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# KETAMINE FOR POSTOPERATIVE PAIN IN ADULTS

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**Elina Brinck**

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**ACADEMIC DISSERTATION**

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*“gutta cavat*
*lapidem non vi sed*
*saepe cadendo”*

*Ovidius*

to Aksel and Tuomas

# CONTENT

# ABSTRACT

Suboptimal pain management after surgery increases complication rates, delays ambulation, and increases health care costs. Furthermore, inadequate postoperative analgesia decreases patient satisfaction and is a risk factor for chronic postoperative pain.

Opioids have traditionally been the pharmacological cornerstone in postoperative pain management, but adverse effects, tolerance, and hyperalgesia due to opioid medication (opioid-induced hyperalgesia) may restrict the feasibility of opioid use for postoperative analgesia.

Multimodal analgesia combines different pain treatment modalities to target different pain signaling pathways, aiming at synergistic and additive analgesic effects. The goals of multimodal analgesia in clinical practice are lower postoperative pain intensity, decreased opioid consumption, fewer opioid-related adverse effects, and better patient experience.

Low-dose ketamine (< 0.5 mg/kg), an N-methyl-D-aspartate receptor (NMDAR) antagonist, attenuates cellular and molecular mechanisms accounting for different pain states, opioid tolerance, and opioid-induced hyperalgesia. There is a substantial amount of data on the use of ketamine as an analgesic adjuvant. However, there are still unanswered questions, such as what the optimal dosing regimen is (including timing of dosing).

The aims of this thesis include determining the efficacy of perioperative intravenous (IV) ketamine as an adjunct analgesic in adult patients, concentrating on the feasibility of S-ketamine as an adjuvant analgesic after lumbar fusion surgery. We wanted to determine whether there exists a dose-response relationship in different ketamine and S-ketamine dosing regimens and to evaluate the effect of timing of dosing on postoperative opioid consumption and pain. Finally, we were interested of the tolerability of perioperative IV ketamine and S-ketamine (Studies I, II and III).

This thesis includes a Cochrane review with meta-analyses (Study I) and two prospective, randomized, double-blind, placebo-controlled clinical trials (Studies II and III).

The Cochrane review (Study I) showed that perioperative IV ketamine moderately decreased both postoperative pain and opioid consumption (by approximately 20%) after surgery. The analgesic effect of ketamine was greater in situations with higher background levels of pain. Study II indicated that intraoperative IV S-ketamine during lumbar fusion surgery in adult patients did not improve postoperative analgesia or decrease opioid requirement after surgery. Study III showed that adjunct S-ketamine in oxycodone intravenous patient-controlled analgesia (IV-PCA) improved analgesia and decreased oxycodone consumption significantly at 24 h after lumbar fusion surgery.

Based on the results of Studies I, II and III, the optimal timing of dosing seems to be in the postoperative period. Studies II and III indicated that, when treating patients undergoing lumbar fusion surgery, administration via IV-PCA in the postoperative period should be favored over intraoperative infusions. The optimal oxycodone:S-ketamine ratio seemed to be 1:0.75. This dosing improved analgesia and reduced opioid requirement after lumbar fusion surgery while lower oxycodone:S-ketamine ratios did not show a beneficial effect (Study III).

Data from Studies I, II and III showed that perioperative IV ketamine was well-tolerated. There was no evidence that perioperative IV ketamine would increase the incidence of central nervous system adverse events. Perioperative IV ketamine reduced the risk of postoperative nausea and vomiting to a small extent.

# TIIVISTELMÄ

Riittämätön kivunhoito leikkauksen jälkeen lisää haittatapahtumien esiintyvyyttä, viivästyttää potilaan kuntoutumista ja kasvattaa terveydenhuollon kustannuksia. Huonosti hoidettu leikkauksenjälkeinen kipu on myös pitkittyneen kivun merkittävä riskitekijä.

Välitön leikkauksenjälkeinen kivunhoito on perustunut pitkälti opioideihin. Niiden käyttöön liittyy kuitenkin merkittäviä haittavaikutuksia, toleranssin kehittyminen ja opiodien aiheuttama herkistyminen kivulle, mitkä voivat rajoittaa opioideista saatavaa hyötyä.

Multimodaalinen kivunhoito yhdistää erilaisia kivunhoidon keinoja. Näiden tarkoitus on vaikuttaa eri kohtiin elimistön kivunsäätelyjärjestelmässä, ja saada aikaan synergistinen ja jopa additiivinen kipua lievittävä vaikutus. Käytännössä multimodaalisen kivunhoidon tavoite on vähentää leikkauksenjälkeisen kivun voimakkuutta, vähentää opioidinkulutusta ja opioideihin liittyvien haittavaikutusten esiintymistä, nopeuttaa toipumista sekä parantaa potilaan kokemusta kivunhoidosta.

Ketamiini on N-metyyli-D-aspartaatti (NMDA) -reseptorin antagonisti. Sen on havaittu pienellä annoksella (< 0.5 mg/kg) vaimentavan kivun synnyn, opioiditoleranssin ja opioidien aiheuttaman hyperalgesian taustalla olevia solujen välisiä ja molekulaarisia mekanismeja. Ketamiinia on tutkittu kivunhoidossa laajasti, mutta sen ihanteellinen annostelu ja annosteluajankohta ovat vielä vakiintumatta.

Väitöskirjatutkimuksen tavoitteena oli selvittää perioperatiivisen (leikkauksen alussa, leikkauksenaikana, leikkauksen jälkeen annostellun) laskimonsisäisen ketamiinin tehoa leikkauksenjälkeisen kivun hoidossa aikuisilla keskittyen erityisesti S-ketamiinin käyttöön lannerangan luudutusleikkauksen yhteydessä. Lisäksi halusimme selvittää, onko ketamiinin vaikutus annosriippuvainen, ja arvioida sen ihanteellista annosteluajankohtaa leikkauksenjälkeisen kivun hoidon kannalta. Lisäksi arvioimme pieniannoksisisen ketamiinin siedettävyyttä kivunhoidossa tarkastelemalla sen aiheuttamia haittavaikutuksia.

Väitöskirja koostui Cochrane-kirjallisuuskatsauksesta meta-analyyseineen (osatyö I) sekä kahdesta prospektiivisesta, satunnaistetusta, kaksoissokkoutetusta, lumekontrolloidusta kliinisestä tutkimuksesta (osatyöt II ja III).

Cochrane-katsauksen perusteella perioperatiivinen laskimonsisäinen ketamiini vähensi leikkauksenjälkeistä kipua ja opiodinkulutusta kohtalaisesti (noin 20 %). Ketamiinin vaikutus oli suurempi tilanteissa, joissa leikkauksenjälkeinen kipu oli kovaa. Tekemämme satunnaistettujen, kliinisten tutkimusten perusteella leikkauksenaikainen S-ketamiini-infuusio ei tuonut merkittävää hyötyä lannerangan luudutusleikkauksen jälkeisen kivun hoidossa (osatyö II), mutta kun S-ketamiini annosteltiin yhdessä oksikodonin kanssa lannerangan luudutusleikkauksen jälkeen ns. kipupumpun kautta (opioid PCA; opioid patient-controlled analgesia; opiodien itseannostelu), S-ketamiinin kipua lieventävä ja oksikodonin kulutusta vähentävä vaikutus oli merkittävä 24 h kohdalla leikkauksen jälkeen (osatyö III).

Sekä Cochrane-katsauksen että kliinisten tutkimusten tulosten perusteella ketamiinin ihanteellinen annosteluajankohta vaikuttaisi olevan leikkauksenjälkeisessä vaiheessa. Kliinisistä tutkimuksista saamiemme tulosten perusteella lannerangan luudutusleikkauksen jälkeisen kivun hoidossa tulisi suosia oksikodonin ja S-ketamiinin yhdistelmää PCA:n kautta annosteltuna (osatyöt II ja III). Oksikodonin ja ketamiinin ihanteellinen annostelusuhde vaikuttaisi olevan 1: 0.75 (osatyö III).

Cochrane-katsauksen ja kliinisten tutkimusten perusteella perioperatiivisesti annosteltu laskimonsisäinen ketamiini ei lisännyt keskushermostohaittavaikutusten esiintymistä. Leikkauksenjälkeisen pahoinvoinnin ja oksentelun riski jopa väheni hieman.

## ABBREVIATIONS

| | |
|---|---|
| ABD | agonist binding domain |
| ATD | amino-terminal domain |
| ACC | anterior cingulate cortex |
| ASICs | acid-sensing ion channels |
| AMPAR | α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor |
| ASA | American Society of Anesthesiologists |
| BDNF | brain-derived neurotrophic factor |
| CGRP | calcitonin-gene related protein |
| CCK | cholecystokinin |
| CI | confidence interval |
| CNS | central nervous system |
| COX-2 | cyclo-oxygenase 2 |
| CTD | carboxyl-terminal domain |
| CYP | cytochrome |
| DOR | delta opioid receptor |
| ERK | extracellular regulatory kinase |
| 5-HT1-7 | serotonin (5-hydroxytryptamine) receptors |
| IC | insular cortex |
| iNOS | inducible nitric oxide synthase |
| IV | intravenous |
| KOR | kappa opioid receptor |

| | |
|---|---|
| LTP | long-term potentiation |
| MOR | mu opioid receptor |
| mTOR | mammalian target of rapamycin |
| NMDAR | N-methyl-D-aspartate receptor |
| NO/NOS | nitric oxide/nitric oxide synthase |
| NRS | numerical rating scale |
| OIH | opioid induced hyperalgesia |
| OR | odds ratio |
| PAG | periaqueductal grey |
| PCA | patient-controlled analgesia |
| PKA | protein kinase A |
| PKC | protein kinase C |
| PONV | postoperative nausea and vomiting |
| RCT | randomized controlled trial |
| RR | risk ratio |
| RVM | rostral ventromedial medulla |
| SD | standard deviation |
| TLR4 | toll-like receptor 4 |
| TMD | transmembrane domain |
| VAS | visual analogue scale |
| VRS | verbal rating scale |
| WDR | wide dynamic range |

## LIST OF ORIGINAL PUBLICATIONS

I

Brinck ECV, Tiippana E, Heesen M, Bell RF, Straube S, Moore RA, Kontinen VK.
**Perioperative intravenous ketamine for acute postoperative pain in adults.**
Cochrane Database of Systematic Reviews 2018, Issue 12. Art.CD012033.
DOI:10.1002/14651858.CD012033.pub4.

II

Brinck ECV, Maisniemi K, Tielinen L, Kankare J, Tarkkila P, Kontinen VK.
**Analgesic effect of intraoperative intravenous S-ketamine in opioid-naïve patients after major lumbar fu-sion surgery is temporary and not dose-dependent: A randomized, double-blind, placebo-controlled clinical trial.**
Anesthesia & Analgesia 2021;132:69-79.

III

Brinck ECV, Virtanen T, Mäkelä S, Soini V, Olkkola KT, Kontinen V,
Tarkkila P, Peltoniemi M, Saari TI.
**S-ketamine in patient-controlled analgesia reduces opioid consumption in a dose-dependent manner after major lumbar fusion surgery: a randomized, double-blind, placebo-controlled clinical trial.**
PLoS ONE 16(6): e0252626.

# 1.

# INTRODUCTION

Acute postoperative pain continues to be undertreated (Joshi and Kehlet 2017). Insufficient postoperative pain management is associated with cardiovascular, pulmonary, and thromboembolic complications which delay ambulation and rehabilitation, and may lead to readmissions, increased health care costs and impaired quality of life (Joshi and Ogunnaike 2005).

Surgical stimulus activates different pain mechanisms: these include nociceptive, inflammatory, and neuropathic mechanisms. Peripheral and central sensitization further contribute to the development of postoperative pain.

Major spinal surgery, such as lumbar spinal fusion, is increasing in frequency and complexity. It is associated with severe postoperative pain (Gerbershagen 2013), which is not easily amenable to regional anaesthesia but requires a multimodal approach. Multimodal analgesia combines two or more analgesic modalities and targets different pain signalling pathways (Mitra et al. 2018). By utilizing synergistic action, multimodal analgesia aims to maximize pain relief while minimizing opioid-related adverse effects, optimizing recovery, and allowing prompt patient discharge. Multimodal analgesia after spine surgery has also gained prominence (Kurd et al.; Cozowicz et al. 2019). It has been shown to reduce postoperative morphine consumption, improve mobilization (and thereby recovery) with low intensities of PONV, sedation and dizziness (Mathisen et al. 2013).

Pain management after major surgery has traditionally relied on opioid analgesics. However, common side effects following opioid administration are pruritus, nausea and vomiting, constipation, sedation, and respiratory depression. Opioids also impair immune function. Development of opioid tolerance requires dose escalation which induces increased adverse effects. Opioid use may paradoxically cause pain in the form of opioid induced hyperalgesia (OIH) which complicates postoperative pain management. These drawbacks may lead to insufficient analgesia in the postoperative setting.

Additionally, opioid use is associated with the risk of addiction, misuse and abuse. The current 'opioid crisis', a major public health problem in the United States, is in part a consequence of liberal opioid prescribing after surgery (Brummett et al. 2017; Hah et al. 2017; Wu et al. 2019).

Ketamine, owing to its antagonistic action on the NMDA receptor, can reduce wind-up and central sensitization, which are mechanisms behind different pain states. Additionally, ketamine has been shown to prevent the development of opioid tolerance and OIH (Laulin et al. 2002).

Ketamine has been extensively studied for acute postoperative pain management. In spite of the active research interest around ketamine's role as an analgesic adjuvant, effective ketamine doses for this indication are yet to be determined. Reasons for this include the fact that only a few multiple-dose studies have been performed and those studies available are relatively heterogeneous and small, with fewer than 50 participants per treatment arm.

The aim of this doctoral thesis is to assess the efficacy of IV S-ketamine in the prevention and treatment of acute postoperative pain, with the specific objectives of establishing the optimal S-ketamine dose and dose-response relationship, and timing of dosing, and evaluating S-ketamine's tolerability in different dosing regimens.

# 2.

# REVIEW OF THE LITERATURE

## 2.1 POSTOPERATIVE PAIN

The International Association for the Study of Pain (IASP) defines pain as "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (Raja et al. 2020). Pain experience is a defense system aiming to promote organism survival.

Surgery induces peripheral tissue injury. Pain-sensing somatosensory primary afferent neurons (nociceptors) cover the skin, connective tissue, muscle, periosteum, synovium and viscera. These detect intense thermal, chemical or mechanical stimuli and convey painful stimuli to the dorsal horn of the spinal cord, where the central ends of the primary afferent nerve fibres terminate. Peripheral tissue injury induced by surgical trauma provokes modifications in the responsiveness of the nervous system. These changes include peripheral sensitization; a reduction in the threshold of afferent nociceptors, and central sensitization; an activity-dependent increase in the excitability of spinal neurons. These changes lead to pain hypersensitivity in the postoperative period and are contributed to by patient-derived factors, such as prior pain experience, injury, or cultural background.

## 2.2 PAIN PATHWAY AND PAIN MATRIX

Pain after lumbar fusion derives from surgically induced trauma from skin, subcutaneous tissue, muscles and bone due to nerve root decompression and transpedicular screw fixation used to stabilize the spine. At molecular level, the tissue injury results in tissue hypoxaemia, excess of hydrogen ions and acidaemia, and release of inflammatory mediators, nerve growth factor, reactive oxygen species, and lactate ions (Julius and Basbaum 2001; Eisenach and Brennan 2018).

Primary afferent nociceptors, A-delta (Aδ) and C fibres, detect these intense chemical and mechanical stimuli. As a result, sustained spontaneous activity of the primary afferent nociceptors results and transmits signals to dorsal horn (Brennan 2011).

The output of primary afferent nociceptors is processed in the dorsal horn of the spinal cord. Some amplification and modulation occur. Then, through a network of cortical and subcortical areas the signal traverses into the brain, and pain is generated from nociception to a pain

experience (Coghill 1999, Cortelli et al. 2013). Based on this processing, the patient perceives either "normal" postoperative pain that fades during the tissue regeneration or abnormal postoperative pain that exists in a larger area than anticipated, is evoked by even light touch or persists longer than the physiological healing processes.

### 2.2.1 NOCICEPTORS

The main types of sensory fibers in the peripheral nervous system are A-beta (Aβ), Aδ, and C. Of these, Aβ fibers respond to light touch and convey tactile stimuli to the CNS. Aδ fibers have a higher activation threshold and convey information about thermal and mechanical stimuli. C fibers has the highest activation threshold and therefore respond to noxious stimuli. Both Aδ and C fibers are called nociceptors as they respond to nociceptive stimuli, which may be of mechanical, thermal, or chemical origin (D'Mello and Dickenson 2008).

Aδ fibers are further subdivided to Types I and II, according to their ability to respond to mechanical, chemical, and thermal stimuli. C fibers can be classified as peptidergic or nonpeptidergic. Further division of nociceptors can be made according to the differential expression of channels that convey sensitivity to heat (TRPV1), cold (TRPM8), acidic environments (ASICS), and chemical irritants (TRPA1). These heterogeneous classes of nociceptor associate with specific functions in the detection of distinct pain modalities (Basbaum 2009).

Cell bodies of the primary afferent nociceptors lie either in the dorsal root ganglia (DRG) (primary afferent nociceptors from the body) or in the trigeminal ganglion (nucleus caudalis; primary afferent nociceptors from the face) (Bourne 2014).

### 2.2.2 DORSAL HORN OF THE SPINAL CORD

Central projections of the primary afferent nociceptors enter the dorsal horn, which is organized anatomically into distinct laminae (Rexed laminae), extending from superficial layers to the deep dorsal horn (Basbaum et al. 2009; Bourne et al. 2014). Laminae I-II lie most superficially and receive nerve endings from nociceptive Aδ and C fibres (Tracey and Dickenson 2012). Neurons in laminae III and IV primarily receive non-noxious stimuli (via Aβ afferents) (D'Mello and Dickenson 2008). ***Figure 1*** presents the laminar structure of the dorsal horn.

Neurons in lamina V receive both noxious and non-noxious input directly from Aδ and Aβ fibres, and as well as indirect C fibre inputs. These are called wide dynamic range (WDR) neurons (Suzuki and Dickenson 2005; D'Mello and Dickenson 2008, Bourne et al. 2014). WDR neurons receive input from all types of sensory fibres and respond to various stimulus intensities (D'Mello and Dickenson 2008). WDR

neurons convey action potentials forward depending on the intensity of the incoming stimulus and have a central role in amplification of the pain transmission (D'Mello and Dickenson 2008).

Noxious stimuli are actively processed in the dorsal horn before they ascend to the brain.

