in this study was the minor, but significant positive effects of adding dexamethasone on some of the outcomes after 6 and 12 months. This is, to our knowledge, not previously reported after volar plate surgery or other surgical interventions, although perioperative measures to reduce the surgical inflammatory response have been hypothesised to be a target to reduce chronic pain after surgery (62, 184-186). Unfortunately, our study was not appropriately powered to conclude on differences in long-lasting pain. This is an interesting area for future studies.

Several mechanisms may explain our findings. Both the anti-inflammatory effect and the analgetic effect of systemic dexamethasone during 1-2 days after administration is well known (62, 187). The reason why dexamethasone prolongs nerve block duration remains unclear. One possible explanation for the prolonged nerve block duration could be a systemic effect of dexamethasone on neurons. Another possible explanation is the general analgesic effect of dexamethasone which results in less pain at block resolution, and therefore a subjective feeling of longer duration of the block. The latter
explanation seems less likely, since we also found prolonged motor block duration in the dexamethasone group.

The prolonged nerve block duration in the dexamethasone group may partly explain our results of lower rebound pain scores in this group, as nociceptive input and pain generally declines consistently during the hours after surgery (4). As the dexamethasone group also experienced shorter duration of strong pain after operation in our study, it may also be a result of less sensitisation of the central nervous system (81). The latter could also be hypothesized to be a part of the explanation for less longlasting pain in the dexamethasone group.

13.1.3 Study 3

The specific aim of this study was to explore the circulatory changes caused by infraclavicular brachial plexus blocks. We investigated changes in both subpapillary and nutritive skin blood flow as well as changes in systemic vascular variables after lidocaine blocks with and without adrenaline added.

We found a substantial increase in subpapillary blood flow in the blocked arm after infraclavicular brachial plexus blocks. In contrast, the sympathetic block did not increase blood flow to the nutritive capillaries in the non-glabrous skin on the dorsal side of the hand where arteriovenous anastomoses are not present. When adrenaline was used as an adjuvant, the nutritive skin blood flow decreased. Compared with the control arm, nutritive blood flow to the skin was lower after blocks with and without adrenaline. The use of adrenaline had no significant effect on cardiovascular variables, but resulted in denser and longer lasting nerve blocks.

Increased blood flow after brachial plexus blocks has been reported in previous studies (118, 120, 188). Use of peripheral nerve blocks is also reported to be beneficial in some clinical settings to prevent tissue ischemia (46-48). The new perspective in this study is the possible reduction in nutritive blood flow. Whether this is an effect of adrenaline or simply a result of the denser blocks in the adrenaline group is not clear. It is also not clear if the nutritive skin blood flow is representable of the nutritive
microcirculation in other microvascular beds, like in skeletal muscles, because of the complexity of microcirculation with regional variations across the body.

The observation of possible reduced nutritive blood flow might be important in several clinical settings. Optimised peripheral circulation may lead to better wound healing and improved outcome after surgery. This is especially important after free-flap surgery, reconstruction surgery, or other types of surgery where the nutritive circulation is important. A possible decreased nutritive blood flow to the skin after brachial plexus blocks may question the use of nerve blocks to improve peripheral microcirculation after some procedures. Our results may lead to the suggestion that adrenaline adjuvant is to be recommended when a strong block for surgery or pain relief is required, whereas a block without adrenaline may be recommended when the purpose of the block is to increase the microcirculation and oxygenation of peripheral cells to improve function and survival of tissue. Both these aspects should be considered when brachial plexus blocks are performed to enhance vascular microcirculation.

The reduced nutritive skin blood flow after infraclavicular blocks with adrenaline adjuvant could be explained by a steal effect caused by the increase in blood flow to the arteriovenous anastomosis in the palms and fingers (116). Circulating adrenaline may also cause direct vasoconstriction in nutritive blood flow to the skin. The vasoconstrictive effect might increase when there is a steal effect in the arteriovenous anastomosis due to the sympathetic blockade.

