Local anesthetics: New insights into risks and benefits
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Summary

Section 6
The present thesis sought to investigate and review the mechanism and management of side-effects or failures of neuraxial anesthesia; investigate nerve injury related to the performance of regional anesthesia, with special focus on patients with pre-existing neuropathy; investigate potential novel actions of local anesthetics on the epigenetic signature of tumour cells; and conclude with a weighing of risks and benefits of regional anesthesia using local anesthetics.

In **Section 1**, an introduction was given to local anesthetics. While *Chapter 1.1* described the aims of this thesis, *Chapter 1.2* reviewed current literature which shows that conventional local anesthetics in contemporary use block the voltage-gated sodium channel by binding to a specific site on the inner facet of the channel pore. This causes a conformational change, and the positive charge of the local anaesthetic further obstructs the channel’s lumen. Only 2-3% of local anaesthetic is thought to participate in nerve blockade, the rest is absorbed into surrounding tissues or the systemic circulation. While small systemic levels of local anaesthetic can have a beneficial effect on some outcomes and vital functions, excessive amounts of free local anaesthetic will cause systemic toxicity.

In **Section 2**, focusing on the clinical application of local anaesthetics for regional anesthesia, two studies concentrated on the use for spinal anesthesia for cesarean section, while one review article described causes and management of failed neuraxial blockade. In *Chapter 2.1*, we present a survey investigating the strategies to prevent or treat hypotension following administration of spinal anaesthesia for caesarean delivery. In comparison to previous surveys in the United States and United Kingdom, we showed a trend toward increased use of phenylephrine to treat hypotension, in keeping with a growing evidence-base suggesting its side-effect profile is superior to ephedrine in most cases. In *Chapter 2.2*, we investigated pulmonary function indices following administration of spinal anesthesia for caesarean section when using bupivacaine, ropivacaine or levobupivacaine. We found that decreases in maternal pulmonary function tests were similar following spinal anaesthesia with bupivacaine, ropivacaine, or levobupivacaine for caesarean delivery. The clinical maternal and neonatal effects of these alterations appeared negligible. This study does not support the clinical
superiority of any of the three investigated long-acting local anaesthetic for spinal anesthesia. In Chapter 2.3, the evidence surrounding failures and their management during neuraxial analgesia is reviewed. Failed epidural anaesthesia or analgesia is more frequent than generally recognized. Reasons for an insufficient epidural include primary erroneous placement, secondary migration of a catheter after correct placement, and suboptimal dosing of drugs. As hinted in Chapter 2.2., when using equipotent doses, the clinical difference between bupivacaine and the newer isoforms levobupivacaine and ropivacaine appears minimal. During continuous infusion, dose is the primary determinant of epidural anaesthesia quality, with volume and concentration playing a subordinate role. Addition of adjuvants, especially opiates and epinephrine, may substantially increase the success rate of epidural analgesia. The method of delivery for postoperative analgesia most supported by literature is patient controlled epidural analgesia with background infusion.

In Section 3, the focus was on nerve damage during regional anesthesia, with a special focus on patients with diabetic neuropathy. In Chapter 3.1, we sought to answer the question whether intraneural needle placement is detrimental. In a large animal model of sciatic nerve block, neurophysiological parameters following nerve trauma and intraneural injection. Needle trauma as well as intraneurial injection of small volumes of saline produced a significant decline in cMAP amplitude, corresponding to severely impaired nerve function. Although the degree of long-term neurological dysfunction in our model is unclear, it could be demonstrated that in the short term, nerve conduction is highly vulnerable to needle trauma and intraneurial injection, arguing against intraneural injection as proposed by some authors. In Chapter, 3.2, current knowledge on regional anesthesia in patients with diabetic neuropathy was summarized. Patients with pre-existing neuropathies or neurological disease may be at increased risk of iatrogenic nerve injury. This line of thought was developed further in Chapter 3.3., where in vitro and in vivo investigations were conducted to investigate effects of local anesthetics on nerve block duration and neurotoxicity in diabetic rats. We found that in vitro, local anesthetic neurotoxicity was more pronounced on neurons from diabetic animals,
but the survival difference was small. *In vivo*, subclinical neuropathy leads to substantial prolongation of block duration. We concluded that early diabetic neuropathy increases block duration, while the observed increase in toxicity was small. In a subsequent experiment (*Chapter 3.4*), we refined this methodology by introducing neurophysiologic monitoring to diagnose diabetic neuropathy before administering sciatic nerve block and measuring nerve block duration as well as neurotoxic effects. We found that nerve blocks last longer in late diabetic animals. Sensitivity of diabetic nerves for local anesthetics seems to correlate with severity of neuropathy. Our results, using a short-acting local anesthetic without additives, do not support the hypothesis that nerve block in diabetic patients increases nerve injury after peripheral nerve block. Lastly, in *Chapter 3.5*, we sought to assess the patterns of practice in the management of diabetic neuropathic patients presenting for regional anesthesia in Europe. While literature is divided on the question whether pre-existing diabetic neuropathy is a risk factor for new neurological deficit after regional anaesthesia, most of the responders of this survey take measures to reduce risks, counsel patients on a possible greater risk of neurologic complications, but only a minority of responders would avoid peripheral regional anaesthesia altogether.

**Section 4** concentrates on a novel mechanism of action of local anesthetics, the modification of the epigenetic signature of human cells. While preliminary evidence had suggested that procaine can modify epigenetics in tumour cells, we could show in *Chapter 4.1* that this was also the case for the classic local anesthetic, lidocaine, at clinically relevant concentrations attained after epidural anesthesia or intravenous administration as part of multimodal pain treatment regimens. In *Chapter 4.2*, we show that lidocaine and ropivacaine, but not bupivacaine, at clinically relevant doses, exert demethylating effects on certain breast cancer cells, and seem to enhance demethylating properties of prototype epigenetic chemotherapeutic, 5-aza, in an additive fashion. At equipotent doses, the demethylating effects of local anesthetics seem to be most pronounced for lidocaine, with decreased demethylating capacity by ropivacaine, and no detectable effect of
bupivacaine. These effects could be of substantial importance in perioperative medicine, with focus on tumour surgery and pain medicine.

In Section 5, the potential benefits and risks of regional anesthesia were compared. Regional anesthesia has become a widely used method to provide intraoperative anesthesia, and postoperative analgesia. This review seeks to address the question whether patient outcomes are improved to an extent that justifies using regional anesthesia as a routine method. During the past decade, a very critical appraisal of risks and benefits of regional anesthetic procedures has taken place. In general, the indications for epidural blockade have decreased, and are limited to individual high-risk patients, major upper abdominal and major vascular surgery, and thoracotomy. We review the changing role of central and peripheral regional anesthesia in the perioperative management of total knee arthroplasty. Immediate perioperative outcome after knee arthroplasty concerning function and pain is improved, and rehabilitation facilitated, by peripheral nerve blockade, but this does not translate into superior functional outcome one year later. A substantial share of the beneficial effects of regional anesthesia on the immune system, haemostasis, pain, and the duration of ileus can be duplicated using intravenous administration of local anaesthetics. In general, the use of regional anesthesia should always be preceded by a weighing of potential risks and proven benefits. Regional anesthesia continues to play a major role in perioperative medicine, but its role keeps getting more defined and less noncommittal.