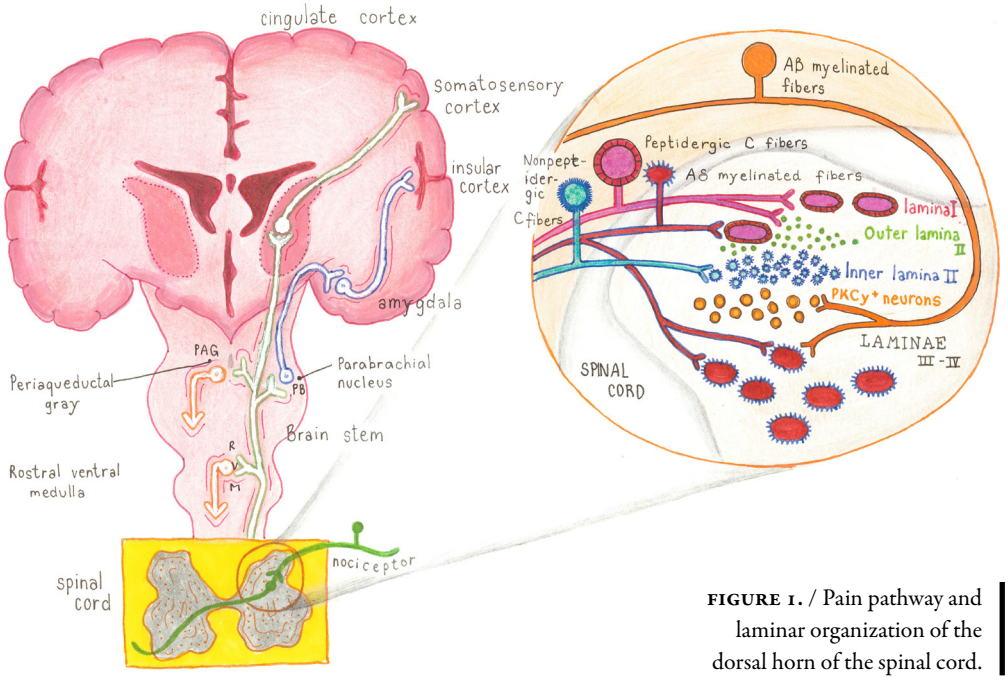



**FIGURE 1.** / Pain pathway and laminar organization of the dorsal horn of the spinal cord.

### 2.2.3 N-METHYL-D-ASPARTATE (NMDA) RECEPTORS

***Figure 2*** shows the modular architecture of an N-Methyl-D-Aspartate (NMDA) receptor. The NMDA receptor (NMDAR) is an ion channel that is activated by the CNS's primary excitatory neurotransmitter, glutamate. NMDARs are important mediators of several forms of neural and behavioural plasticity, neuronal development, learning and memory, and are involved in several neurological and psychiatric conditions (Cull-Candy et al. 2001; Larsson and Broman 2011; Ogden and Traynelis 2011; Trujillo 2000; Traynelis et al. 2010). The NMDAR is a fundamental initiator of central sensitization (Woolf and Thompson 1991). NMDARs are abundant in the brainstem, basal ganglia, cerebellum, hippocampus, and temporal cortex (Benarroch 2011).

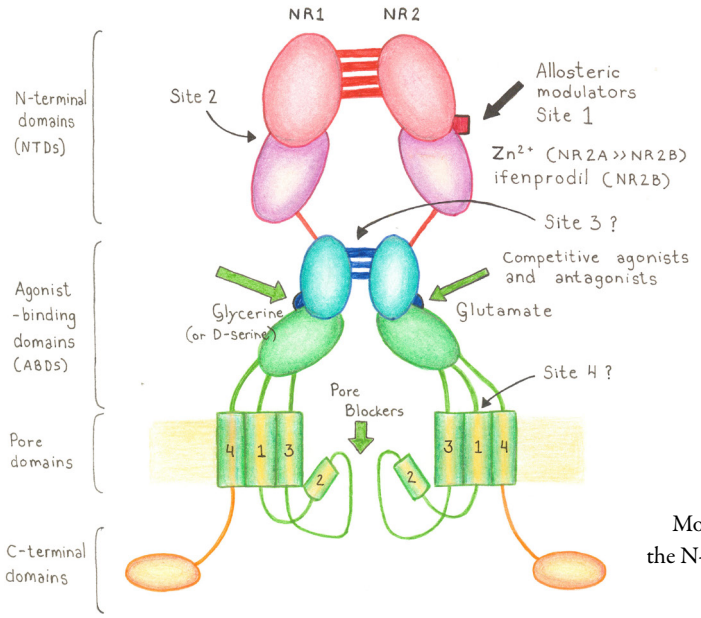



**FIGURE 2.** / Modular architecture of the N-Methyl-D-Aspartate (NMDA) receptor.

## The NMDA receptor – a heterotetramer complex

The NMDAR is a heterotetramer composed of four subunits (Paoletti 2011). Three different subunits have been identified; GluN1, GluN2 and GluN3. These are further divided into subtypes: a GluN1 subunit, four different GluN2 subunits (GluN2A, 2B, 2C and 2D) and two different GluN3 subunits (GluN3A and GluN3B) (Hansen et al. 2018; Paoletti 2011). Different combinations of subunits result in many different NMDAR subtypes coexisting in the CNS (Paoletti and Neyton 2007; Traynelis et al. 2010; Paoletti et al. 2013).

All NMDAR subtypes are thought to comprise two GluN1 subunits, which are "obligatory", and two copies of GluN2A-D and/or GluN3A-B subunits (Sanz-Clemente et al. 2013; Hansen et al. 2018). The potential structure of an NMDAR is di-heteromeric (2•GluN1+2•GluN2A/B/C/D) or tri-heteromeric (2•GluN1+GluN2A/B/C/D+GluN3A/B) (Vieira et al. 2020).

The various subtypes affect the NMDAR's pharmacological, biophysical and signalling properties (Paoletti et al. 2013). For instance, NMDAR subunit composition influences the receptor's Mg2+ blockade and Ca2+ permeability, thus affecting its role in synaptic integration and plasticity. The four distinct GluN2 subunits (GluN2A-D) are major determinants of functional heterogeneity of an NMDAR (Kreutzwiser and Tawfic 2019; Paoletti et al. 2013; Zhu et al. 2016). For example, NMDARs containing GluN2A subunits have a higher open state probability and a

faster deactivation time than GluN2B-containing ones (Sanz-Clemente et al. 2013). NMDAR subunit composition is not constant but changes according to neuronal activity and during development (Paoletti et al. 2013). For example, GluN2B and GluN2D subunits predominate in the neonate brain but are later replaced by GluN2A and GluN2C subunits (Cull-Candy et al. 2001). GluN1 subunit is associated with the crosstalk occurring between μ opioid receptors (MOR) and NMDARs in the development of opioid tolerance (Garzón et al. 2012).

**Modular architecture of the NMDA receptor**

The NMDAR has a modular architecture consisting of four different domains (Fig. 2): a clamshell-like extracellular domain comprising the amino-terminal (ATD); the agonist-binding domain (ABD); a transmembrane domain (TMD); and an intracellular carboxyl-terminal domain (CTD) (Zhu et al. 2016; Hansen et al. 2018). The four subunits are noncovalently bound to each other and form a central ion channel pore (Kreutzwiser and Tawfic 2019). The ATD has modulatory properties and can bind zinc (in the case of GluN2A subunit) (Hansen et al. 2018). It can be either open or shut: the shut conformation inhibits the receptor's function. The ABD binds glutamate (subunits GluN2A-D) and glycine or serine (subunits GluN1 or GluN3A-B). The TMD forms an ion pore through the cell membrane. The CTD is responsible for receptor trafficking, anchoring, and coupling to signalling molecules (discussed below) (Burnell et. al. 2019; Zhu et al. 2016).

**Characteristics of the NMDA receptor;**
**glutamate, co-ligands, calcium and magnesium**

In the resting state, the NMDAR is blocked by a Mg2+ ion sitting in the transmembrane pore (Petrenko et al. 2003; Vieira et al. 2020). NMDAR activation requires the simultaneous binding of two distinct agonists: glutamate and glycine or serine. A membrane depolarization is required to dislodge the Mg2+ ions from the channel pore. Once a depolarization of sufficient amplitude and duration occurs, the ion channel pore is opened, allowing Ca2+ influx to the cell (Kreutzwiser and Tawfic 2019; Paoletti et al. 2013).

Increased intracellular Ca2+ in a postsynaptic neuron initiates signalling events specific to NMDARs. These intracellular events include Ca2+ binding to calmodulin (CaM) which activates several proteins, including kinases (e.g. protein kinase C (PKC)), phosphatases, and neuronal nitric oxide synthase (nNOS). The increase in intracellular Ca2+ eventually leads to changes in the postsynaptic neuron, and either short- or long-term changes in synaptic strength.

### 2.2.4 GLUTAMATE

Glutamate is the major excitatory neurotransmitter in the mammalian CNS and is essential for pain signalling at every anatomical level throughout the CNS. Glutamate content is approximately 5-15 mmol/kg in brain tissue, the concentration varying depending on the cell type and location in the CNS (Rae 2014). The highest concentrations are found in synaptic vesicles in nerve terminals whence it can be released by exocytosis into the synaptic cleft. There are no extracellular enzymes that degrade glutamate: instead, extracellular glutamate concentration is controlled by cellular uptake proteins expressed at the cell surface of glia and neurons, as well as by a cystine/glutamate antiporter (Zhou and Danbolt 2014; Rae 2014). There are four major subtypes of glutamate receptor: NMDAR; α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPAR); kainate; and metabotropic receptors (mGluR) (Rae 2014). GluN2 subunits in an NMDAR bear the binding site for glutamate, with subunit GluN2B expressing higher affinity for glutamate than does subunit GluN2A (Sanz-Clemente et al. 2013).

Glutamate action on synaptic NMDARs triggers a cascade of intracellular processes that promote cell survival. In the normal brain, increased glutamate levels are related to increased metabolic activity (Rae 2014). Excessive glutamate levels are neurotoxic, as the entry of Ca2+ through extrasynaptic NMDARs leads to mitochondrial dysfunction and apoptosis (Sanz-Clemente et al. 2013).

### 2.2.5 ASCENDING PAIN PATHWAYS

Projection neurons in laminae I, II and V constitute the major output from the dorsal horn to the brain. The neurons cross to the opposite anterolateral part of the spinal cord, forming the spinothalamic tract, which ascends to the thalamus. Spinothalamic tract is the key pathway for pain (Suzuki and Dickenson 2005, Bourne et al. 2014). A subset of the projection neurons traverses to the hypothalamus and transmits information about the location and intensity of the stimulus to supraspinal structures (Bourne et al. 2014; Ong et al. 2019).

Spinomesencephalic tract originates in laminae I and IV-VI and descends to periaqueductal grey (PAG), pretectal nucleus, red nucleus (nucleus ruber), Edinger-Westphal nucleus, and interstitial nucleus of Cajal (Tracey and Dickenson 2012; Bourne et al. 2014). Projection neurons connect in the parabrachial nucleus in the brain stem and transmit information to cingulate and insular cortices and to the amygdala, contributing to the affective component of the pain experience (Suzuki and Dickenson 2008, Xiao and Zhang 2018).

The spinoreticular tract carries nociceptive information from dorsal horn to reticular formation of pedulla and pons and is relevant to poorly localized pain (Basbaum et al. 2009; Tracey and Dickenson 2012).

Further, the ascending pathway accesses neurons of the rostral ventromedial medulla (RVM) and PAG in the midbrain (Fig. 1), activating descending inhibitory or facilitatory feedback systems that regulate the ascending output from the spinal cord (Basbaum 2009; Bourne 2014; Feizerfan 2015).

### 2.2.6 SUPRASPINAL MECHANISMS OF PAIN PERCEPTION

The requisite of pain-sensing ability to detect tissue injury has emerged from studies showing that processing of pain is distributed across multiple, functionally distinct areas within the human brain (Coghill et al. 1999). This ensures the ability to detect injury even in the face of extensive CNS damage.

Supraspinal structures involved in the representation and modulation of the acute pain experience include the primary and secondary somatosensory cortices, anterior cingulate cortex (ACC), insular cortex (IC) and amygdala in the limbic system, prefrontal cortex, orbitofrontal cortex, cerebellum and thalamus (Boadas-Vaello et al. 2017; Bourne et al. 2014; Ong et al. 2019; Vania Apkarian et al. 2005). Brainstem nuclei related with pain processing include PAG, locus coeruleus, RVM, and red nucleus (nucleus ruber). These areas are highly interconnected and have multiple processing roles (Coghill et al. 1999).

Pain experience comprises intensity processing, cognitive evaluation of the painful stimulus, attention, motor control, autonomic response, and affect (Coghill et al. 1999; Cortelli et al. 2013). ***Figure 3*** illustrates how emotions, previous experiences and expectations about pain among many other psychological factors affect to the pain experience.

Intensity processing is distributed across multiple regions and the structures identified as involved in this include cerebellum, insula, anterior somatosensory cortex, ACC, putamen, and thalamus, which all activate bilaterally to painful stimuli. The primary somatosensory cortex and supplementary motor areas activate contralaterally. Activation of the ventral premotor area occurs ipsilaterally after pain-inducing stimuli (Coghill 1999). The number of activated structures corresponds to the magnitude of the intensity of the stimulus (Price 2000).

Inputs from several nociceptive pathways to primary and secondary somatosensory cortices and to the mid-cingulate cortex associate with perceptual, discriminative and cognitive aspects of pain (Price 2000; Tolomeo et al. 2016; Vania Apkarian et al. 2005).

Pain-induced activity in the prefrontal cortex relates to memory and evaluation of painful stimuli (Vania Apkarian et al. 2005). The orbitofrontal cortex contributes to decision-making about pain (Winston et al. 2014). Impaired spatial working memory due to reduced connectivity of the prefrontal cortex and mediodorsal thalamus has been associated with inflammatory pain (Boadas-Vaello et al. 2017).

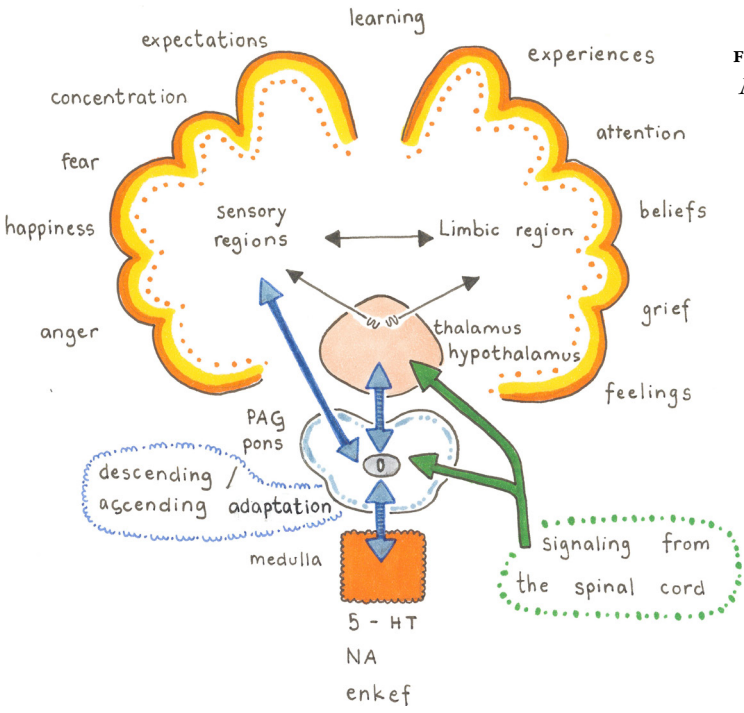



**FIGURE 3.** / Pain experience. *Modified from an illustration by Vesa Kontinen*

Attentional processing of painful stimuli take place in the ACC, primary somatosensory cortex and ventral premotor cortex. Cerebellum, putamen/globus pallidus, supplementary motor and ventral premotor cortices and ACC are engaged in the motor control of pain (Coghill et al. 1999).

Brain regions related to the affective and emotional dimensions of pain, such as pain-related anxiety, include the ACC, IC and amygdala (Bliss et al. 2016; Coghill 1999; Cortelli et al. 2013; Zhou et al. 2018). The posterior part of the IC associates with sensory aspects and the anterior part participates in emotional aspects of pain experience (Vania Apkarian et al. 2005). Neuroplastic changes in the amygdala associate with pain-related cognitive deficits (Ren and Neugebauer 2010; Thompson and Neugebauer 2017). Pain-induced unpleasantness probably relates to ACC-prefrontal cortical interactions (Price 2000) and pain-induced anxiety is linked to increased activity of cells in the locus coeruleus (Boadas-Vaello et al. 2017).

The autonomic system interacts with the nociceptive system at each level in the nociceptive pathway. Spinothalamic neurons in the dorsal horn and neurons of the nucleus tractus solitarius and parabrachial nuclei project to pons and medulla, PAG, hypothalamus, IC, ACC and amygdala. These areas are involved in autonomic responses following noxious stimuli (Benarroch 2006, Cortelli et al. 2013).

The PAG receives afferent input from the peripheral and central nervous systems. The lateral and dorsolateral PAG initiate sympathoexcitatory responses (hypertension, tachycardia), and the ventrolateral PAG induces sympathoinhibitory responses (hypotension, bradycardia), after a noxious stimulus. The PAG exerts both inhibitory and excitatory control on nociceptive transmission in the dorsal horn of the spinal cord and trigeminal nucleus (Cortelli et al. 2013).

The RVM is considered the relay station where inhibitory or facilitatory modulation of pain occurs via activation of ON and OFF cells (Bannister and Dickenson 2017; Cortelli 2013).

### 2.2.7 DESCENDING PAIN PATHWAYS

The descending inhibitory or facilitatory control pathways modulate spinal nociceptive outputs and serve as an endogenous analgesic system (Lau and Vaughan 2014). These descending pathways comprise outputs from PAG, RVM, locus coeruleus, amygdala, and ACC (Basbaum and Fields 1984; Bourne et al. 2014; Lau and Vaughan 2014). The RVM is considered the relay station where inhibitory or facilitatory modulation occurs: here there are specific neurons, ON, OFF, and neutral cells. Neuronal discharges from ON cells have a facilitatory effect on ascending nociceptive output: inhibition of these by opioids promotes nociception (Cortelli et al. 2013). Discharges from OFF cells or neutral cells have an inhibitory effect or no effect at all, respectively. Activation of OFF cells by opioids inhibits nociception (Cortelli et al. 2013)

Descending noradrenergic actions mediate inhibitory effects, while serotonergic action can be either facilitatory (through 5-HT2 and 5-HT3 receptors) or inhibitory (5-HT7). Additionally, GABAergic and opioidergic actions are present in the descending inhibitory or facilitatory pathways (Bannister and Dickenson 2016; Bannister and Dickenson 2017; Bannister 2019).

### 2.2.8 SPINAL MECHANISMS OF PAIN MODULATION

#### 2.2.8.1 Wind-up

Noxious stimuli are actively processed in the dorsal horn of the spinal cord. Repetitive stimulation of WDR neurons in lamina V by primary afferent

nerve fibres (C fibres) in the dorsal horn causes an amplification of their response and increased post-discharges with each stimulus. This short-lasting form of synaptic plasticity is termed wind-up. This is an intrinsic mechanism that causes hyper-excitability to constant noxious stimuli and enhances afferent inputs (Suzuki and Dickenson 2005). Wind-up is dependent on the activation of the NMDARs (Suzuki and Dickenson 2005). The constant stimulation of WDR neurons by primary afferent nerve fibres activates NMDAR by removing the Mg2+ plug from the ion channel. Once this is opened, co-release of glutamate, Substance P and CGRP (calcitonin-gene related peptide) results in a prolonged depolarization of the cell membrane, thus inducing wind-up (D'Mello and Dickenson 2008). The duration of wind-up is short, lasting a few seconds and it can be reduced and abolished by competitive and non-competitive NMDAR antagonists, such as ketamine, both in vivo and in vitro (Dickenson 1990).