Adrenaline is known to prolong block duration due to vasoconstriction at the injection site leading to slower removal of local anaesthetics from the paraneural compartment and an enhanced diffusion of local anaesthetics into the nerve fibres (78). We found denser and more long-lasting blocks when adrenaline was added to lidocaine. Similar observations on block quality are also reported in other studies (77, 80). The longer duration and better quality of the adrenaline supplemented blocks in our study may explain the greater changes in subpapillary and nutritive skin blood flow. Better block
quality after addition of adrenaline might also cause a stronger steal effect to the nutritive skin perfusion compared with the blocks without adrenaline.

In our study, we observed no systemic effect of adrenaline that can explain our results. The systemic effect of adrenaline might depend on the total dose of adrenaline and the blood circulation near the injection site. Our findings are in contrast to other studies on peripheral nerve blocks (axillary brachial plexus blocks and paracervical blocks) where significant changes in haemodynamics were found when adrenaline was used as an adjuvant to lidocaine or bupivacaine in similar doses as in our study (80, 189).

13.1.4 Overall discussion

The general aim of this thesis was to evaluate the clinical and physiological benefits of infraclavicular brachial plexus block in some dedicated areas to improve its benefits and avoid undue harm. The findings in our three studies may add knowledge to improve the clinical use of brachial plexus blocks.

Study 1 and 2 demonstrate the importance of a multimodal pre-operative pain treatment. Infraclavicular brachial plexus blocks have a preemptive effect worth considering. Anti-inflammatory prophylaxis with etoricoxib may reduce opioid requirements postoperatively. The addition of dexamethasone further reduces pain intensity and shortens the duration of moderate to severe postoperative pain. To achieve a good clinical outcome after fracture surgery, sufficient pain relief is important. It enables the patients to do exercises needed for optimal rehabilitation. Our studies show that peripheral nerve blocks combined with anti-inflammatory prophylaxis including dexamethasone are important parts of a multimodal perioperative analgesic regime.

Whereas no patients in study 1 received anti-inflammatory prophylaxis, all patients in study 2 received etoricoxib. When looking at the results from the study 1 and 2, we may speculate that the anti-inflammatory effect of etoricoxib is an important reason for less opioid consumption in study 2. This could be a relevant topic for further
studies. However, anti-inflammatory prophylaxis with etoricoxib alone did not seem to reduce the high pain scores at block resolution.

The inflammatory reaction is a major cause of postoperative pain. An infraclavicular brachial plexus block has no direct anti-inflammatory effect in the wounded area. Nevertheless, it may be argued that a brachial plexus block may have a small anti-inflammatory effect due to its ability to increase peripheral circulation and thus potentially induce increased “washing out” of inflammatory mediators. However, when the surgery is performed with tourniquet applied, the effect of increased peripheral circulation after pre-operative brachial plexus block will be diminished. In study 1, we found better postoperative analgesia when the infraclavicular block was performed before compared to after surgery. This is probably mainly due to the preemptive effect of the blockade, counteracting peripheral and central sensitisation, and not due to the possible anti-inflammatory effect of increased peripheral circulation.

The exact mechanism behind why a perioperative single dose of intravenous or perineural dexamethasone increases block duration and reduces postoperative pain is not known. The systemic effect was demonstrated in study 2. Whether or not perineural dexamethasone also has a local action is unclear. There are several possible explanations for a local action. Dexamethasone may decrease the absorption of local anaesthetics through vasoconstriction due to local action on glucocorticosteroid receptors (190). It may also suppress transmission of pain signals in c-fibres by reducing spontaneous discharge of the membrane potential of the nerve cells (191). It could also be through a potential neurotoxic effect causing a transient nerve injury. An interesting study with bilateral saphenous nerve blocks, with the addition of dexamethasone on one side, aimed to answer the question if the mechanism of dexamethasone on nerve block duration is solely systemic, or if dexamethasone has any local perineural effect. The study only found an inconsistent and modest block prolongation on the side with local dexamethasone of minor clinical importance (192). Hence the local effect of dexamethasone seems to be minor.
Our studies support that brachial plexus blocks have the potential to improve clinical outcome after operations by reducing acute and possibly also long-lasting postoperative pain. When the block is used to improve peripheral microcirculation, a block without adrenaline may be recommended.

