Local anesthetics: New insights into risks and benefits
Lirk, Philipp

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Chapter 1.1

Outline of Thesis
A brief history of Regional Anesthesia

Local anesthetics (LA) are indispensable in contemporary regional anesthesia and pain management. Introduced in Western medicine in the late 19th century, the prototype substance cocaine had been widely used by South American cultures for thousands of years. However, these tribes were used to chewing coca leaves, which dried out during shipping to Europe, such that the real breakthrough of cocaine was made possible only by the isolation of cocaine in 1859. Cocaine was used in oral form for various psychiatric diseases and fatigue by, among others, Sigmund Freud. However, it was his colleague, Carl Koller, who is widely credited for the first experimental topical application of cocaine. Koller was ophthalmologist at the Vienna General Hospital, and had been looking for ways to alleviate the pain of cataract surgery.

The discovery of the topical numbing properties of cocaine led to the development of regional anesthesia in its modern form, with the basic principle that injection of cocaine next to nerves produces a transient and reversible interruption of pain propagation, sensory and motor function. Over the following decades, many types of nerve block and neuraxial (epidural and spinal) anesthesia and analgesia were introduced. However, insufficient materials and medications with a narrow therapeutic range hampered widespread acceptance. For example, the first published administration of continuous epidural anesthesia in 1949 was achieved by an urethral catheter introduced into the epidural space. Another anecdote is the first performance, in 1889, of spinal anesthesia by Bier, which was successful from a pharmacological point of view, but the large needle used led to days of severe post-dural-puncture headache.

The introduction of the first short-acting amide-type local anesthetic, lidocaine, in 1947, and the standard long-acting amide-type local anesthetic, bupivacaine, were pharmacological milestones in regional anesthesia. In parallel, improved needle and catheter equipment meant that regional anesthesia could be applied in a more reliable and safe manner. In the 1990s, ultrasound-guided regional anesthesia was coined by a group of physicians in the in the Vienna General Hospital, the very workplace where hundred years earlier Carl Koller had made his
ground-breaking discovery. Stephan Kapral and Peter Marhofer described the guidance of the regional anesthesia needle by ultrasound, sparking renewed interest in regional anesthesia techniques.\(^4\)

If scientific publications can be taken as surrogate markers of clinical relevance, regional anesthesia is experiencing a surge in technical advances. At the same time, these publications reflect the quest to define evidence-based indications for these blocks on a procedure- and patient-based foundation.

**Contemporary focus**

Regional anesthesia has become an integral component of the anesthesiologist’s armamentarium. Perceived benefits include the reduction in postoperative opioid demand, and attenuation of postoperative symptoms and complications such as nausea and vomiting, and ileus.\(^5\) The endocrine stress response to surgery can be substantially alleviated when regional anesthetic techniques are employed.\(^6\) However, it is increasingly acknowledged that these beneficial effects are not relevant in all types of surgery and patients. Many of the beneficial effects of regional anaesthesia can be copied by the systemic administration of local anesthetics.\(^7\) Current consensus is to consider epidural anesthesia and analgesia in high risk patients, thoracotomy, and major upper abdominal and vascular surgery, to treat most cases of lower abdominal and laparoscopic surgery using multimodal analgesia, and to use peripheral regional anesthesia for extremity surgery as targeted and distal as possible.\(^8\) Currently, a large share of the current research efforts in Regional anesthesia is dedicated to defining patient- and procedure-based indications for the different techniques.

Despite being accepted as a relatively safe anesthetic technique, toxic effects of local anesthetics themselves can present a considerable risk. Importantly, in a dose-dependent manner, every local anesthetic is potentially toxic to virtually any kind of tissue.\(^9\) The question whether specific local anesthetics are more toxic than others remains unanswered. For example, there are studies suggesting that lidocaine is more toxic than bupivacaine in vivo\(^10\) while other studies found no
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difference \textsuperscript{11} and clinical evidence suggests that lidocaine is involved in nerve
damage more often than bupivacaine.\textsuperscript{12}

Epidemiological studies suggest that after neuraxial (spinal, epidural)
anesthesia, neurological complications such as transient radicular irritation (back
pain with radiation down one or both buttocks or legs occurring within 24 h after
surgery \textsuperscript{13}) may follow up to 30 \% of spinal anesthetics \textsuperscript{13} \textsuperscript{14}, and devastating
complications such as cauda equina syndrome (severe low back pain, lower
extremity motor weakness and sensory loss, bladder dysfunction, bowel
incontinence) affect roughly 1:8000 patients.\textsuperscript{12} \textsuperscript{15} This is in accordance with a recent
retrospective analysis of more than 100.000 neuraxial anesthetics, in which the
incidence of presumed neurological complication was 1:1000, but when imaging
techniques were used to validate these assumptions, the incidence was 0.07:1000
(with a 95\% confidence interval of 0.02 – 0.13/1000).\textsuperscript{16}

This may be of special importance in the collective of patients presenting
with diabetic neuropathy. Patients in the latter collective frequently feature relevant
cardiovascular or renal comorbidities that would predispose them to undergo many
types of surgery under regional anesthesia. On the other hand, limited
epidemiological and experimental evidence suggests that neuropathic nerves are
more susceptible to local anesthetic-induced neurotoxicity.\textsuperscript{17} \textsuperscript{18}

In the past, our group demonstrated involvement of the p38 Mitogen
Activated Protein Kinase (MAPK) (= MAPK 14) in local anesthetic-induced
neurotoxicity in vitro and in vivo.\textsuperscript{11} \textsuperscript{19-23} In particular, the p38 is specifically
activated in cell cultures incubated with lidocaine.\textsuperscript{23} In the Habilitationsschrift
(Innsbruck Medical University, 2010), we proposed a General Hypothesis that
exposure of primary sensory neurons to local anesthetics triggers opening of calcium
channels, resulting in an increase in cytosolic calcium, leading to a subsequent
activation of the p38 MAPK. Potential downstream modulators include the
lipoxygenase family of enzymes. Furthermore, we postulated that when local
anesthetic is deposited at the axon, these events unfold at the neuron’s periphery,
without necessarily involving the cell body. We believe this causes not only an
immediate neuronal injury apparent within hours, but also a prolonged inflammatory response combined with sustained tissue damage still detectable after several days.\textsuperscript{22}

Aims of this thesis

On the basis of these previous results, the investigations forming the basis of the current thesis aimed 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.

References

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