#### 2.2.8.2 Long-term potentiation

Another cellular mechanism of synaptic plasticity is long-term potentiation (LTP). LTP at synapses in hippocampus has been regarded as the principal model for learning and memory whereas LTP in pain pathways contributes to hyperalgesia (Bliss and Collingridge 1993; Sandkühler 2007). LTP in nociceptive pathways has been identified at the synapses between primary afferent C fibres and neurons in the superficial layer of the dorsal horn in the spinal cord.

LTP is defined as an increase in synaptic strength (Sandkühler 2007; Ruscheweyh et al. 2011). It can be induced by strong stimulation (noxious heat and pinching), and application of formalin and capsaicin or certain pharmacological agents (such as Substance P and Neurokinin A). Abrupt withdrawal of opioids can also evoke LTP at synapses between C fibres and dorsal horn neurons (Ruscheweyh et al. 2011). LTP results in increased postsynaptic current in response to a presynaptic action potential, leading to enhanced signal transduction.

Different from wind-up, which is a short-lasting form of synaptic plasticity, LTP may last between hours and several days (Ruscheweyh et al. 2011). In human volunteers, induced LTP causing hyperalgesia has been found to last for one day. (Klein et al. 2006). This duration represents the contributing role of LTP to hyperalgesia and secondary hyperalgesia following strong noxious stimulation, which are features of pain amplification in acute postoperative pain.

There are several elements required for LTP induction, one of which being NMDAR activation (Li et al. 2019). A common feature is a rise in postsynaptic Ca2+ concentration. Activation of metabotropic glutamate receptors and Neurokinin 1 receptors release Ca2+ from intracellular stores, and opening of T-type calcium channels, Ca2+-permeable AMPARs and postsynaptic NMDARs results in a rise in postsynaptic Ca2+ concentration. Activated glial cells also contribute to the induction of LTP, possibly via the NO pathway (Ruscheweyh et al. 2011). The rise in intracellular Ca2+ concentration will lead to activation of calcium-dependent signalling pathways and eventually enhanced signal transduction (Sandkühler and Gruber-Schoffnegger 2012). Ketamine, by blocking NMDARs, has been shown to inhibit the induction of LTP, both in vivo and in vitro (Drdla and Sandkühler 2008; Ruscheweyh et al. 2011).

#### 2.2.8.3 Central sensitization

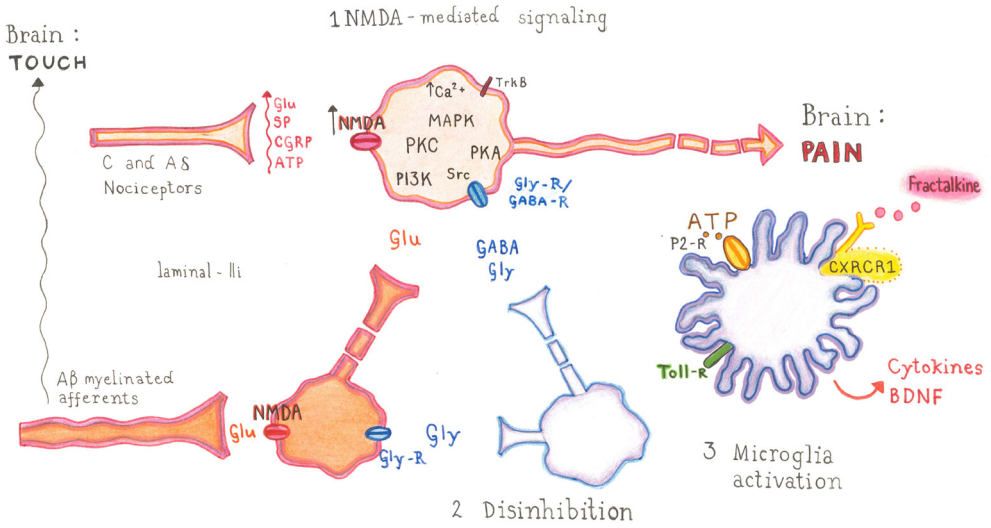
Central sensitization is defined as an increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input. This heightened synaptic transmission results in a reduction in pain threshold, an amplification of pain response and a spread of pain sensitivity to uninjured areas (Woolf 2014; Ji et al. 2003).

Central sensitization represents an enhancement in the function of neurons and circuits in nociceptive pathways caused by increased membrane excitability and synaptic efficacy as well as to reduced inhibition. It manifests that the somatosensory nervous system adapts in response to activity, inflammation and neural injury. It is recognized that in addition to occurring in the dorsal horn of the spinal cord, other CNS structures associated with pain (such as spinal nucleus pars caudalis, parabrachial nucleus, PAG, thalamus, superior colliculus, amygdala, ACC, and prefrontal cortex) also exhibit changes compatible with increases in excitability (Latremoliere and Woolf 2009).

For central sensitization to be generated, the noxious stimulus must exceed certain level of intensity, be repeated and sustained (Latremoliere and Woolf 2009). Additionally, input from several nociceptive afferent fibres is required. The repetitive input from C fibres and Aδ fibres lasts seconds and leads to a summation of potentials. This generates an increased and long-lasting depolarization in dorsal horn neurons that lasts for minutes.

The main mechanisms behind central sensitization include NMDA receptor -mediated hypersensitivity, loss of inhibition and microglia activation (Basbaum et al. 2009). These are summarized in ***Figure 4***.

**FIGURE 4.** / Enhanced NMDA-mediated signaling (1) is the first step in the development of central sensitization. Inhibitory interneurons normally control the excitability of lamina I neurons via release of GABA and glycine. (2) The inhibitory control is lost under excessive NMDA receptor activation, such as in case of injury. (3) Nerve injury activates microglial cells. Activated microglia releases cytokines that further contribute to central sensitization. *Modified from Basbaum et al. Cellular and molecular mechanisms of pain. Cell 2009; 139:267-284.*




The early phase of central sensitization is characterized by high levels of nociceptor input and a resulting excessive transmitter release. This activates multiple receptors expressed on the dorsal horn neurons and downstream activation of intracellular kinases leading to alteration of receptor function (Basbaum et al. 2009).

The delayed phase of central sensitization involves changes in gene transcription in dorsal horn neurons and reduction in the action of inhibitory transmitters and inhibitory interneurons, resulting in disinhibition (=loss of inhibition) (Basbaum et al 2009). These changes are responsible for the long-lasting strengthening of the synapse (Latremoliere and Woolf 2009).

#### 2.2.8.3.1 Molecular mechanisms responsible for central sensitization

Molecular mechanisms and intracellular pathways that are responsible for central sensitization are complex. Central sensitization is initiated by excessive release of glutamate, an excitatory amino-acid. Glutamate binds to several receptors on postsynaptic membrane; N-methyl-D-aspartate (NMDAR), amino-3-hydroxy-5-methyl-isoxazole propionate (AMPAR)

and kainate receptors as well as several metabotropic glutamate receptor subtypes.

Activation of NMDARs in the superficial laminae of the dorsal horn is a prominent step in the induction of central sensitization (Suzuki and Dickenson 2005; D'Mello and Dickenson 2008). Binding of glutamate to the NMDAR results in calcium (Ca2+) influx into the neuron, as well as release of Ca2+ from the endoplasmic reticulum. The resulting increase in intracellular Ca2+ initiates phosphorylation of several kinases (such as PKC, PKA, extracellular regulatory kinases 1 and 2 (ERK)) (Kawasaki et al. 2004).

These kinases change the activity of NMDARs (and AMPARs) trafficking to or from the synaptic membrane. These include an increase of NMDAR function through phosphorylation of its GluNR1 subunit and enhanced NMDAR activity by increasing its response to glutamate. Phosphorylation of GluNR2B subunit of the NMDAR increases the opening of the ion channel and prevents endocytosis of activated receptors. PKC reduces Mg2+ block of the NMDAR, thus increasing the probability of channel opening and facilitating the activated state of the receptor.

ERK produces a decrease in K+ currents, leading to an increase in synaptic membrane excitability.

In addition to glutamate, several other transmitters are involved in the generation of central sensitization. These include Substance P, which causes a long-lasting membrane depolarization and contributes to the temporal summation of synaptic potentials caused by C fibre stimulation. CGRP potentiates effects of Substance P and activates PKA and PKC. CGRP also enhances release of brain-derived neurotrophic factor (BDNF), which activates NMDA-receptor mediated C-fibre evoked responses and further activates PKC and ERK several signalling pathways in spinothalamic track neurons. PKC, PKA and ERK are also activated by bradykinin.

Further, PKC decreases descending inhibition from the PAG. NMDAR-mediated processes may also suppress endocannabinoid-mediated synaptic inhibition (Yan and Burrel

2019). Additionally, microglia effects central sensitization via microglial mediators. Primary afferent nociceptor activation leads to release of inflammatory cytokines such as TNF and IL-1ß from microglia. TNF causes subsequent glutamate release and further ERK phosphorylation and activation. This drives central sensitization further via positive regulation of NMDAR and AMPAR (Chen et al. 2018).

Loss of inhibition (= disinhibition) leaves dorsal horn neurons more susceptible to activation. As a result, phosphorylation of NMDARs (and AMPARs) results in increases in activity and density of these receptors, and disinhibition lead to postsynaptic hyperexcitability, the key feature of central sensitization (Woolf and Chong 1993; Latremoliere and Woolf 2009; South et al. 2003; Kawasaki et al. 2004). The net result is a self-feeding cycle where reactions are uncoupled from the initial painful event and central sensitization is capable to generate pain itself.

#### 2.2.8.3.2 Clinical manifestations of central sensitization

Clinical manifestations include increase in the response to noxious stimuli (hyperalgesia) and a decrease in the pain threshold, both at the site of injury (allodynia) and in the adjacent, uninjured tissue (secondary hyperalgesia). ***Figure 5*** illustrates central sensitization, where even a light touch, here a feather, can evoke pain. Nociceptor afferents arising from muscles and joints have a longer lasting action in producing central sensitization than those arising from the skin (Woolf 2011). It could be assumed that major surgery with more tissue injury induces more central sensitization compared with surgery with minimal tissue trauma.

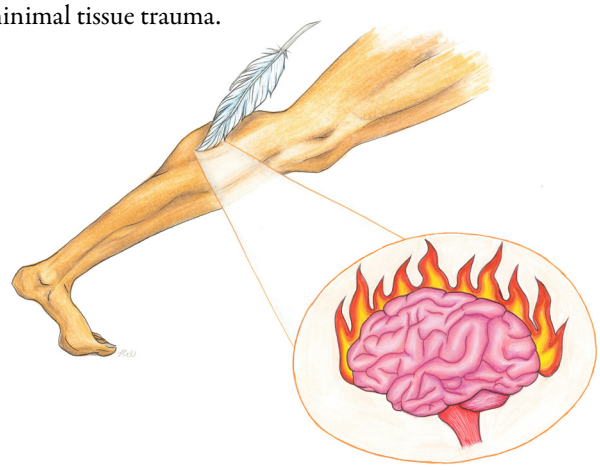


**FIGURE 5.** / Illustration of central sensitization. A light touch can evoke pain.

Central sensitization contributes to several clinical conditions characterized by persistent pain. These include fibromyalgia, rheumatoid arthritis, osteoarthritis, temporomandibular disorders, neuropathic pain, miscellaneous musculoskeletal disorders (e.g. pain associated with whiplash) and complex regional pain syndrome (CRPS) (Arendt-Nielsen 2015; Woolf 2011).

The size of secondary hyperalgesia around the surgical wound has been shown to have an effect on long-term pain; extent of wound hyperalgesia corresponded to an increased risk of chronic pain at 3, 6 and 9 months postoperatively (Salengros et al. 2010). Central sensitization is involved in acute postoperative pain that derives from both tissue injury from incisional pain and surgically induced neuropathic pain.

## 2.3 IMPORTANCE OF ADEQUATE ANALGESIA AFTER SURGERY

Inadequately treated pain after surgery increases stress response in the organism and activates the autonomic nervous system. These changes associate with changes in endocrine, metabolic and inflammatory responses (Joshi and Ogunnaike 2005). Consequences include cardiovascular, pulmonary, and thromboembolic complications. Additionally, impaired immune function increases susceptibility to postoperative infections (Joshi and Ogunnaike 2005). Wound healing may be compromised (Akca et al. 1999). These will lead to increased morbidity, delayed ambulation and recovery time, delayed rehabilitation as well as unplanned readmissions. For instance, poorly managed postoperative pain is the second most common reason for readmission after lumbar spine surgery in the US (Kurd et al. 2017). Further, suboptimal postoperative analgesia decreases patient satisfaction and is a risk factor for chronic postoperative pain. Sequelae include impaired quality of life and increased health-care costs. Despite of the well-known consequences of inadequate postoperative pain relief, acute postoperative pain continues to be undertreated (Apfelbaum et al. 2003; Breivik and Stubhaug 2008; Fletcher et al. 2008; Joshi and Kehlet 2017; Maier et al. 2010; Mathiesen et al. 2012; White and Kehlet 2010).

Several surgical, environmental, and patient-related preoperative risk factors for acute postoperative pain have been identified (Andersen and Kehlet 2011; Caumo et al. 2002; Haroutiunian et al. 2013; Ip et al. 2009; Kambur et al. 2018; Kaunisto et al. 2013; Kehlet et al. 2006; Mancuso et al. 2017; Papaioannou et al. 2009; Kambur et al. 2018; Rawal 2016; Sipilä et al. 2017). These are summarized in Table 1.

TABLE 1. / Predictors of acute postoperative pain.

| PATIENT DERIVED RISK FACTORS | SURGERY INDUCED RISK FACTORS |
|---|---|
| Psychological risk factors<br>• anxiety<br>• preoperative depressive symptoms | Type of surgery:<br>• orthopedic surgery<br>• thoracic surgery |
| Chronic opioid use | Surgical technique:<br>• nerve injury<br>• tissue ischemia |
| Impaired pain modulation | Postoperative period:<br>• repeat surgery |
| Genetic variations | |
| Sleep disorders | |
| ASA III | |
| Moderate to severe pain prior to surgery | |

ASA: American Society of Anesthesiologists

There are several pharmacologic compounds to utilize for postoperative pain management. These can include pharmacologic agents that target the processes responsible for induction of central sensitization, such as ketamine, an N-methyl-D-aspartate receptor antagonist.

## 2.4 KETAMINE

### 2.4.1 HISTORY: FROM PHENCYCLIDINE TO CI-581

Extensive studies on safety and toxicology of phencyclidine (1-(1-phenylcyclohexyl) piperidine HCl), in 1956 ended up in a development of a unique series of phencyclidine derivatives. Preclinical pharmacological testing in animals showed that one of the compounds, given the clinical investigation number CI-581, produced

excellent and short-acting anaesthesia. It was named ketamine as the molecular structure consisted of a ketone together with an amine (Domino 2010). The first human was given ketamine on August 3, 1964 (Domino 2010). Pharmacologic actions of ketamine were first published in 1965 (Domino et al. 1965). The report concluded that ketamine was an effective analgesic and anaesthetic agent in IV doses of 1-2 mg/kg, with an onset of action within 1 minute and duration of action 5-10 minutes. Undesirable effects included hypertension and tachycardia but minimal emergence delirium (Domino et al. 1965). Their special note was that the anaesthesia ketamine induced was unusual: study participants seemed to be disconnected from the environment. Ketamine was therefore termed a "dissociative anaesthetic" (Domino 2010). The chemical structure of ketamine is shown in ***Figure 6***.

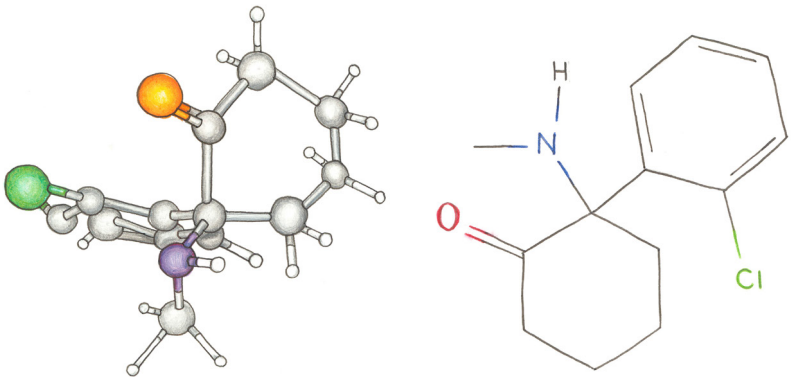



**FIGURE 6.** / Chemical structure of R-, S-ketamine.

### 2.4.2 PHYSICOCHEMICAL CHARACTERISTICS OF KETAMINE

Ketamine has a chiral structure, consisting of two optical S(+)- and R(-)-enantiomers with an asymmetric carbon atom in the C2 position. The racemic mixture contains two enantiomers in equal quantity. The S(+)-enantiomer is twice as potent as the racemic mixture, and four times as potent as the R(-)-enantiomer (Peltoniemi et al. 2016).

Ketamine molecule is lipid-soluble with a dissociation constant (pKa) 7.5 and a melting point of 260°C (Mion and Villevieille 2013; Peltoniemi et al. 2016).

### 2.4.3 KETAMINE PHARMACOKINETICS

After IV administration, ketamine is distributed into highly perfused tissues including the central nervous system. Ketamine binds to plasma proteins with low affinity (10-30%) The alpha half-life is short, 2-4 minutes but ß half-life is longer being 2-4 hours.

Steady-state volume of distribution is large, 160-550 L/70 kg. Systemic clearance is 60-147 L/h/70kg, equalling the liver blood flow (Peltoniemi et al. 2016).

R (+)-enantiomer inhibits the clearance of S-enantiomer, which is shown as higher systemic clearance (26.3 +/- 3.5 ml/kg/min) of S-ketamine when administered alone than in the racemate. (Peltoniemi et al. 2016; Zanos 2018). Ketamine clearance is approximately 20% higher in women. (Sigtermans et al. 2009).

The elimination half-life of S-ketamine is longer than that of the racemate, being approximately 5 hours (Peltoniemi 2012). Repeated administration may prolong ketamine's elimination time (Zanos et al. 2018).

### 2.4.4 KETAMINE METABOLISM

Ketamine undergoes oxidative metabolism in the liver where ketamine is N-methylated primarily via cytochrome (CYP) P450 enzymes CYP3A4 and less via CYP2B6 and CYP2C9 hepatic cytochromes. There exists stereoselectivity in the demethylation of ketamine. CYP3A4 demethylates the S(-)-enantiomer more rapidly than the R(+)-enantiomer. This explains the higher clearance of S(-)-ketamine compared to R(+)-enantiomer discussed above (Mion and Villevieille 2013).

CYP2B6 demethylates both enantiomers of ketamine equally (Zanos et al. 2018).

Polymorphism of P450 enzymes may cause interindividual variability in ketamine metabolism (Zanos et al. 2018).