13.2 Main strengths and limitations of the studies

13.2.1 Study 1

There are several limitations in this study that need to be addressed. We did not classify the types of fracture, apart from all patients being in need of a volar plate fixation. Nor did we record if the patients had associated soft tissue injuries. Thus, there could be differences between the two groups in fracture severity. Still, because of randomisation, we assume the two groups to be similar with regards to severity of the fractures and soft tissue injuries.

Despite randomisation, we have some small variations in our baseline characteristics in pre-operative risk factors for pain that need to be addressed. The duration of surgery tended to be slightly longer in the pre-operative group. This could be an indication of more complicated surgery in the pre-operative group. There were also more cigarette smokers in the pre-operative group, 15 (60%) compared with 4 (15%) in the postoperative group. Smoking may affect both acute and chronic pain conditions, and animal studies have demonstrated increased sensitivity to pain stimuli with nicotine withdrawal (193, 194). These possible confounders may have influenced on our results in terms of more pain in the pre-operative group. Therefore, they should not have affected our main conclusion of less postoperative pain in the pre-operative block group.

The 20 min period from the application of infraclavicular blocks to emergence of anaesthesia in the postoperative group might have been too short to make all blocks work sufficiently before the patients were awake. Our clinical experience is that the blocks may continue to develop during the first hour after application. Yet, previous studies have shown that successful infraclavicular blocks can be obtained at 20 min
We decided to keep the patients in general anaesthesia for the minimal time needed for a sufficient block, 20 min, to minimise the extra time used in the operating theatre in a busy day care unit. We tested the sensory blocks 30 min after emergence from general anaesthesia (i.e. 50 min after block procedure in the postoperative group) to allow the patients to recover from anaesthesia and be able to cooperate in order to perform the test procedure. All but one block in each group were successful at this time according to our predefined criteria.

We registered actual pain at 30 min, 1, 2, 8 and 24 hours after surgery, and the worst pain score experienced during first 24 hours. The data obtained from these points in time might not be representable for the patients average pain experience first 24 hours. The duration of medium to strong postoperative pain is another important measure we did not register in this study.

Due to our study design, we did not include enough patients for appropriate statistical power on our endpoints after 6 months. In addition, several patients were lost to follow up at the 6-months interview. With only 17 patients left in each group at the 6 months interview, the potential to find statistically significant differences between the two groups was reduced.

The study also has several strengths. The topic is relevant and of clear clinical importance. Other strengths include the randomised double-blind design, the high success rate of the blocks, the registration of systemic serum stress response markers and the use of rebound pain as outcome.

13.2.2 Study 2

This study also has several limitations. Despite randomisation, more patients in the placebo group had injuries in the dominant hand. This may influence the incidence of both pain and the ability to work unimpeded, as this hand is used more than the other. A smaller number of women in the dexamethasone group may have affected the outcome since women are reported to experience more pain (196). However, women are also reported to have longer duration of nerve blocks (68). A slightly higher pain
catastrophizing incidence and higher expectation of pain in the placebo group could also explain a higher pain intensity in that group (197). Otherwise, the two groups were similar in preoperative risk factors of postoperative pain, including pain threshold measured before the operation. The differences in worst pain and block duration between our two study groups were large, robust and strongly significant. Hence, these outcomes can not be explained by minor differences between the two groups in confounding factors.

Another potential limitation may be that some of the nerve blocks might have resolved in the middle of the night when the patients were asleep, with subsequent overestimation of block duration in patients with low or no pain. However, as 81% of our patients (i.e. both groups pooled) were in need of rescue opioid shortly after resolution of the block, we do not consider this aspect to be of any major importance.

To estimate block duration, we used the duration of motor blockade as a surrogate for the endpoint of nociceptive blockade. Because the patients were at home when the nerve blocks wore off, we decided to use a simple test, which the patients could easily perform themselves. End of block duration was therefore defined as time to lift a pen to the face area. It may be argued that this will be an overestimation as patients may hesitate to try this manoeuvre shortly after block resolution. However, the patients were instructed to check this frequently when they started to feel the nerve block wear off, and if pain should be the cause of delayed registration of block resolution, this should be more evident in the control group.

Some may argue the use of anti-inflammatory prophylaxis with etoricoxib is a limitation of the study, and that a study with only dexamethasone as anti-inflammatory prophylaxis compared with placebo would have been a cleaner and better design. However, etoricoxib was introduced as a standard premedication before volar plate surgery in our department prior to study 2. We wanted to find out if dexamethasone has an additional anti-inflammatory effect to etoricoxib worth considering. It could also be considered unethical and make recruitment more difficult if we had offered our study patients an analgesic regime inferior to the standard regime in our department.
Our sample size was determined to find differences in highest pain score during the first 24 hours after surgery. We did not include enough patients to achieve appropriate statistical power on some of our secondary outcomes. To evaluate the true incidence of long-lasting pain after such operations, a higher number of patients would be needed, both because of lower incidence of pain and less difference in pain scores after 6 months and one year. As we evaluated several variables, it is possible to have statistical significance by chance on some of the variables with a low level of significance (i.e. 0.01-0.05 range) at 6 and 12 months.

We found no side effects from dexamethasone in our study, and did not study blood glucose levels, which are reported to be transiently elevated in many previous studies (74, 198, 199). However, serious side-effects related to dexamethasone, such as delayed wound healing or wound infection, are very rare and were not reported in the study of more than 18000 orthopaedic surgery patients by Vuorinen et al (200).

The strengths of our study include the clinically relevant topic, the randomised double-blind design, the uniform patient population, the high success rate of blocks, and the low dropout rate at 6 and 12 months.

### 13.2.3 Study 3

A limitation of this study is the selection of participants that may not be representable for the typical patient in a clinical setting. All our participants were predominantly young, healthy and non-smoking males. We did not include women because female reproductive hormones may influence on the non-noradrenergic mechanisms of vasoconstriction (126). Older patients may have age related alterations in skin blood flow. Therefore, the results may not apply in women or in older patients. Our results apply to infraclavicular blocks with lidocaine 15 mg/ml using adrenaline 5 µg/ml as an adjuvant with an injection volume of 0.4 ml/kg. The use of other local anaesthetics, dosages, and adrenaline concentrations could lead to different results.

Further, an acclimatisation period of 20 minutes in a temperature controlled operation theatre might have been too short to ensure stable baseline circulation measurements.
in some of the volunteers. This may have affected the measurements in the control arm as well as the anaesthetised arm during the course of our registrations.

Because of a small sample size in our study, we might have type 2 errors in our statistical calculations.

The short block duration in the blocks without adrenaline might have affected the capillary video microscopy measurements in some of our subjects. Median (IQR [range]) block duration was only 67(62-72[30-93]) min in these blocks. The time from needle out until all measurements were completed was about 30-35 min. Hence, the effect of the blocks was probably about to wear off in some of our volunteers during the microscopy session at 30 min after nerve block. Therefore, we might have underestimated changes in nutritive blood flow after nerve blocks without adrenaline.

Due to technical failure with the Hydra Series II data logger, we had to replace it and used a C28 K type thermometer with temperature measurements every 5 minutes on two volunteers on day two. A Hydra Series III data logger was used on one volunteer on day two. Even though all the equipment was calibrated, the different measuring methods might have given us minor inaccuracies in the temperature results. However, because our temperature results were robust and highly significant, this has probably not affected our main conclusions.