Ketamine is metabolized mainly to norketamine and further to hydroxynorketamine and dehydronorketamine (Mion and Villevieille 2013; Peltoniemi et al. 2016).

Norketamine analgesic properties have been reported to be 20-30% when compared with ketamine (Mion and Villevieille 2013) yet some studies have found the opposite effect (Olofsen et al. 2012).

A lesser extent, approximately 5% of ketamine is directly transformed into hydroxy-ketamine (4-hydroxy-ketamine and to 6-hydroxy-ketamine). This metabolism involves the kidneys, the intestine and the lungs (Mion and Villevieille 2013). Ketamine metabolites are excreted in bile and urine after glucuronidation.

CYP3A, CYP2B6 and CYP2C9 enzyme inhibitors clarithromycin, grapefruit juice and ticlopidine decrease ketamine metabolism and thus increase ketamine plasma concentrations. CYP3A4 inducers rifampicin and St. John's wort have a contrary action as they enhance ketamine metabolism and reduce plasma concentrations after oral and IV S-ketamine administration (Peltoniemi et al. 2016).

Ketamine's oral bioavailability is limited to 8-11% for S-ketamine and to 16-29% for the racemate due to the extensive hepatic first-pass metabolism (Peltoniemi et al. 2012; Zanos et al. 2018). Oral bioavailability of ketamine is increased in conditions with decreased hepatic blood flow, such as in the elderly or in patients with hepatic cirrhosis (Fanta et al. 2015).

### 2.4.5 KETAMINE PHARMACODYNAMICS

#### 2.4.5.1 N-methyl-d-aspartate receptor antagonism

NMDAR antagonism is considered as the main mechanism of action behind ketamine's anaesthestic, analgesic, amnesic, antidepressant and neuroprotective properties (Mio and Villeivieille 2013; Zanos et al. 2018). This mechanism of action on N-methyl-D-aspartate receptors was discovered as it was shown that ketamine causes a selective depression of cat polysynaptic reflexes by antagonizing N-methyl-D-aspartate (NMDA) receptors (Anis et al. 1983).

Binding of an NMDAR antagonist inhibits the channel opening. This can be achieved by occluding the ion channel pore or by attaching to the amino- (N-) terminal domain (ATD) (Paoletti and Neyton 2007). Ketamine is a non-competitive antagonist of the NMDAR. Ketamine's action requires prior activation of the receptor i.e. pore opening. Ketamine is capable to inhibit the function of NMDARs in three different ways (Kreutzwiser and Tawfic 2019):

1. Once the ion channel is opened, ketamine binds to an intra-channel site of the NMDAR and decreases the channel opening time for calcium.

2. Ketamine also binds at a second site located in the hydrophobic domain of the NMDAR and thus decreasing the frequency of channel opening.

3. Ketamine acts as an allosteric antagonist of the NMDAR.

Compounds that block the ion channel pore of an NMDAR usually discriminate poorly between different subtypes. For ketamine, there is approximately equal selectivity towards the different subtypes (NR2A~2B~2C~2D) (Paoletti and Neyton 2007). The lack of selectivity translates to the fact that ketamine does not discriminate but acts on various NMDAR subtypes.

#### 2.4.5.2 Other mechanisms of action

In addition to NMDAR activity, ketamine interacts with many other receptors and ion channels (Mion and Villevieille 2013; Sleigh et al. 2014; Zorumski et al. 2016). These include mu, delta, and kappa opioid receptor agonisms, which potentiate opioid analgesia (Hirota and Lambert 2011).

Activation of the monoaminergic system by ketamine-induced stimulation of the norepinephrinergic neurons, release of norepinephrine, dopamine and serotonin, and inhibition of catecholamine uptake. Further, inhibition of cholinergic receptors is postulated to underlie the psychic phenomena caused by ketamine (Mion and Villevieille 2013).

Inhibition of HCN1 channels in the forebrain contributes to the hypnotic actions of ketamine (Benarroch 2013; Chen et al. 2009; Zhou et al. 2013).

Ketamine has local anesthetic properties by interacting with Na+-channels. Inhibition of spinal GABA receptors by ketamine plays a role in spinal analgesia (Mion and Villevieille 2013). Activation of BK channels by ketamine in microglia produces an analgesic effect on neuropathic pain (Hayashi et al. 2011). Activation of nitric oxide-cyclic guanosine monophosphate (NO-cGMP) pathway at supraspinal level also contributes to the analgesic effect of ketamine (Bulutcu et al. 2002).

Ketamine inhibits inducible nitric oxide synthase (iNOS), generating anti-inflammatory effects (Li et al. 1997).

Inhibition of L-type Ca2+-channel underlies the airway smooth muscle cell relaxant effect (Yamakage et al. 1995).

Ketamine induces dysregulation of purinergic neurotransmission, postulated to account for its toxic effects on the urinary tract (Bell 2012; Mion and Villevieille 2013).

## 2.5 INTRAVENOUS ADMINISTRATION OF KETAMINE FOR ANAESTHESIA

Ketamine induces anaesthesia with doses of 1-2 mg/kg administered intravenously or S-ketamine 0.5-1mg/kg IV (Zanos et al. 2018). Anaesthesia is maintained with a continuous infusion of racemic ketamine 1-6mg/kg/h or with 0.5-3mg/kg/h of S-ketamine (Peltoniemi et al 2016). As previously described, the S(+)-enantiomer of ketamine has a higher affinity for the NMDAR than racemic ketamine, thus lower doses of S-ketamine are needed to produce anaesthesia (Peltoniemi et al. 2016).

Ketamine produces a functional and electrophysiological dissociation between thalamocortical and limbic systems. Sensory inputs may reach cortical receiving areas but are not perceived in the association areas (Mion and Villevieille 2013). Ketamine-induced dissociative anaesthesia is a state that lacks complete unconsciousness but is characterized by amnesia, catalepsy and catatonia (Aroni et al. 2009; Zanos et al. 2018).

As stated above, ketamine stimulates noradrenergic neurons and inhibits catecholamine uptake. This induces a hyperadrenergic state (release of norepinephrine, dopamine and serotonin) characterized by hypertension, tachycardia and preservation of cardiac output (Mion and Villevieille 2013). Therefore, ketamine is an attractive anaesthetic choice for haemodynamically unstable patients. Additionally, ketamine preserves protective laryngeal and pharyngeal reflexes and sustains respiration, contributing to its beneficial properties as a battlefield anaesthetic where sources of organ support are limited (Mulvey et al. 2006; de Rocquigny et al. 2020).

Ketamine doses 0.5 mg/kg or more interfere with human electroencephalography. Entropy and bispectral index (BIS) devices used to estimate the depth of anaesthesia during propofol, thiopental and volatile anaesthesia, are therefore not appropriate for estimating the state of hypnosis during ketamine anaesthesia (Peltoniemi et al. 2016).

In addition to IV administration, other routes include intramuscular, subcutaneous, oral, nasal, epidural and rectal (Andrade et al. 2017; Bell et al. 2006; Bell et al. 2016; Malinovsky et al. 1996). Feasibility of administration routes other than intravenous can be assessed on the basis of where ketamine is used.

Intramuscular administration may be practical in the emergency setting or for uncooperative patients. Subcutaneous ketamine infusions are commonly used in the palliative setting (Bell 2006). Intranasal administration is non-invasive, results in rapid systemic absorption, and avoids first-pass hepatic metabolism (Malinovsky et al. 1996). This may be beneficial in ambulatory settings and is currently used when treating patients with depression. Ketamine has also been used as an adjuvant for epidural analgesia (Lavand'homme 2001). As discussed above, ketamine's oral bioavailability is limited. However, the oral route may be preferable when using ketamine as an adjunct analgesic in the surgical ward. Oral bioavailability of ketamine is increased in conditions with decreased hepatic blood flow, such as in the elderly or in patients with hepatic cirrhosis (Fanta et al. 2015).

## 2.6 KETAMINE FOR ANALGESIA

Subanaesthetic ketamine, i.e a dose that is lower than that required to produce anaesthesia, is defined as < 1 mg/kg of racemic ketamine or < 0.5mg/kg of S-ketamine administered intravenously. Ketamine at such doses have analgesic properties. In experimental pain models,

concentrations of 100-160 ng/ml of racemic ketamine have been required to produce analgesic effect. (Peltoniemi et al. 2016).

Ketamine produces antinociceptive action by inhibiting NMDARs and activating descending inhibitory monoaminergic pain pathways. By blocking NMDARs in the dorsal horn of the spinal cord, ketamine attenuates wind-up and central sensitization (processes behind increased and altered pain sensitivity), mitigates the development of opioid tolerance and, in case of opioid exposure, attenuates OIH (Bell 1999; Dickenson 1990; Kissin et al. 2000; Laulin et al. 2002; Wu et al. 2015).

In addition to the effects on pain modulation at spinal level, further effects may arise from ketamine's ability to decrease brain connectivity in areas responsible for pain processing and modulation. Animal and human studies indicate that ketamine and S-ketamine decrease connectivity in the ACC and amygdala, and thereby reduce the affective component and aversiveness of pain (Niesters et al. 2012, Spreng 2006, Zhou et al. 2018). Ketamine also modulates descending pain inhibition (Niesters et al. 2012). Spreng et al. (2006), using subanaesthetic S-ketamine dosing in their neuroimaging study, showed that the attenuated activity in insular and secondary somatosensory cortices was dose-dependent. Further, they observed that ratings in pain intensity were less affected than were ratings of pain unpleasantness.

There are a substantial number of studies assessing ketamine as an analgesic adjuvant. Since the 1990s, several literature reviews have been published, with increasing numbers of studies.

Schmid and others (Schmid et al. 1999) assessed low-dose ketamine given via oral, intramuscular, subcutaneous, IV and intraspinal routes. Based on 10 studies with IV administration, ketamine was shown to be effective in reducing postoperative pain intensity.

In 2004, Subramaniam and colleagues reviewed studies where ketamine was given intravenously or epidurally (Subramaniam et al 2004). An analysis based on 28 studies with IV administration found that adjuvant ketamine reduced pain intensity at 24 h after surgery.

Elia and Tramér published their review in 2005 with 53 RCTs assessing ketamine in adults and children (Elia and Tramér 2005). Of these, 16 RCTs tested IV ketamine in adults undergoing general anaesthesia. An analysis of these studies in various surgical settings showed that ketamine was beneficial in decreasing postoperative pain intensity up to 48 h and postoperative cumulative morphine consumption at 24 h.

The first Cochrane review on this topic was published in 2006 by Bell and colleagues (Bell et al. 2006). They included 37 RCTs with epidural, intramuscular and IV administration routes. Of these, 22 RCTs investigated intravenously administered ketamine, as an intraoperative infusion (11 studies), as a single bolus at wound closure (5 studies), as an intraoperative ketamine infusion followed by an IV ketamine-morphine PCA (2 studies), or as ketamine administered solely in the postoperative period via morphine-PCA (4 studies).

In 2011, Laskowski and co-workers reviewed the role of intravenously administered ketamine in postoperative analgesia for adult and paediatric patients that had undergone a surgical procedure under general anaesthesia (Laskowski et al. 2011). Of the 70 studies that met their inclusion criteria, 47 provided data in a form suitable for quantitative analysis.

Jouguelet-Lacoste and colleagues published a review of studies using exclusively IV administration of ketamine (Jouguelet-Lacoste et al. 2015). Different types of infusions were distinguished in this publication that included 39 studies.

### 2.6.1 KETAMINE AS AN ADJUNCT TO AN OPIOID PATIENT-CONTROLLED ANALGESIA DEVICE (IV-PCA)

The following reviews have focused on ketamine given via IV-PCA:

Carstensen and Möller (2010) based their review on 11 double-blind RCTs assessing ketamine added to opioid in an IV-PCA device. The opioid-ketamine ratio in the studies was predominantly 1:1.

Wang and others included 36 RCTs in their review, where they assessed the addition of ketamine to morphine/hydromorphone PCA to treat postoperative pain (Wang et al. 2016). The morphine:ketamine ratios in these studies ranged between 1:0.5 and 1:2.5.

Assouline and colleagues (Assouline et al. 2016) analyzed 19 RCTs and reviewed whether ketamine added to an opioid-PCA would decrease pain intensity, decrease cumulative opioid consumption and decrease the risk of respiratory effects with a no more than two-fold increased risk of hallucinations.

### 2.6.2 KETAMINE IN OPIOID-TOLERANT PATIENTS

As for specific patient populations, the effect of adjunct ketamine in the opioid-tolerant patient population after lumbar fusion surgery is well established. Loftus and co-workers (2010) has shown an opioid-sparing effect of IV low-dose ketamine after spine surgery in opioid-dependent patients. This was later confirmed by Nielsen and colleagues (Nielsen et al. 2017) in a more carefully standardized study setting. Additionally, Loftus (Loftus et al. 2010) and Nielsen (Nielsen et al. 2017) have concluded that the opioid-sparing effect of ketamine directly depends on the amount of preoperatively consumed opioid.

Nielsen and colleagues (Nielsen et al. 2018) have also shown that perioperative IV S-ketamine reduces analgesic use and pain while improving labour market participation of opioid-dependent patients one year after spine surgery. Recent study has further confirmed that postoperative low-dose ketamine infusion reduces

hydromorphone requirements for the first 24 h after spinal fusion surgery in opioid-tolerant, but not in opioid-naïve patients (Boenigk et al. 2019).

In conclusion, the beneficial effect of adjunct IV ketamine in reducing postoperative opioid consumption and pain in the opioid-tolerant patient population after lumbar fusion surgery is well established but the effect in the opioid-naïve population is less evident.

### 2.6.3 SAFETY ASPECTS

Ketamine is currently used for new indications such as depression, chronic pain and treatment of addiction (Bahji et. al 2021; Daly et al. 2018; Ezquerra-Romano et al. 2018; Gilbert and Zarate Jr 2020; Noppers et al. 2010; Sigtermans et al. 2010; Romano et al. 2018). It can be anticipated that ketamine administration for these conditions will continue.

Ketamine has been regarded as a safe anaesthetic and analgesic with well-known potential dose-dependent adverse effects. There is no report involving a lethal dose of ketamine in humans (Zanos et al. 2018). Animal studies conducted with rats have reported lethality with both racemic and S-ketamine doses of 40 mg/kg administered intravenously, whereas animals receiving the same dose of R-ketamine survived (Marietta et al. 1977). Urotoxicity, hepatotoxicity and cognitive deficits have been reported in the addiction literature concerning the recreational use of ketamine. Urotoxicity and hepatotoxity are possible adverse effects of ketamine in pain therapy (Bell 2012). In animal studies, high ketamine doses have been associated with excitotoxic neuronal injury (Acevedo-Diaz et al. 2020).

#### 2.6.3.1 Ketamine misuse

Psychedelic effects and dissociative sensations caused by ketamine have contributed to ketamine's recreational misuse (Sassano-Higgins et al. 2016). Ketamine is a popular party drug, especially in Asia and in Great Britain. Ketamine for recreational use is typically obtained in a powder form and administered through snorting or inhaling (Morgan et al. 2011).

A ketamine-high ("trip to a K-land") is described as a disconnection from the surroundings, a floating feeling of being separated from one's body and a feeling of relaxation. Higher doses have reported to induce a dreamlike state called "K-hole" with near-death experiences, sensations of loss of time and identity (Liu et al. 2016; Williams et al. 2019).

The possibly serious adverse effects of ketamine, such as urotoxicity, gastrointestinal and hepatotoxicity and neurocognitive impairment, are well-documented in the addiction literature (Morgan et al. 2011).

#### 2.6.3.2 Urotoxic effects caused by ketamine

Ketamine-related cystitis is characterized by pollacisuria, haematuria and dysuria. Typical features are a contracted bladder, bladder wall thickening, and ulcerative cystitis with a bleeding mucosa. Microscopic findings include denuded urothelium that is infiltrated by inflammatory cells. The pathogenesis is complex, involving a direct toxic effect of ketamine and/or its metabolites, bladder barrier dysfunction, inflammation mediated by nitric oxide synthase, immunoglobulin E, and neurogenic cells. Further, overexpression of carcinogenic genes, abnormal apoptosis and autoimmunity triggered by either circulating or urinary ketamine contribute to ketamine-related cystitis and damage to the urinary tract ( Jhang et al. 2015; Liu et al. 2015; Wood et al. 2011).

#### 2.6.3.3 Gastrointestinal and hepatotoxic effects of ketamine

Regular ketamine use has been associated with gastric and hepatic pathology (Noppers 2011; Bell 2012). Abdominal pain caused by ketamine is typically moderate to severe and dull or cramping ("K cramps"). This has been associated with cholestasis and dilatation of the com mon hepatic and bile duct and impairment of the smooth muscle of the sphincter of Oddi (Sassano-Higgins 2016; Wong et al. 2009). Elevated liver enzymes (alanine aminotransferase and alkaline phosphatase) have been found among ketamine abusers and among patients being treated with repeated courses of ketamine for chronic noncancer pain (Yiu-Cheung 2012; Noppers et al 2011).

The exact mechanism by which ketamine may cause liver injury is not fully understood. In vitro, supraclinical doses (i.e.doses that are greater than would be used in treatment of a medical condition) of ketamine have been reported to inhibit gluconeogenesis in hepatocytes, increased lipid peroxidation and the formation of free radicals (Dundee et al. 1980, Noppers et al. 2011; Sear 2011). S-ketamine has been shown to induce DNA fragmentation and apoptosis in vitro through a Bax-mitochondria-caspase protease pathway (Lee et al. 2009).

#### 2.6.3.4 Neurocognitive impairment associated with ketamine use

The repeated recreational use of ketamine is associated with neurocognitive impairment (Bell 2012; Morgan et al. 2004; Morgan and Curran 2011). Ketamine users have been reported to exhibit both impaired short- and long-term memory, impaired spatial working memory and impaired pattern recognition memory, as well as impaired performance in verbal recognition memory (Morgan et al. 2009; Morgan and Curran 2011). In a study examining spatial memory processing among ketamine users, subjects in the ketamine group reported taking a mean of 3.9 ± 3.73g ketamine per session and a mean of 5.0 ± 1.15 days per week and for 9.7 ± 3.62 years (Morgan et al. 2014). Route of administration was not described in the trial. In another study, frequent ketamine users were reported to average an intake of 2.77 g of ketamine on an average 20 days per month (Morgan et al. 2009). Some neurocognitive deficits may be reversible while impairments to episodic memory and attentional functioning have reported to be long-lasting (Morgan et al. 2004).

For comparison, typical ketamine doses for clinical use are presented in Table 3 and compared with doses used for recreational purposes (Clements et al. 1982; Cohen et al. 2018; Farroks et al. 2021; Kalsi et al. 2011; Morgan et al. 2009; Morgan et al. 2014; Peltoniemi et al. 2016; Schwenk et al. 2018; White et al. 1985)

Repeated ketamine infusions (racemic ketamine 0.5mg/kg for 40 minutes) have been associated with significant improvements in neurocognitive performance (visual memory, simple and complex working memory) when used to treat depression (Shiroma et al. 2014). However, this could be explained by alleviation of depressive symptoms. In another study with healthy volunteers, receiving an increasing analgesic-range infusion of ketamine elicited acute but transient effects on visuospatial working memory and spatial planning (Hayley et al. 2018). In the study, the average bolus dose was 0.38 mg/kg, followed by a maximal infusion rate of 0.25mg/kg/h for a total infusion time of 3 h.

#### 2.6.3.5 Ketamine and its effects on neurotoxicity, intracranial pressure, and neuroprotection

When evaluating ketamine's feasibility in neuroanesthesia, two different mechanisms must be considered: its potential neurotoxicity, and its effects on cerebral blood flow and intracranial pressure.

Preclinical studies have shown pathological neuronal changes after repeated ketamine exposure and exacerbated cortical neuroapoptosis under hyperoxic conditions in the developing brain (Hayashi et al. 2002; Wu et al. 2018). However, some studies have shown a neuroprotective effect through inhibition of inflammation in the developing rat brain (Anand et al. 2007; Shu et al. 2012). Recent data leave it unclear as to whether ketamine is neurotoxic or neuroprotective in the developing infant's brain: it is recommended that repeated nonurgent surgeries with ketamine be avoided before age of 4 years (Davidson 2011; Yan and Jiang 2014).

Traditionally, ketamine has been used cautiously in neuroanesthesia and when treating patients with brain injury because initial studies have associated its use with an elevation in intracranial pressure (Takeshita et al. 1972; Shapiro et al. 1972; Himmelseher and Durieux 2005).

Though ketamine does not disrupt autoregulation (Engelhard et al. 2001), a study with eight healthy male volunteers has shown that, at anesthetic concentrations (i.e. that produce a loss of consciousness), S-ketamine, when used as a sole anesthetic, increases whole brain blood flow by 36%. The greatest regional increase has been detected in the insula. However, S-ketamine does not provoke a decrease in cerebral metabolism (Långsjö et al. 2005), a desirable feature for anesthetic agents used in neuroanesthesia practice. Anesthetic ketamine induces a state of hyperperfusion in the brain, manifesting as an increase in cerebral blood volume by 52% (Långsjö et al. 2005).

Another study with nine healthy, spontaneously breathing male volunteers has shown that three different doses of subanesthetic ketamine induce a global, concentration-dependent increase in cerebral blood flow. The greatest changes have been detected in the anterior cingulate cortex, putamen, thalamus, and frontal cortex (Långsjö 2003), i.e. in structures that are associated with pain processing. Further, at subanesthetic doses, ketamine did not alter the cerebral metabolic rate for oxygen, and the regional oxygen extraction fraction was even decreased. At subanesthetic doses, ketamine induced only minor changes in cerebral blood volume (Långsjö et al. 2003). In clinical practice, ketamine's feasibility as a component of multimodal analgesia for craniotomy has not been established (Ban et al. 2019).

It seems that in conditions where compensatory mechanisms to prevent a rise in intracranial pressure are depleted, and an elevation in intracranial pressure is imminent (such as in emergency cases with isolated brain trauma),

ketamine may not be feasible as the sole anesthetic agent (Långsjö et al. 2018). On the other hand, in situations with hypovolemia and hypotension (such as in polytrauma patients), hemodynamic stimulation induced by ketamine may be beneficial in maintaining cerebral perfusion pressure.

**TABLE 2 / Comparison of clinical ketamine doses and ketamine doses used for recreational purposes**

| | Intravenous | Intramuscular | Oral | Intranasal |
|---|---|---|---|---|
| **INDUCTION OF GENERAL ANESTHESIA (mg/kg)** | 1-2 *<br>0,5-1 ** | 2-4 | | |
| **ACUTE PAIN (bolus mg/kg; infusion mg/kg/h)** | 0,3-0,5* bolus<br>< 0,5 **bolus<br>0,1-1* infusion | | | |
| **CHRONIC PAIN (bolus mg/kg; Infusion mg/kg/h)** | up to 0,35mg/kg* bolus<br>0,5-2 mg/kg/h* infusion | | | |
| **DEPRESSION (mg/kg intravenous or mg bolus intranasal)** | 0.5*<br>Used as an infusion over 40 minutes | | | 28 -84 mg** bolus initial phase, twice a week (weeks 1-4). Maintenance: 28-84 mg ** once a week (weeks 5-8), then biweekly |
| **WITHDRAWAL SYMPTOMS (mg/kg/h)** | 0.24* | | | |
| **TYPICAL RECREATIONAL DOSE (single dose, mg)** | 50-100 | 75-125 | 200-300 | 60-250 |
| **BIOAVAILABILITY (%)** | 100 | 93 | 17-20 | 25 |

*Racemic ketamine; **S-ketamine

Recent data indicate that, in the intensive care unit (ICU) setting, ketamine as an additional sedative agent does not increase intracranial pressure in patients with traumatic brain injury or in patients with nontraumatic neurological illness (Zeiler et al. 2014; Gregers et al. 2020). In these circumstances, the patients have been sedated with a first-line sedative agent (such as propofol, fentanyl, sufentanil, morphine, midazolam, or etomidate) and mechanically ventilated (Zeiler et al. 2014; Gregers et al. 2020). However, the overall level of evidence concerning the use of ketamine in brain injury is low because studies are heterogeneous in methods and design (Gregers et al. 2020).

There are preliminary data that ketamine can prevent spreading depolarizations, abrupt, near-complete breakdown of neuronal transmembrane ion gradients: these phenomena are associated with secondary injury, and poor neurological outcome after traumatic brain injury and aneurysmal subarachnoid hemorrhage (Carlson et al. 2019; Godoy et al. 2021; Santos et al. 2019; Stevens and Koehler 2019). This neuroprotective effect is likely to be mediated via NMDAR antagonism, making ketamine a promising candidate drug to improve neurological outcomes after traumatic brain injury (Godoy et al 2021; Carlson et al. 2019).

## 2.7 OPIOIDS

Sumerians, who inhabited what is today Iraq, cultivated poppies (Papaver somniferum) and isolated opium from poppy seed pods at the end of the 3rd millennium BC. There are several written records of the early opium use, such as in The Odyssey by Homer as he described Helen giving 'a cocktail' to Telemachus and his friends to overcome their grief over Odysseus' absence: "Presently, she cast a drug into the wine of which they drank to lull all pain and anger and bring forgetfulness of every sorrow" (Brownstein 1993). Additional example is Celsus, who advised taking opium before surgery in De Medicina (Hamilton and Baskett 2000). Presumably, opium spread from Sumeria to the remainder of the Old World.

A German pharmacist Friedrich Sertürner isolated an alkaloid from opium in 1806. He named this active ingredient of opium morphium after Morpheus, the Greek god of dreams (Mehendale et al. 2013). After the invention of the hollow needle in the 1840s and the hypodermic syringe in the 1850s, morphine use was established as a premedication, as an adjunct for general anaesthesia and for postoperative and chronic pain conditions. In an effort to develope a safer and non-addicting opiate, heroin was synthesized in 1898, followed by the discovery of meperidine in 1939 and methadone in 1946 (Brownstein 1993).

Opioid receptors were discovered in 1970s, followed by isolation of the opioid peptides and classification of opioid receptors (Pasternak 2014). Mu (μ), delta (δ) and kappa (κ) opioid receptors (MOR, DOR, KOR, respectively) have been identified, with the MOR being the main analgesic target. Opioid receptors are G-protein-coupled receptors and are widely distributed the CNS. Localizations occur in the cerebral cortex, hypothalamus, thalamus, locus coeruleus and PAG in the brain stem, laminae I-II of the medullary and spinal cord dorsal horns, and in DRGs (Mao 1999). Binding of an agonist, such as morphine, to an opioid receptor modulates intracellular processes, resulting in suppression of electrical excitability in neurons. Activation of opioid receptors suppresses both the reflexive and affective components of pain. PAG in the midbrain and (especially) the descending PAG-RVM pathway are the central sites of opioid analgesic activity in the CNS (Lau and Vaughan 2014; Mercadante et al. 2019).

Since the isolation of morphine, several synthetic opioids have been developed. Currently, analgesic practice in Finland relies on fentanyl, alfentanil, remifentanil, sufentanil and oxycodone in the perioperative period. Worldwide, morphine is the most widely used opioid analgesic and the 'gold standard' against which synthetic opioids for postoperative pain relief are compared (Hamilton and Baskett 2000). Opioid analgesia is widely used for post-operative pain management, though the many side effects range from bothersome to life-threatening. ***Table 3*** shows the wellknown adverse effects of opioids (Ballantyne and Mao 2003; Nevantaus et al. 2013).

Physiologic responses to opioid exposure include the development of opioid tolerance and OIH, the mechanisms of both being complex. The development of acute opioid tolerance and OIH both involve NMDARs (Trujillo 2002).

**TABLE 3 / Adverse effects of opioids**

| SIDE EFFECTS OCCURRING SHORTLY AFTER USE | SIDE EFFECTS OCCURRING WITH PROLONGED USE |
|---|---|
| Nausea and vomiting | Tolerance |
| Pruritus | Addiction |
| Confusion | Cognitive decline |
| Hallucinations | Depression |
| Dizziness | Euphoria |
| Sedation | Dysphoria |
| Respiratory depression | Opioid-induced hyperalgesia* |
| Opioid-induced hyperalgesia* | |
| Constipation | Hormonal effects (reduced fertility, reduced libido) |
| Urinary retention | Immunosuppression |
| Dry mouth | Sweating |
| Miosis | Myoclonus* |
| Myoclonus* | |

*Myoclonus can occur both at acute and chronic use of opioids. Opioid-induced hyperalgesia has been reported to occur also shortly after remifentanil-anesthesia (Celerier et al. 2006)

### 2.7.1 OPIOID TOLERANCE

The US Food and Drug Administration (FDA) defines opioid tolerance as the use of ≥ 60 mg of morphine equivalent per day for a period of 7 days or longer (Volkow and McLEllan 2016). Clinically, opioid tolerance is defined as a requirement for increased doses of an opioid analgesic to achieve the same analgesic effect (Hayhurst and Durieux 2016).

Opioid tolerance develops from desensitization of opioid receptors, altered cellular excita-bility and signalling, as well as induction of immune-competent cells (opioid-induced neuroinflammation). The mechanism underlying MOR desensitization may depend on the spe-cific opioid agonist. For example, fentanyl recruits cytosolic ß-arrestin while morphine de-sensitizes MORs via NMDAR activity (Garzón et al. 2012; Lau and Vaughan 2014; Mer-cadante et al. 2019). Additionally, NMDAR

activation by painful stimuli may also induce opioid receptor internalization and desensitization (Hirota and Lambert 2011; Patierno et al. 2005).

As regards neuroinflammation, opioids activate the glia within the CNS. Animal studies suggest that glial activation associated with opioid tolerance occurs mainly at the spinal level (Jokinen et al. 2018). Activated glia induce alterations in both intracellular signalling cascades and signalling between neurons. One particularly important factor in the activa-tion of the opioid-induced neuroinflammatory response is toll-like receptor 4 (TLR4) which is activated by morphine. This results in upregulation of genes encoding proinflammatory cytokines and chemokines, inducible nitric oxide synthase (iNOS), NADPH synthase responsible for generating reactive nitrogen and oxygen species, and cyclo-oxygenase 2 (COX-2) that is essential in prostaglandin synthesis (Lueptow et al. 2018; Mercadante et al. 2019).

Ongoing opioid administration ultimately involves a number of changes in the downstream intracellular signalling pathways. Signalling proteins involved in the development of opioid tolerance include NMDARs, NOS, PKA, PKC, mitogen-activated protein kinases (MAPK), protein phosphatases, calcium (Ca2+)/CaM-dependent kinase II (CaMKII), DOR and the regulators of G protein signalling. The NMDAR/NOS/CaMKII pathway seems to have a central role in the development of opioid tolerance (Garzón et al. 2012). Purinergic receptors on microglia also upregulate proinflammatory cytokines and activate astrocytes, leading to NMDAR activation and neuronal excitability (Lueptow et al. 2018).

Other neuropeptides such as cholecystokinin (CCK) also regulate the development of opioid tolerance in the descending pain pathway (Lueptow et al. 2018).

Recent studies suggest that the gastrointestinal microbiome plays a role in the development of opioid tolerance by enteric glial cell activation. Activated glia release a variety of cytokines that affect extrinsic sensory afferents whose cell bodies lie within the DRG and induce tolerance to opioids (Abkarali and Dewey 2017; Guo et al. 2019).

#### 2.7.1.1 Interaction between NMDA receptors and μ-opioid receptors

Opioid-induced alterations occur at multiple levels in the antinociceptive/nociceptive nerv-ous system. At first stage, opioid receptors react to opioid exposure by internalization and desensitization. Then, there is bidirectional interplay between MORs and NMDARs. NMDARs and MORs share a similar distribution pattern in the CNS. The CNS structures that are supplied with both receptors include

- Putamen
- Nucleus caudatus

- Lamina II in the dorsal horn (spinal cord)
- Nucleus accumbens
- Nucleus tractus solitarius
- Periaqueductal grey (PAG)

NMDARs and MORs have a direct physical association in post-synaptic membranes (Garzon et al. 2012). The mu- opioid receptor is a G protein-coupled receptor with seven transmembrane loops. The C-terminal sequence of the MOR can associate directly with the C1 segment of the GluN1 subunit of an NMDAR (Garzon et al. 2012).

The close association between the C-terminus of the MOR and the C1 segment of the GluN1 subunit of an NMDAR operates as a regulatory loop between these two receptors. As an opioid agonist binds (and activates) the MOR, information is carried to the NMDAR. Activation of an NMDAR then negatively influences MOR signalling and evokes opioid desensitization (Garzon 2012; Mao 1999).

Use of NMDAR antagonists, such as ketamine, can mitigate the development of toler-ance by inhibiting NMDAR-mediated opioid receptor internalization, opioid-induced neurotoxic changes, and undesirable intracellular processes involved in the development of opioid tolerance. Low doses of NMDAR antagonists can inhibit the development, but not the expression of opioid tolerance. In other words, they can be effective in preventing opioid tolerance when co-administered with opioid analgesics but cannot reverse opioid tolerance once an individual has already developed it. This occurs without affecting opioids' analgesic effects (Trujillo 1995)

A condition that shares similar clinical characteristics with opioid tolerance is OIH.

### 2.7.2 OPIOID-INDUCED HYPERALGESIA

OIH is defined as a state of nociceptive sensitization caused by exposure to opioids (Lee et al. 2011). OIH is characterized by aggravated pain compared with pain experienced before opioid use, or with the de novo development of pain in the absence of pathology (Higgins 2019). OIH appears clinically as allodynia (pain elicited by normally innocuous stimuli) and hyperalgesia (enhanced sensitivity to noxious stimulation) (Hayhurst and Durieux 2016). Typically, OIH differs in location and quality from the initial pain complaint. Distinguished from opioid tolerance, where escalating opioid doses may be help-ful, OIH results in decreased opioid analgesic efficacy.

Circumstances under which OIH occurs include high opioid doses, long-term opioid treatment or abrupt changes in drug concentrations (Wilder-Smith and Arendt-Nielsen 2006). Both experimental and clinical studies have shown that OIH may develop in the perioperative period (Célerier et al. 2000; Minville et al. 2010; Vinik and Kissin 1998).

The development of OIH is complex and includes sensitization of primary afferent neu-rons and increased release of glutamate by these, hyperexcitability of postsynaptic/second-order neurons and enhanced release of nociceptive neuromodulators by de-scending pain controls. Neuroinflammation induced by activated glia cells also underlies the increased nociception in OIH (Grace et al. 2014; Hayashi et al. 2016; Lee et al. 2011; Roeckel et al. 2016). ***Figure 7*** presents the multifaceted process of the development of OIH.

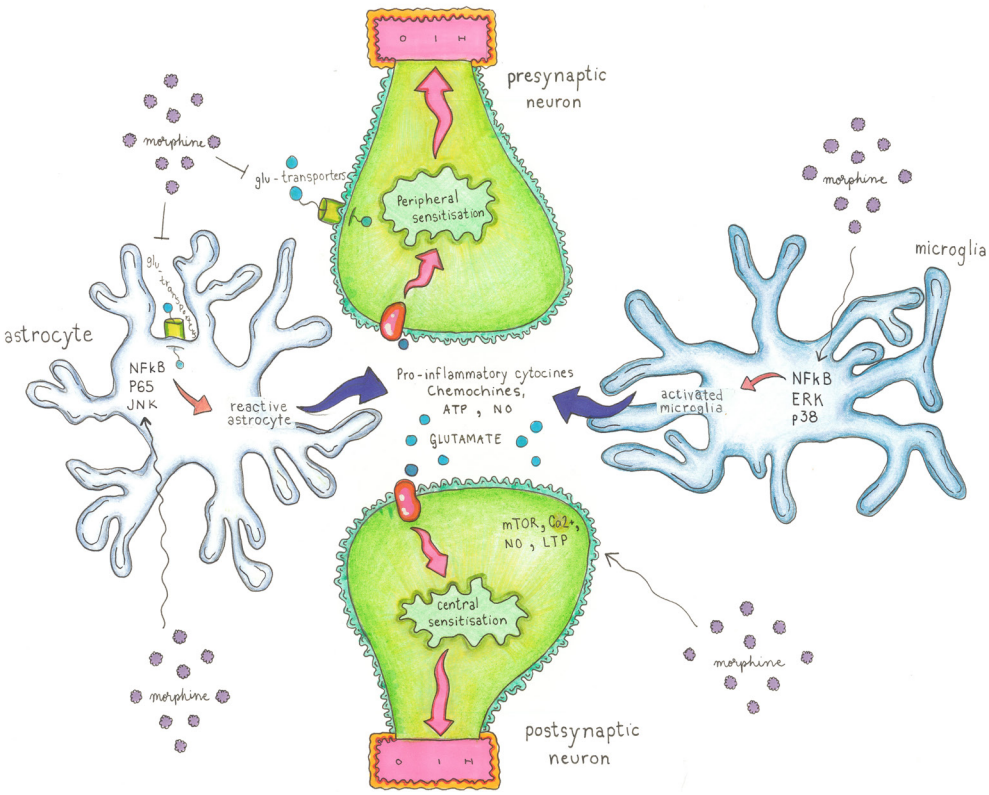



**FIGURE 7.** / The development of opioid-induced hyperalgesia (OIH) includes sensitization of primary afferent neurons, excessive glutamate release and hyperexcitability of postsynaptic neurons. Opioids also activate microglial cells. Activated microglia participate in the development of OIH by releasing pro-inflammatory cytokines and reinforcing neuroinflammation. *Modified from Roeckel et al. Opioid-induced hyperalgesia: cellular and molecular mechanisms. Neuroscience 2016; 338:160-182.*

Neuronal processes involved in OIH include neuroexcitatory mechanisms, long-term potentiation and descending pain facilitation (Roeckel et al 2016). Neuroexcitatory mechanisms involve the kinase mammalian target of rapamycin (mTOR) and tyrosine receptor kinase B (TrkB), inhibition of glutamate reuptake, and reduced expression of K+/Cl- cotransporter which results in disturbed intracellular chloride homeostasis (Roeckel et al. 2016).