The major strengths of this study are the novelty, its potential clinical relevance, the randomised double-blinded design and the use of several different methods to evaluate the different aspects of microcirculation.

13.3 Clinical implications

With the studies in this thesis, we have tried to evaluate different clinically relevant outcomes after infraclavicular brachial plexus blocks to help improve its clinical use. All strategies we have evaluated are easy to incorporate in a clinical practise.

Study 1 and 2 clearly demonstrate the importance of preventive analgesia. The results highly support the use of pre-operative brachial plexus block combined with pre-
incisional intravenous dexamethasone and perioperative NSAIDs in patients undergoing volar plate fixations for distal radius fractures unless there are contraindications.

Both study 1 and several other studies have demonstrated one of the major clinical challenges of using single injection brachial plexus blocks: the strong rebound pain at block resolution (2, 85, 109). Several strategies may be used to try to diminish this problem: use of continuous block catheters; use of adjuvants to local anaesthetics to prolong block effect; or more aggressive preemptive analgesic regimens. In study 2, we found both reduced worst pain scores and reduced duration of moderate–severe pain after block resolution (to a satisfactory level for most patients) after a combination of oral etoricoxib and intravenous dexamethasone. The simplicity of this treatment, which is considered safe and is well established, compared with time-consuming nerve block catheter techniques or unlicensed use of perineural adjuvants like dexamethasone, favours the use of intravenous dexamethasone in a clinical setting (62, 75, 201).

In light of the current focus of eliminating unnecessary perioperative opioid consumption, the possible reduced opioid consumption in patients receiving anti-inflammatory prophylaxis is important. Also, the potential positive effects of a single intravenous dose of dexamethasone on long-lasting pain after 6 and 12 months is a novel and interesting finding that should be further investigated.

Study 3 may have important implications when brachial plexus blocks are used to improve peripheral circulation. We found increased subpapillary blood flow after brachial plexus blocks. This is also reported in previous studies (118, 120). The new and important perspective in this study is the effect on nutritive skin blood flow. A significant reduction in nutritive skin blood flow was found after blocks with adrenaline adjuvant, which enhance the block density and duration. Compared with the control arm, nutritive blood flow to the skin was lower both after blocks with and without adrenaline. A possible decreased nutritive circulation after brachial plexus blocks may question the use of nerve blocks to improve peripheral microcirculation.
after surgery where the nutritive circulation is important. According to our results, it may be beneficial to avoid adrenaline adjuvant if the purpose of the nerve block is to increase the microcirculation and oxygenation of peripheral cells. Further studies are needed to confirm these findings.
14. Conclusions

14.1 Paper 1 (specific research question A)

A pre-operative brachial plexus block leads to a small, but significant improvement in early postoperative pain compared with postoperative administration of the block, and possibly a lower analgesic consumption up to one week after surgery. However, a pre-operative block does not attenuate strong pain during block resolution and does not seem to have an impact on the high incidence of minor persistent pain.

14.2 Paper 2 (specific research question B)

The addition of intravenous dexamethasone to oral paracetamol and etoricoxib provides longer duration of brachial plexus blocks, improved acute postoperative analgesia, and may also reduce the development of chronic pain after volar plate hand surgery.

14.3 Paper 3 (specific research question C)

Subpapillary skin blood flow increases after lidocaine infraclavicular brachial plexus blocks whereas nutritive blood flow to the non-glabrous skin does not increase. Adrenaline as additive did not have a significant effect on cardiovascular variables, but resulted in denser nerve blocks and a significant decrease in nutritive skin blood flow.