Cessation and withdrawal of remifentanil infusion has been shown to induce potentia-tion of the synapse between nociceptive C fibres (primary afferents) and projection neu-rons in the superficial lamina of the dorsal horn of the spinal cord. Neuronal excitation leads to high intracellular Ca2+ concentrations and induces LTP. Additionally, activated glial cells will also enhance LTP.

Hyperalgesic priming is a neuroplastic change occurring in primary afferent nociceptors. A painful stimulus initiates signalling that travels via peripheral terminal nociceptors from the site of injured tissue to the cell body. The signal is then transmitted back to the terminal nociceptor where it mediates enhanced sensitization of the primary affer-ent nociceptor and prostaglandin E2-induced hyperalgesia. Fentanyl acting at MORs has been shown to initiate hyperalgesic priming and acute hyperalgesia, in both central and peripheral nociceptor terminals (Araldi et al. 2015; Araldi et al. 2018).

Morphine administration increases ON cell discharge in the RVM. This results in tonic ac-tivation of descending pain facilitation from the RVM to the dorsal horn of the spinal cord (Vanderah et al. 2001). Opioid administration also upregulates the production of spinal dynorphins, increasing excitatory neurotransmitter release from the primary afferent neurons. This is further associated with enhanced responsiveness of second-order neu-rons in the dorsal horn of the spinal cord (Ossipov et al. 2005).

#### 2.7.2.1 Molecular factors for opioid-induced hyperalgesia

A key molecular factor for the development of OIH is the NMDA-glutamatergic system. Morphine administration has been shown to increase the NMDAR 1 subunit expression in brain. NMDARs can upregulate β-arrestin production and activity, inducing morphine receptor desensitization. Additionally, opioid administration enhances presynaptic NMDAR activity in the dorsal horn of the spinal cord while decreasing postsynaptic NMDAR activity. This contributes to NMDAR trafficking to the plasma membrane, and increased release of glutamate. Together with decreased levels of glutamate transporters, the net effect is abundant levels

of glutamate in the synaptic cleft and overstimulation of the synapse, leading to hyperalgesia. Remifentanil, an ultra-short-acting MOR agonist widely used in the intraoperative period, directly activates the NMDAR system and provokes dif-ferent types of NMDAR subunits to bind each other (Hahnenkampf et al. 2004). Novel evidence shows that prolonged opioid treatment enhances association of NMDARs with MAPKs in the spinal cord. MAPKs contribute to tonic activation of presynaptic NMDARs in the spinal cord, which is responsible both for OIH and opioid tolerance (Deng et al. 2019).

Additional molecular participants in the induction of OIH include (Roeckel et al. 2016):

- K+/Cl- cotransporter and disruption of Cl- homeostasis in the dorsal horn of the spinal cord
- Transient receptor potential vanilloid 1 (TRPV1) activation
- Transient receptor potential melastatin 8 (TRPM8) suppression
- 5-HT3 (serotonin) receptor excitation
- EphrinB receptors that regulate the development of glutamatergic synapses
- Mammalian target of rapamycin (mTOR)
- Serine/threonine kinase
- Protein kinases (such as PKB and PKC)
- Cholecystokinin (CCK)
- Neuropeptide FF
- Orphanin

#### 2.7.2.2 Neuroinflammation

Binding of morphine at TLR4 on microglia activate microglial cells. Neuroinflammation, induced by the activated neuroinflammatory cells (oligodendrocytes, astrocytes, micro-glia, perivascular macrophages, endothelial cells and infiltrating immune cells) participates in the development of OIH. Activated microglia release inflammatory mediators (IL-1β, TNF-α, IL-6, BDNF and NO). Astrocytes release further proinflammatory cytokines, reinforcing neuroinflammation (Roeckel et al. 2016).

Intraoperative remifentanil administration is associated with increase in postoperative pain and analgesic requirements, suggesting acute opioid tolerance and hyperalgesia (Guignard et al. 2000; Vinik and Kissin 1998). Perioperative administration of NMDAR antagonists has been shown to reduce OIH after remifentanil-based anaesthesia (Wu et al. 2015).

In addition to preventing NMDAR-mediated central sensitization and hyperalgesia, keta-mine reduces opioid-induced hyperexcitability of neurons and modulates the development of OIH. Further, inhibiting 'big potassium' (BK) channels in the microglia may be an additional mechanism in ketamine's preventative effect on OIH (Angst and Clark 2006; Hayashi et al. 2011; Hayashi et al. 2016; Lee et al. 2011; Roeckel et al. 2016).

### 2.7.3 ACUTE OPIOID TOLERANCE VERSUS OPIOID-INDUCED HYPERALGESIA

Clinically, the development of both acute opioid tolerance and OIH presents as increased pain intensity. In OIH, opioid exposure has lowered pain thresholds, resulting in increased pain. In opioid tolerance, increased pain levels are caused by decreasing the effect of an opioid analgesic. In clinical practice, more intense pain in the postoperative period is intuitively treated with higher opioid doses, but these will worsen OIH whereas, with opioid tolerance, escalating opioid doses may be helpful.

Both OIH and opioid tolerance seem to have a dose-response relationship, with high doses of potent opioids increasing the magnitude of OIH and opioid tolerance (Angst 2015; Hayhurst and Durieux 2016). Opioid tolerance and OIH may also develop with a short-lasting exposure to a high potency opioid, such as an intraoperative remifentanil infusion (Guignard et al. 2000).

## 2.8 PATIENT-CONTROLLED ANALGESIA

Opioids are widely used to treat acute postoperative pain. PCA is a delivery system with which an individual self-administers doses of an analgesic, based on her/his perceived level of pain. The concept was developed in the 1960s and, over decades, PCA use has been established as an analgesic therapy option in the postoperative period (Nardi-Hiebel et al. 2020).

PCA use is associated with lower pain intensity and greater patient satisfaction when compared to conventional (oral, subcutaneous, intramuscular or combined) administration routes (McNicol et al. 2015).

PCA systems are based on the use of an electronic reusable pump or a disposable device (usually an elastomeric pump). Reusable electronic pumps are often used for IV drug administration while disposable elastomeric pumps are used for regional anaesthesia.

PCA delivery routes include IV, epidural, subcutaneous, transdermal and intranasal, and peripheral nerve catheters that administer local anaesthetics to the perineural space.

The delivery system comprises a reservoir of an analgesic and a Y-shaped tube between the reservoir and patient's IV line containing anti-reflux and anti-syphon valves.

PCA reservoirs are prepared by physicians or nursing staff and are accessible only with a specific key and/or a code. This is to prevent unauthorized access to or misuse of the drug and ensure the safety of the PCA system.

Basic programming variables for a PCA system include a loading dose, a bolus dose, lock-out interval, background infusion rate, and a dose-limit per unit of time. The initial loading dose is activated by a nurse or a physician in the early recovery period in the post-anaesthesia care unit and titrated to achieve a minimal level of analgesia. The bolus (or demand) dose is the amount of analgesic the patient receives when she or he activates the PCA. The lockout interval is the time period in which no drug delivery occurs even when the patient tries to activate the system. Optional background infusion ensures a constant infusion of the analgesic drug, whether the patient activates the PCA pump or not. This may be advantageous during rest or sleep. The dose-limit per unit of time is a restriction on the cumulative dose per time unit, e.g. the maximum number of doses that can be delivered in one hour.

IV-PCA in the postoperative period is predominantly used for delivery of opioids. The choice of opioid in the PCA device and the programmable variables depend on the patient and clinical protocols. Morphine is the most frequently used opioid in PCA though oxycodone use is associated with higher satisfaction scores (Dinges et al. 2019; McNicol et al 2015).

As stated above, PCA provides better pain relief and greater patient satisfaction than conventional drug administration routes. This may be due to enhanced patient autonomy as the analgesic drug is readily available and thus the fear of insufficient analgesia is reduced. Opioid PCA is associated with a higher incidence of pruritus but incidence of other adverse events, such as nausea and vomiting, sedation, respiratory depression, urinary retention or withdrawals due to adverse events or lack of efficacy, does not significantly differ between individuals who receive opioid PCA or opioid medication via conventional routes (McNicol et al. 2015).

Adjunct pharmacological agents can be combined with opioid PCA to enhance analgesia, and reduce opioid consumption and opioid-related adverse events. Ketamine added to opi-oid PCA is beneficial in reducing pain intensity, opioid consumption and PONV (Assouline et al. 2016; Carstensen and Möller 2010; Wang et al. 2016). However, due to huge heterogeneity of studies (different opioids or different versions of ketamine used) the optimal opioid-ketamine ratio in a PCA device has not yet been established.

## 2.9 MULTIMODAL ANALGESIA

A multimodal analgesic regimen combines nonopioid pharmacologic agents with neuraxial and/or local anesthetic techniques. The rationale behind combining various methods is to target different pain signaling pathways, aiming at synergistic and additive analgesic effects (Helander et al. 2017; Mitra et al. 2018). In clinical practice, multimodal analgesia aims to lower postoperative pain intensity, decrease opioid consumption, and minimize opioid-related adverse effects. The goal is to optimize patient recovery and allow prompt patient discharge (Wick et al. 2017).

Multimodal analgesia after spine surgery has also gained prominence (Kurd et al. 2017; Cozowicz et al. 2019). It has been shown to reduce postoperative morphine consumption, improve mobilization (and thereby recovery), with lower levels of PONV, sedation and dizziness (Mathisen et al. 2013).

Nonopioid pharmacologic agents frequently used in multimodal analgesic regimens include paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), dexamethasone, gabapentinoids, serotonin-norepinephrine reuptake inhibitors (SNRIs) such as duloxetine, and alpha-2 adrenergic receptor agonists (Dahl et al. 2014; Helander et al. 2017).

Paracetamol's mechanism of action is incompletely understood but it probably exerts its analgesic effect centrally by inhibiting the cyclooxygenase enzyme (Helander et al. 2017). Though paracetamol is well-tolerated, alone it is insufficient to relieve acute postoperative pain after spine surgery.

NSAIDs act by inhibiting cyclooxygenase and prostaglandin synthesis. They are effective analgesics but their use may be limited by adverse effects, such as on the renal, gastrointestinal, hematological, and cardiovascular systems (Dahl and Kehlet 1991; Helander et al. 2017; Trelle et al. 2011).

Dexamethasone prevents pro-inflammatory gene expression, eventually inhibiting prostaglandin synthesis (Watanabe and Bruera 1994). Dexamethasone has been shown to reduce acute pain during mobilization after lumbar disk surgery (Nielsen et al. 2015).

Gabapentinoids, such as gabapentin and pregabalin, were initially introduced as anti-epileptics and later indicated for treatment of chronic neuropathic pain conditions (Fabritius et al. 2016). Their action is mediated by binding to the alpha-2-delta subunits of voltage-gated calcium channels, causing a decrease in excitatory neurotransmitters (substance P, glutamate, and calcitonin gene-related peptide) (Tiippana et al. 2007). Gabapentinoids have been frequently used for almost any type of pain, including acute postoperative pain (Goodman and Brett 2017). However, recent reviews do not support the routine use of gabapentinoids as a part of multimodal analgesia regimens, nor for the management of acute postoperative pain in adults.

This is due to lack of efficacy and a greater risk of adverse events (Fabritius et al. 2016; Kumar and Habib 2019; Verret et al. 2020).

SNRIs such as duloxetine are commonly used for neuropathic pain. These act centrally by activation of descending inhibitory pathways, and by blocking voltage-gated sodium channels (Bellingham and Peng 2010; Helander et al. 2017). There are only preliminary data concerning the use of SNRIs for the treatment of acute postoperative pain (Helander et al. 2017).

Alpha-2 adrenergic receptor agonists such as dexmedetomidine act in the locus coeruleus and in the dorsal horn of the spinal cord (Kaye et al. 2020). They inhibit norepinephrine release, resulting in sedation, analgesia, and centrally mediated sympatholytic effects (Helander et al. 2017; Kaye et al. 2020). Data on the efficacy of alpha-2 adrenergic receptor agonists in the treatment of acute postoperative pain have been promising (Gabriel et al. 2019). However, a recent study found that dexmedetomidine did not improve postoperative analgesia or reduce postoperative opioid consumption after multilevel spinal fusion surgery in adults (Naik et al. 2016). Side effects of alpha-2 adrenergic receptor agonists include bradycardia and hypotension, which may limit their use in hemodynamically unstable patients (Kaye et al. 2020).

### 2.9.1 KETAMINE AS A PART OF MULTIMODAL ANALGESIA

The incidence of opioid-related adverse events increases with increased opioid use. Further, opioid-related adverse events are associated with an increase in length of hospital stay and costs, as well as decreased survival from in-hospital resuscitation attempts (Wu and Raja 2011).

Ketamine blocks NMDARs and reduces wind-up, LTP and the development of central sensitization. Via NMDAR inhibition, ketamine also reduces hyperexcitability of neurons due to opioid administration and mitigates the development of opioid tolerance and OIH. Inhibition of BK channels in the microglia may be an additional mechanism in S-ketamine's analgesic effect (Hayashi et al. 2011). The effect of ketamine as an adjuvant in reducing postoperative pain and opioid consumption has been well documented in the past two decades. However, due to huge heterogeneity of studies (different opioids or different versions of ketamine used), the optimal dosing regimen and timing of dosing have not yet been established (Bell et al. 2006; Wang et al. 2016).

# 3.

# AIMS OF THE STUDY

The objective of the research presented in this doctoral thesis was to assess the role of IV ketamine and S-ketamine in the prevention and treatment of acute postoperative pain in adults. Specific aims were the following:

To determine the efficacy of perioperative IV ketamine and S-ketamine as an adjunct analgesic in adult patients who have had surgery under general anesthesia (Study I) with specific attention to patients who have undergone lumbar spinal fusion surgery (Studies II and III).

To establish whether there exists a dose-response relationship in different ketamine and S-ketamine dosing regimens (Studies II and III) when used as an analgesic adjuvant for lumbar spinal fusion surgery patients.

To evaluate the effect of timing of dosing of S-ketamine on postoperative opioid consumption and pain (Studies I, II and III).

To assess the tolerability of perioperative IV ketamine and S-ketamine (Studies I, II and III).

# 4.
# PATIENTS AND METHODS

## 4.1 STUDY DESIGN

Study I was a systematic review and meta-analysis based on Cochrane methodology. The literature review evaluated the efficacy and safety of perioperative IV ketamine in adult patients when used for the treatment or prevention of acute postoperative pain after general anesthesia.

Studies II and III were prospective, randomized, double-blind, placebo-controlled clinical stud-ies. Publication II was conducted at Töölö Hospital, Helsinki University Hospital during 2013-2015 (Publication II) and Publication III was conducted at Töölö Hospital and at Turku University Hospital during 2017-2019 (Publication III). They compared two different doses of intraoperative IV S-ketamine to placebo (Publication II) and three different doses of S-ketamine administered in conjunction with oxycodone via PCA to placebo (Publication III), respectively.

## 4.2 RANDOMIZATION AND BLINDING

For study II, 198 patients gave their written informed consent at the preoperative clinic. They were introduced to the numerical rating pain scale (NRS) and learned how to use the PCA system. On the day of surgery, we allocated them into three study groups of similar size. The groups were based on a computer-generated randomization list. A senior anesthesiologist had prepared the randomization numbers in blocks of six. He had concealed the group assignments in consecutively numbered, sealed, opaque envelopes together with detailed information of the study drug preparation. Thereafter, he was no longer involved in the study. On the day of surgery, a nurse unaffiliated with patient care opened an envelope containing data for study group assignment, prepared study medication outside the operating room, and labeled the syringes as "study medication" with patient number. She or he then brought the study medication to the operating room.

For study III, 100 patients gave their informed consent at the preoperative clinic. They learned to use the PCA system and NRS to assess pain. A statistician unaffiliated with patient care cre-ated computer-generated randomization lists using permutated block randomization. She sent the lists to the hospital pharmacies of Turku University Hospital and Helsinki University Hospital, respectively. After recruitment of a study patient, the hospital pharmacy prepared

study drugs in coded PCA reservoirs marked with a study number. The PCA reservoir was then delivered to the operating room on the day of surgery to ensure double blinding.

In both studies II and III, patients, researchers, and clinical staff in the operating room, in the PACU and in the surgical ward were blinded to group allocation.

## 4.3 INTERVENTIONS

In the studies included in the Cochrane review (Study I), racemic ketamine, S-ketamine or R-ketamine were administered intravenously: at induction (such as a bolus dose); during (as a continuous IV infusion or as repeated boluses); or after general anesthesia as a continuous IV infusion or via an IV-PCA.

In Study II, the study intervention was the following:

1. Group C (placebo) received a pre-incisional bolus of IV NaCl (0.9%) at the induction of anaesthesia followed by NaCl (0.9%) infusion.
2. Group K2 received a pre-incisional bolus of IV S-ketamine (0.5 mg/kg) at the induction of anaesthesia, followed by S-ketamine infusion of 0.12 mg/kg/h.
3. Group K10 received a pre-incisional bolus of IV S-ketamine (0.5 mg/kg) at the induction of anaesthesia, followed by S-ketamine infusion of 0.6 mg/kg/h.

All study infusions continued until the beginning of wound closure or up to 8 h.

In Study III, the study interventions were the following:

1. Group 1 (G1) received oxycodone 1 mg/ml alone.
2. Group 2 (G2) received oxycodone 1 mg/ml + S-ketamine 0.25 mg/ml.
3. Group 3 (G3) received oxycodone 1 mg/ml + S-ketamine 0.5mg/ml.
4. Group 4 (G4) received oxycodone 1mg/ml + S-ketamine 0.75 mg/ml.

The PCA systems (CADD®-Solis VIP, Smiths Medical and CADD-Legacy® PCA Pump Model 6300, Smiths Medical) delivering study drugs were initiated at the end of surgery. Study pa-tients used the study drug up to 24 h after surgery. At 24 h, all study patients' PCA reservoirs were changed to contain only oxycodone 1 mg/ml and the patients continued to use PCA up to 72 h after surgery.

## 4.4 POPULATION

In the Cochrane review (Study I), 130 studies with adult patients (≥ 18 years) undergoing a surgical procedure under general anesthesia were included. Ketamine was given to 4588 participants and 3753 received control treatment. Studies were required to be prospective, randomized, double blind, with ≥ 10 participants completing in each treatment arm, and with full journal publication. Additionally, for a study to be included, it had to fulfil one of the following criteria:

- Ketamine alone or placebo was given intravenously as a study drug.
- Ketamine was administered in addition to a basic analgesic such as opioid or non-steroidal anti-inflammatory drug (NSAID) in one study group and compared with a group receiving the same basic analgesic (but without ketamine) in another group.
- Pain intensity, opioid consumption, or time to first request of opioid analgesia were reported as outcomes.

For Studies II and III, 198 and 107 adult (≥ 18 years old) opioid-naïve patients were recruited for the study, respectively.

Study participants for Studies II and III underwent elective decompression and posterolateral fusion of the lumbar spine.

***Figures 8, 9 and 10*** represent the study flow diagrams for each study, respectively.

R-ketamine were administered intravenously: at induction (such as a bolus dose); during (as a continuous IV infusion or as repeated boluses); or after general anesthesia as a continuous IV infusion or via an IV-PCA.

**FIGURE 8 / Study I, flow**

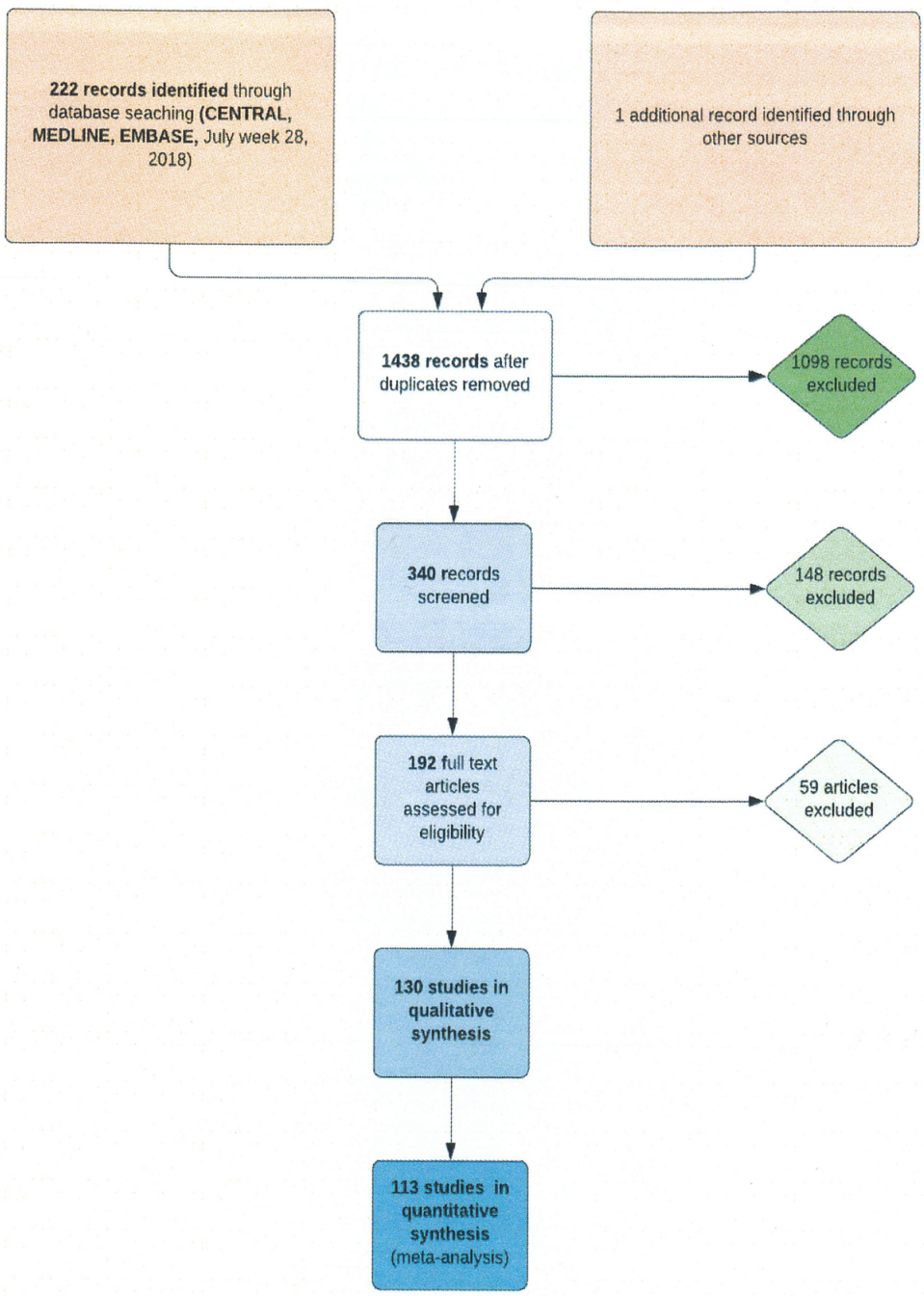


**FIGURE 9 / Study II, flow**

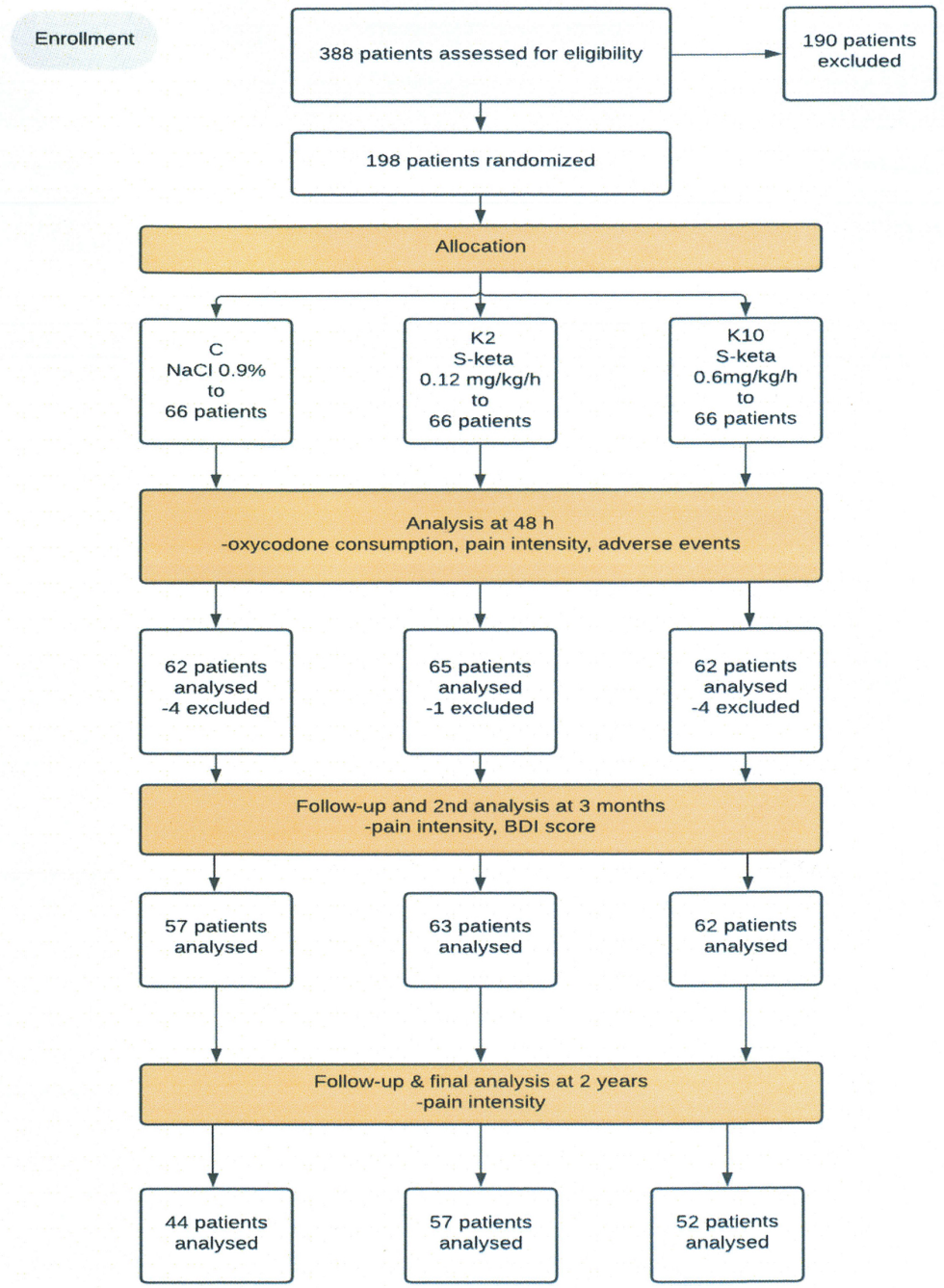
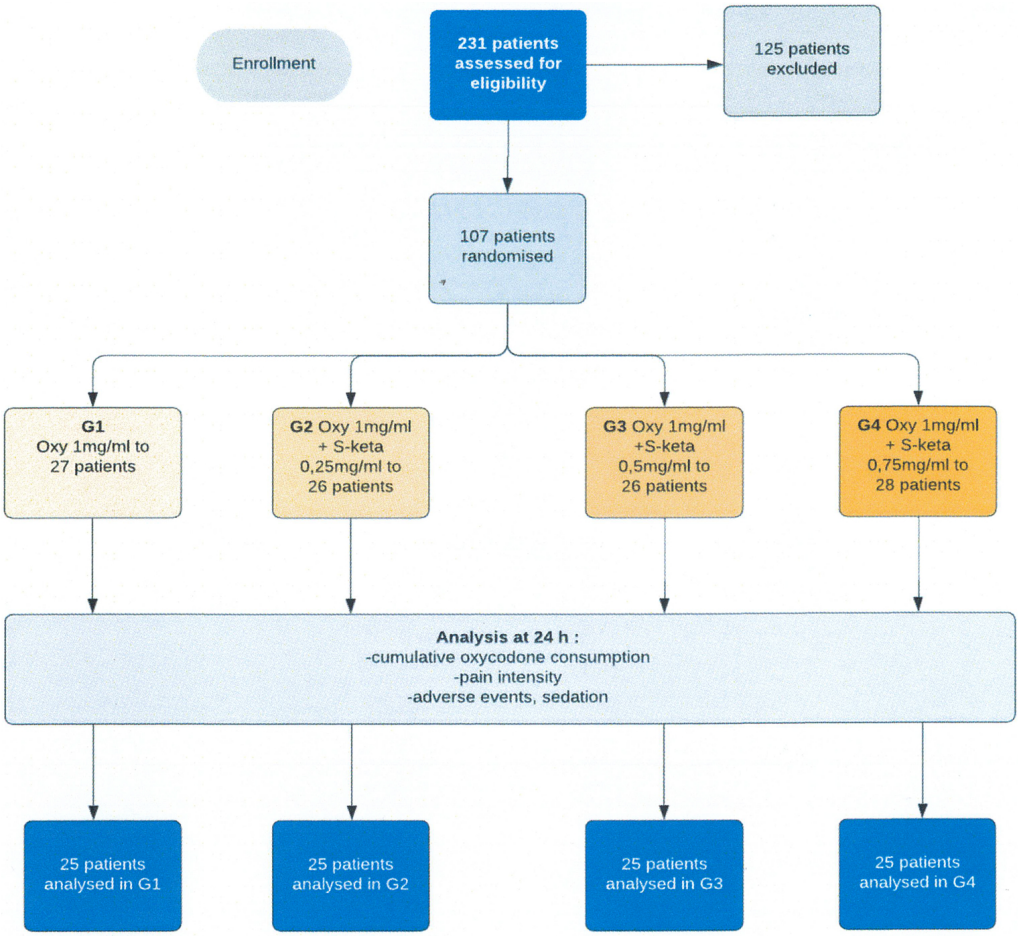


**FIGURE 10 / Study III, flow**



## 4.5 OUTCOMES

Primary and secondary outcomes were prespecified and recorded.

**The primary outcomes were the following:**

- Total consumption of opioids in mg of morphine equivalent for up to 48 h after surgery (Study I).
- Cumulative oxycodone consumption at 48 h after lumbar spinal decompression and posterolateral fusion (Study II).
- Cumulative oxycodone consumption at 24 h after lumbar spinal decompression and posterolateral fusion (Study III).
- Pain intensity assessed by means of subjective pain scales (such as visual analogue scale (VAS), numerical rating scale (NRS), and verbal rating scale (VRS) at rest and during movement at 24 h and 48 h after surgery (Study I).

In the literature review (Study I), primary outcomes were assessed in a non-stratified study population and by surgery type.

Sensitivity analyses for postoperative opioid consumption were performed using only studies with a treatment group size of ≥ 30 patients.

Sensitivity analyses for postoperative pain intensity were performed using only studies with treatment group sizes of ≥ 30 and ≥ 50 patients and for studies with a background pain scores > 40/100 mm.

**Secondary outcomes included:**

- Pain intensity assessed by NRS (Study II and III).
  - For Study II, pain was assessed at 1, 2, and 3 h in the post-anesthesia care unit (PACU) and at 4, 6, 8, 18, 24, 32, 42 and 48 h in the surgical ward. At 18 h, pain was assessed while moving from supine to sitting position. Final pain assessments were made at 3 months and 2 years after surgery, asked as the average pain rating for the last few days preceding these time points.
  - For Study III, pain intensity was recorded in the PACU at 5, 15, 30, 60 and 240 min after surgery and in the surgical ward at 8, 24, 48 and 72 h after surgery.
- Postoperative nausea and vomiting (Publications I, II and III).
  - Occurrences of PONV were recorded as dichotomous data up to 48 h after surgery (Study I and II) and up to 72 h after surgery (Study III)

- Central nervous system adverse events such as hallucinations, nightmares, dizziness, blurred vision, sedation (Publications I, II and III). CNS adverse events were recorded up to 48 h after surgery (Publications I and II) and up to 72 h after surgery (Study III).
- Time from end of surgery to first request for analgesia or first trigger of PCA (Study I).
- Postoperative hyperalgesia (e.g., area of hyperalgesia around the surgical wound in cm2) (Study I).
- Postoperative sedation using the Richmond Agitation Sedation Scale (RASS) (Publications II and III).Postoperative confusion using a Mini-Mental State Exam (MMSE) (Study II).
  - MMSE was assessed in the PACU two hours after extubation. A predefined sub-group analysis of MMSE values in study participants > 65 years old was performed.
- The quality of sleep in the night following surgery using a four-point scale (Study II).
- Assessment of postoperative depression using the Beck Depression Inventory (BDI-II). Patients completed this at their preoperative visit and 3 months postoperatively (Study II).

## 4.6 RISK OF BIAS

For the literature review (Publication I), the quality of each included study was determined by assessing the risk of bias using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2017).

Each risk of bias domain was judged as "low risk", "unclear risk" or "high risk" and supported with a detailed judgement.

## 4.7 QUALITY (CERTAINTY) OF EVIDENCE

For the literature review (Study I), quality of evidence for each outcome was assessed using the GRADE system (GRADE 2004) and the guidelines in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2017).

## 4.8 FOLLOW-UP

The immediate postoperative study periods lasted 48 h (Studies I and II) and 72 h (Study III). At three months, patients made a routine postoperative visit to the outpatient clinic (Study II). The study patients had their final follow-up at one year (Study III) or two years after surgery (Study II). Pain was assessed at those time points.

## 4.9 STATISTICAL METHODS FOR THE CLINICAL STUDIES

### SAMPLE SIZE AND STATISTICAL METHODS (STUDY II)

A coefficient of variation of 0.64 (standard deviation (SD)/mean oxycodone consumption) for the power analysis was obtained from studies examining lumbar fusion surgery patients and previous experience from our clinic. The initial sample size calculation by a two-sample t-test indicated that 192 patients were needed for the study, using 30% as a clinically important reduction in postoperative opioid consumption, if 48 h oxycodone consumption would follow normal distribution and aiming at 0.05 significance level (sample size calculator: Lenth, R.V. (2006). Java Applets for Power and Sample Size [Computer software], retrieved in September 2011 from http://www.stat.uiowa.edu/-rlenth/Power). We decided to recruit 198 patients to allow for dropouts. After data collection, the results for 48 h oxycodone consumption seemed to distribute non-normally but were log-normal. Using the attained sample sizes in each study group, the coefficient of variation above ($\delta = 0.64$) and a Bonferroni-corrected significance level of 0.025, the actual power to detect a 30% reduction in 48 h opioid consumption was 0.89 for control vs each of Groups K2 and K10.

Study groups were compared at baseline by using standardized differences (standardized differences < 10% indicate a negligible imbalance in a baseline covariate).

The variables were assessed regarding normal distribution by visual inspection, Q-Q plots, and the Kolmogorov-Smirnov test. The Mann-Whitney U–test was used for data with non-normal distribution (48 h oxycodone consumption, postoperative NRS pain scores, level of sedation, quality of sleep). Differences for data with a confounding variable (preoperatively assessed values) were analysed by ANCOVA (MMSE for confusion, BDI-II for depression). A chi-squared test was used for dichotomous data (PONV, CNS adverse events).

The analyses were performed using IBM® SPSS version 22 software for Windows (SPSS, Chicago, IL).

### SAMPLE SIZE AND STATISTICAL METHODS (STUDY III)

If 25% would be a clinically significant reduction in postoperative oxycodone consumption, using a level of significance 0.05 and obtaining a power of 80% for the study, a power analysis indicated that 25 participants per group were needed for the study. As this was a clinical study, a few additional patients were recruited to allow for dropouts, the total number recruited being 107.

The data were evaluated for normality of distribution using probit plots, Q-Q plots, and the Shapiro-Wilk W-test. Log-transformation was conducted prior to statistical analysis when applicable, but non-transformed results were reported.

Cumulative opioid consumption at 24 h was analyzed using a multivariate linear model, including the following factors: PCA dosing groups G1-G4, age (as a continuous covariate), sex, cumulative amount of dose requests during PCA, weight, study cite, smoking (yes/no), chronic pain (yes/no), prior use of opioids (yes/no), prior use of gabapentinoids (yes/no), ASA physical status classification (1-5). Non-significant terms were excluded from the final model.

Mean change in NRS over time between study groups was assessed by a hierarchical linear mixed model including time as a within-factor (with 5 time points), PCA dosing group as a between-factor, and finally their interaction. The time factor was treated as categorical to estimate all possible shapes of mean change over time. NRS value were standardized before analysis by centering and scaling to have a mean of 0 and SD of 1.

Differences in NRS and sedation were analyzed with the Kruskal Wallis test. Effect sizes were computed as the eta squared, based on the H-statistic.

Differences in PONV, itching and unpleasant dreams (yes/no) were evaluated with ordinal logistic regression. The effects of age, sex, weight, chronic pain, and prior use of opioids or gabapentinoids on the results were tested as covariates. To analyze the effect of adjuvant ketamine treatment on these parameters, we included change in parameter during the previous 24 h in the model.

Statistical analyses and graphical presentations were performed using R software (version 3.6.0; R Core Team) and ggplot2 (version 2.2.1).

For the literature review (Study I), analyses were performed by using RevMan 5 software (Review Manager 2014).

## 4.10 DATA REPORTING

Descriptive data were presented as the actual numbers and percentages, mean (SD) or median (IQR) where appropriate. Continuous data were presented as mean values and standard deviations (SD) or median values with interquartile range (IQR). Dichotomous data were presented as actual numbers (%) and as relative risks (RR). Numbers needed to treat (NNT) were used for an additional beneficial outcome.

Certainty in each result was expressed as 95% confidence intervals (CI) (Studies I and III) or as 97.5% CI (Study II).

Additionally, in the literature review (Study I), a 'Characteristics of included studies' was created for each study. These included the following: number of participants with percentage of women/men specified, characterization of intervention, outcomes reported in the study, type of surgery, number of participants in each group after end of study, age of patient population in each study group and whether there was a source of funding.

In the literature review (Study I), main findings were presented in a 'Summary of findings' table which included information concerning number of participants and studies providing data for each outcome, the quality of evidence and the magnitude of effect of the intervention examined.

## 4.11 ETHICAL ASPECTS

For the clinical studies, relevant ethical approvals for the study protocols were applied prospectively.