14.4 Overall conclusions

To obtain the optimal efficacy for management of both acute and long-lasting postoperative pain and reduce total opioid requirement after volar plate surgery for distal radius fractures, brachial plexus block should be performed pre-incisionally rather than postoperatively and be combined with NSAIDs and intravenous
dexamethasone. When a brachial plexus block is performed for the purpose of increasing the microcirculation and oxygenation of peripheral cells, the best approach may be to use a block without adrenaline added.
15. Future area of research/interest

Intravenous dexamethasone demonstrated clear positive tendencies for preventing long-term pain in our study. Further studies with focus on possible long-term pain reducing effects of dexamethasone and other interventions would be an area of interest. A thorough evaluation of the affective qualities of long lasting pain (fear, anger, sadness, frustration, feelings and hopelessness), as well as an evaluation of the other aspects of long-lasting pain would also be of interest.

Even though intravenous use of dexamethasone are considered safe and well established with low incidence of side effects (62), many clinicians are still concerned about possible adverse effects like wound infections, delayed wound healing and increased levels of blood glucose. The literature is scarce on safety data on perineural use of dexamethasone and its benefits over intravenous use (75). Large studies exploring possible side effects of both intravenous and especially perineural use of dexamethasone would be interesting and important. Such studies would require a high number of included patients. Also, studies on repeated doses of dexamethasone will be of interest in order to elucidate any potential enhanced prolongation effect versus any increased risk of side effects.

Another area of interest is to find the optimal dose of dexamethasone for pain relief after volar plate surgery and other operations. Is there a major difference between 4 mg, 8 mg or 16 mg regarding the reduction in both acute and long-lasting pain? What are the median effective dose (ED50) and the dose required to achieve the desired effect in 95% of the patients (ED95)? Studies with a similar perioperative design as our study, or with an increasing or repetitive dose of glucocorticoid would be interesting. The latter have been reported beneficial on pain in a study of orthopedic hip surgery (202).

More studies evaluating the effect of the combination of several agents on both peripheral nerve blocks and postoperative pain would be interesting. A Korean group recently published a study where the intravenous combination of dexmedetomidine 1
µg/kg and dexamethasone 0.11 mg/kg substantially increased the duration of analgesia after interscalene brachial plexus blocks for shoulder arthroscopy from 10.9 hours to 66.3 hours (203).

An area of growing interest is to evaluate pre-operatively individual patients risk factors for high levels of postoperative pain. Such mapping of risk factors may enhance the precision of pain-prophylactic measures, by providing extra analgesia for those at high risk, while the low risk patients will not be exposed to drugs that they do not need.

Regarding circulatory changes after brachial plexus block, our finding of reduced nutritive blood flow to the non-glabrous skin after blockades with adrenaline adjuvant needs to be confirmed. Compelling studies comparing the nutritive microcirculation in different microvascular beds, to evaluate the use of skin microcirculation as a biomarker for the microcirculation in general, would be interesting. Studies on women, where female reproductive hormones may influence on the non-noradrenergic mechanisms of vasoconstriction, would be important and interesting (126). Also studies on older patients regarding both microcirculatory and hemodynamic changes are needed because of age related alterations in skin blood flow and age related haemodynamic changes. Studies to compare our results with lidocaine and adrenaline with other local anaesthetics, to see if they cause similar changes in microcirculation, would also be interesting.
16. References

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17. Errata list

Name of candidate: Anne Holmberg

Title of thesis: Plexus brachialis anaesthesia: Optimising clinical aspects


By an editing error, some of the references appear in the wrong format in the original manuscript. They have been changed to the correct format.

By an editing error, the references 175 and 176 appear out of sequence early in the manuscript (after reference 136 on pages 64 and 65). However, all given numbers of references in the text are corresponding to the correct numbers in the reference list. Therefore no changes have been made to the original manuscript.

The original reference number 27 and 195 refers to the same article. No change has been made to the original manuscript.

No changes have been made to the original text of the thesis, only corrections to the reference list. All changes made are summarised in the table below:

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<td>30, 40, 42, 65, 95, 189</td>
<td>Corrected the format of the references</td>
<td>Removed ”table of contents” after the page numbers in the reference or included correct page numbers.</td>
<td>Wrong format of references</td>
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