For Study II, Finnish National Committee on Medical Research Ethics (TUKIJA) and Finnish Medicines Agency (FIMEA) approved the study protocol (TUKIJA ref: 36/06.00.02/2012, FIMEA, KL 38/2012). The study was registered at ISRCTN registry (ISRCTN44502772) and in EudraCT database (KETTO 2012-000747-26) prior to patient enrolment.

For Study III, the Institutional Review Board (IRB) of the Hospital District of Southwest Finland and the Finnish Medicines Agency (FIMEA) approved the study protocol (IRB number: 103/1800/2016, FIMEA, KL 135/2016). The study was registered prior to patient enrolment at clinicaltrial.gov (NCT02994173) and in the EudraCT database (2016-002887-14).

# 5.
# RESULTS

The studies included in the Cochrane review the included studies exhibited a variety of surgical procedures under general anesthesia, including ear, nose or throat surgery, wisdom tooth extraction, thyroid surgery, thoracotomy, mastectomy, lumbar fusion surgery, microdiscectomy, hip joint replacement, knee joint replacement, knee arthroscopy, anterior cruciate ligament repair, hemorrhoidectomy, abdominal surgery (laparotomy and lumbotomy), laparoscopic surgery, and elective caesarean section.

Ketamine was given to 4588 participants and 3753 received control treatment. Most studies (n = 119) investigated racemic ketamine. S-ketamine was used in ten studies. One study investigated R-ketamine. A single, pre-incisional ketamine bolus was given in 24 studies. Most studies (n = 84) gave ketamine as a continuous infusion or as repeated boluses during surgery and, in some studies, continuing up to 72 h after surgery. In 16 studies, ketamine was given in the postoperative period, either as a continuous infusion or via PCA. In six other studies, ketamine was administered more than once, e.g., as a pre-incisional bolus and around the time of wound closure. Racemic ketamine doses were heterogeneous: 35 studies used a bolus dose that was < 0.25 mg/kg; in 15 studies, the racemic ketamine bolus was 0.3 mg/kg; 21 studies used a bolus dose ranging from 0.5 to 1 mg/kg; a bolus dose > 1mg/kg was used in 6 studies.

In the 42 studies investigating continuous racemic ketamine infusions, the dose was 2–5 μg/kg/min, corresponding to 0.12-0.3 mg/kg/h. The lowest and highest infusion rates were 0.7 μg/kg/min (0.042 mg/kg/h) and 42 μg/kg/min (2.5 mg/kg/h).

S-ketamine was given as a bolus varying from 0.075 to 0.5 mg/kg. Infusion rates varied between 0.25 μg/kg/min (0.015 mg/kg/h) to 6.7 μg/kg/min (0.4 mg/kg/h). R-ketamine was used in one study, as a single bolus of 1 mg/kg.

## 5.1 POSTOPERATIVE OPIOID CONSUMPTION

### 5.1.1 THE EFFECT OF PERIOPERATIVE INTRAVENOUS KETAMINE

***Tables 4 and 5*** present the estimated difference in postoperative opioid consumption 0 to 24 h and 0 to 48 h in all studies included in the literature review (Study I).

**TABLE 4 / Perioperative intravenous ketamine compared to placebo for acute postoperative pain: opioid consumption at 24 h (mg morphine equivalents)**

| Surgery | No. of participants (studies) | Measured with placebo (mg) | Difference (mg) with perioperative IV ketamine (95% CI) | Quality of evidence (GRADE) |
|---|---|---|---|---|
| All studies | 4004 (65 RCTs) | 31 | MD – 8 (-9, -6) | Moderate |

CI: Confidence interval; MD: mean difference; RCT: randomized controlled trial

**TABLE 5 / Perioperative intravenous ketamine for acute postoperative pain: opioid consumption at 48 h (mg morphine equivalents)**

| Surgery | No. of participants (studies) | Measured with placebo (mg) | Difference (mg) with perioperative IV ketamine (95% CI) | Quality of evidence (GRADE) |
|---|---|---|---|---|
| All studies | 2449 (37 RCTs) | 59 | MD – 13 (-15, - 10) | Moderate |

CI: Confidence interval; MD: mean difference; RCT: randomized controlled trial

### 5.1.2 THE EFFECT OF IV S-KETAMINE AFTER LUMBAR FUSION SURGERY

When assessing the effect of intraoperative IV S-ketamine infusion (K2: S-ketamine 0.12 mg/kg/min; K10: S-ketamine 0.6 mg/kg/min) on oxycodone consumption in patients undergoing lumbar fusion surgery (Study II), the cumulative oxycodone consumption at 48 h did not significantly differ between the intervention groups and placebo. Estimated median difference (97.5% CI) was -24 mg (-73.8 to 31.5; p = 0.170) between K2 and control. Estimated median difference (97.5% CI) between K10 and control was -18.5 mg (-78.5 to 29.5; p = 0.458).

Postoperative cumulative oxycodone consumption was significantly reduced in the group G4 with the highest ketamine concentration (oxycodone: S-ketamine 1:0.75) compared with the control group (G1: oxycodone alone). Mean differences between G4 and control were -21 mg (95% CI -41 to -0.2; p = 0.048), -26 mg (95% CI -55 to – 6.2; p = 0.044) and -41 mg (-68 to -14; p = 0.003) at 24, 48 and 72 h after surgery, respectively. PCA with lower S-ketamine doses added to oxycodone did not show a significant oxycodone-sparing effect.

## 5.2 POSTOPERATIVE PAIN

### 5.2.1 THE EFFECT OF PERIOPERATIVE IV KETAMINE

Based on the data obtained from 130 RCTs in the literature review, pain at rest was 19% and 22% lower than that experienced by control patients at 24 and 48 h after perioperative IV ketamine administration, respectively.

Perioperative IV ketamine reduced pain during movement at 24 h by 14% and at 48 h by 16% from that experienced by control patients. Actual numerical data for reductions in postoperative pain intensity at 24 and 48 h, both at rest and during movement, after perioperative IV ketamine administration are shown in ***Tables 6-9***.

**TABLE 6 / Perioperative intravenous ketamine for acute postoperative pain: postoperative pain intensity (vas) at rest at 24 h**

| Surgery | No. of participants (studies) | Measured with placebo (mg) | Difference (mg) with perioperative IV ketamine (95% CI) | Quality of evidence (GRADE) |
|---|---|---|---|---|
| All studies | 5004 (65 RCTs) | 25 | MD – 5 (-7, -4) | High |
| Pain in control patients >40/100 mm | 860 (14 RCTs) | | MD – 17 (-25, -9) | |

CI: confidence interval; MD: mean difference; RCT: randomized controlled trial; VAS: pain intensity measured at visual analogue scale 0-100 mm; 0 denotes no pain and 100 denotes extreme pain. Measured with placebo denotes baseline values measured in patients who did not receive ketamine. Pain in control patients >40/100 mm denotes those studies where control patients with higher background level of pain [VAS >40/100 mm] were identified.

Sensitivity analyses using only studies where control group pain (VAS) exceeded 40/100 mm were performed. The data for reductions in pain intensity for these studies with higher background levels of pain are shown in Tables 6 - 9 for the time points, both at rest and during movement.

**TABLE 7 / Perioperative intravenous ketamine for acute postoperative pain: postoperative pain intensity (vas) during movement at 24 h**

| Surgery | No. of participants (studies) | VAS measured with placebo (mm) | Difference (VAS, mm) with perioperative IV ketamine (95% CI) | Quality of evidence (GRADE) |
|---|---|---|---|---|
| All studies | 1806 (29 RCTs) | 43 | MD – 6 (-1, 1) | Moderate |
| Pain in control patients >40/100 mm* | 1300 (19 RCTs) | | MD – 7 (-14, 0) | |

CI: confidence interval; MD: mean difference; RCT: randomized controlled trial; VAS: pain intensity measured at visual analogue scale 0-100 mm; 0 denotes no pain and 100 denotes extreme pain. Measured with placebo denotes baseline values measured in patients who did not receive ketamine. *Pain in control patients >40/100 mm denotes those studies where control patients with higher background level of pain [VAS >40/100 mm] were identified.

**TABLE 8 / Perioperative intravenous ketamine for acute postoperative pain: postoperative pain intensity (vas) at rest at 48 h**

| Surgery | No. of participants (studies) | VAS measured with placebo (mm) | Difference (VAS, mm) with perioperative IV ketamine (95% CI) | Quality of evidence (GRADE) |
|---|---|---|---|---|
| All studies | 2962 (49 RCTs) | 21 | MD – 5 (-9, -6) | High |
| Pain in control patients >40/100 mm | 259 (6 RCTs) | | MD – 7 (-19, -1) | |

CI: confidence interval; MD: mean difference; RCT: randomized controlled trial; VAS: pain intensity measured at visual analogue scale 0-100 mm; 0 denotes no pain and 100 denotes extreme pain. Measured with placebo denotes baseline values measured in patients who did not receive ketamine. Pain in control patients >40/100 mm denotes those studies where control patients with higher background level of pain [VAS >40/100 mm] were identified.

**TABLE 9 / Perioperative intravenous ketamine for acute postoperative pain: postoperative pain intensity (vas) during movement at 48 h**

| Surgery | No. of participants (studies) | Measured with placebo (mm) | Difference (VAS, mm) with perioperative IV ketamine (95% CI) | Quality of evidence (GRADE) |
|---|---|---|---|---|
| All studies | 1353 (23 RCTs) | 37 | MD – 6 mm (-10, -1) | Low |
| Pain in control patients >40/100 mm | 379 (8 RCTs) | | MD – 10 (-14, -6) | |

CI: confidence interval; MD: mean difference; RCT: randomized controlled trial; VAS: pain intensity measured at visual analogue scale 0-100 mm; 0 denotes no pain and 100 denotes extreme pain. Measured with placebo denotes baseline values measured in patients who did not receive ketamine. Pain in control patients >40/100 mm denotes those studies where control patients with higher background level of pain [VAS >40/100 mm] were identified.

### 5.2.2 THE EFFECT OF IV S-KETAMINE AFTER LUMBAR FUSION SURGERY

There was a temporary, significant decrease in NRS pain intensity after both intraoperative IV S-ketamine infusions (0.12 mg/kg/min and 0.6 mg/kg/min), compared to placebo group at 4 h postoperatively after lumbar fusion surgery (Study II) but no significant differences were observed later during the 48-h study period, at 3 months, and 2 years after lumbar spinal fusion surgery.

The postoperative mean change in NRS measured at rest over the first 24 h differed significantly between the groups G4 (oxycodone:S-ketamine ratio 1:0.75) and G1 (control: oxycodone alone): the standardized effect size was 0.17 (95% CI 0.013 to 0.32; p = 0.033). Other group differences were nonsignificant: between group G3 and control, the standardized effect size was -0.097 (95% CI -0.25 to 0.059; p = 0.223); between G2 and control, the standardized effect size was -0.052 (95% CI -0.21 to 0.10; p = 0.51). There were no significant differences between the dosing groups when tested at the end of PACU treatment at 4 and 24 h after the start of PCA (p = 0.49 and 0.045, respectively) (Study III).

### 5.2.3 EFFECT OF TIMING OF DOSING

In Study I, we evaluated studies (n=19) that administered ketamine as a pre-incisional bolus at the beginning of surgery and studies that administered ketamine in the

postoperative period (n=9). When assessing the effect on opioid consumption and pain intensity at 24 h, there was no evidence of a difference between preoperative and postoperative ketamine administration (P= 0.28 for difference in opioid consumption and P= 0.55 for difference in pain intensity).

At 48 h after surgery, the test for difference in opioid consumption showed evidence of a difference between pre-incisional and postoperative ketamine administration (P=0.000001). The test for difference in pain intensity at 48 h postoperatively showed no evidence of a difference (P= 0.39).

## 5.3 ADVERSE EVENTS

### 5.3.1 CNS ADVERSE EVENTS

Based on 105 studies with 6538 participants in the literature review (Study I), perioperative IV ketamine did not induce significantly more CNS adverse events compared to controls (RR 1.2; 95% CI 0.95 to 1.4). The randomized, clinical placebo-controlled trials (Studies II and III) showed similar results: in Study II, neither the lower (0.12 mg/kg/h) nor the higher (0.6 mg/kg/h) intraoperative IV S-ketamine infusion induced significantly more CNS adverse events during the 48h study period after lumbar fusion surgery. The RR for CNS adverse events was 0.7 (97.5% CI 0.2 to 2.4) for those who received S-ketamine 0.12 mg/kg/min vs placebo and 1.3 (97.5% CI 0.4 to 3.7) for those who received S-ketamine 0.6 mg/kg/min vs placebo. Neither did adjunct S-ketamine with an oxycodone IV-PCA after lumbar fusion surgery (Study III) induce CNS adverse events significantly differently when compared to patients who received control treatment. Table 13 shows RR for any CNS adverse event after perioperative IV ketamine administration when data from Studies I, II and III are combined.

### 5.3.2 POSTOPERATIVE NAUSEA AND VOMITING

Based on 95 studies with 5965 participants in the literature review (Study I), perioperative IV ketamine treatment reduced PONV by a small extent (RR 0.88; 95% CI 0.81 to 0.96). However, in the RCTs (Studies II and III), a decrease in PONV after S-ketamine administration was not seen. In Study II, the RRs for PONV were similar after both intraoperative IV S-ketamine doses (0.12 mg/kg/h and 0.6 mg/kg/h) to that in the placebo group. In Study III, postoperative adjunct S-ketamine with an oxycodone IV-PCA did not influence PONV (odds ratio (OR) 3.86; 95% CI 0.68 to 4.66). Further, at 24 h when the study PCA was changed to oxycodone only, the incidence of PONV did not change (OR 0.53; 95% CI 0.62 to 4.66). ***Table 10***

shows the RR (95% CI) for PONV after perioperative IV ketamine administration, when data from Studies I, II and III are combined.

**TABLE 10 / RR for CNS adverse events and PONV after perioperative IV ketamine administration**

| | Control | IV ketamine | RR | 95% CI | GRADE |
|---|---|---|---|---|---|
| CNS adverse event, N (%) | 164 (4) | 203 (5) | 1.2 | 0.9 to 1.5 | High |
| PONV, N (%) | 786 (27) | 791 (23) | 1.1 | 1.1 to 1.3 | High |

### 5.3.3 POSTOPERATIVE SEDATION

Intraoperative IV S-ketamine infusion in Study II at a rate of 0.6 mg/kg/h induced significantly more sedation on arrival in the PACU, compared with participants who had received the lower (0.12 mg/kg/min) S-ketamine infusion or placebo intraoperatively. At 2 hours after extubation, there were no significant differences in RASS sedation scores between study groups. In Study III, any dose of adjunct S-ketamine with an oxycodone IV-PCA did not induce significant differences in sedation scores with those who received oxycodone alone.

### 5.3.4 OTHER

Ketamine reduced the area of hyperalgesia by 7 cm2 (95% CI -11.9 to -2.2) around the surgical wound in comparison to participants who received control treatment (Study I).

Intraoperative IV S-ketamine did not induce postoperative confusion, recorded as MMSE scores (Study II). A subgroup analysis of participants > 65 years did not show significant differences in postoperative MMSE scores between study groups either. Few patients responded to the postoperative BDI-II questionnaire assessing depression: there were no significant differences between groups.

Time to first request of analgesia was delayed after perioperative IV ketamine administration by 22 minutes (95% CI 15 to 29) (Study I).

# 6.

# DISCUSSION

This doctoral thesis is based on a Cochrane review with 130 included studies (8341 participants) and two prospective, randomized, double-blind, placebo-controlled clinical trials, one with 198 and one with 100 participants.

The rationale for using ketamine as an adjunct in postoperative analgesia is based on ketamine's ability to prevent wind-up and central sensitization, opioid tolerance and OIH, and possibly to ameliorate the affective component of pain (Trujillo et al. 1994; Stubhaug et al. 1997; Robu and Lavand'homme 2019).

Most previous studies have utilized racemic ketamine, evident in our Cochrane review (Study I). Here, 119 out of 130 studies investigated racemic ketamine, ten used S-ketamine, with only one investigating R-ketamine. In the clinical studies (Studies II and III), we chose to use S-ketamine because of its more selective NMDAR antagonistic effect. Additionally, the elimination half-life of S-ketamine is longer than that of the racemate, potentially a useful feature for an analgesic (Peltoniemi et al. 2016). Furthermore, since most studies assessing ketamine's feasibility as an adjunct analgesic in spinal surgery have used the racemic drug (Garg et al. 2016; Hadi et al. 2010; Kim et al. 2013; Loftus et al. 2010; Nielsen et al. 2017; Yamauchi et al. 2008), there was a lack of data on the effect of S-ketamine in this patient population.

Spinal fusion surgery is known to cause severe postoperative pain (Gerbershagen et al. 2013), and, as populations age, spinal fusion surgery is increasing in frequency and complexity. This has been a fruitful area of research at Töölö Hospital, as approximately 200 spinal fusion procedures are performed here annually. At the time this study began, there was a clinical need to enhance postoperative pain treatment among this patient population, and, in addition to the academic objectives, we had the practical goal of increasing the use of PCA among spinal surgery patients.

## 6.1 EVIDENCE FOR EFFICACY OF PERIOPERATIVE IV KETAMINE AND S-KETAMINE IN IMPROVING POSTOPERATIVE ANALGESIA

### 6.1.1 EFFECT OF KETAMINE ON POSTOPERATIVE PAIN INTENSITY

Based on meta-analyses, the Cochrane review (Study I) revealed that the use of perioperative IV ketamine resulted in an approximately 20% decrease in postoperative

pain scores, both at rest and during movement, at 24 h after different types of surgery. At 48 h, pain scores decreased by 14% at rest and 16% during movement.

There are numerous studies and reviews with substantial amounts of data on ketamine's efficacy on postoperative pain and analgesic consumption.

Previously, Schmid and colleagues assessed low-dose ketamine given via different routes. Based on nine studies with IV administration, they concluded that low-dose ketamine as the sole analgesic agent reduces pain significantly (Schmid et al. 1999) but did not provide quantitative measures. However, most of the included studies were methodologically invalid (Clausen et al. 1975; Jahangir et al. 1993; Joachimsson et al. 1986; Owen et al. 1987; Wilder-Smith et al. 1998), or very small, with fewer than 10 participants per treatment arm (Edwards et al. 1993; Maurset et al. 1989), thus providing only low-quality evidence.

In 2004, Subramaniam and co-workers reviewed studies where ketamine was given intravenously or epidurally (Subramaniam et al. 2004). After analyzing 28 studies with IV administration (as a single bolus, as a continuous infusion, or as an adjunct in PCA), they recommended the use of ketamine by continuous IV infusion, finding that adding ketamine to morphine PCA was not useful. They also recommended focusing on patient groups at high risk of opioid-resistant acute postoperative pain when exploring the analgesic effect of ketamine.

A year later, Elia and Tramér (2005) assessed ketamine in adults and children. In their review, 16 RCTs tested IV ketamine in adults undergoing general anesthesia. An analysis of these studies showed that ketamine induced a statistically significant decrease in pain intensity at rest compared with controls at 6 h postoperatively, with effects lasting up to 48 h. Five RCTs in this review investigated ketamine added to an opioid in an IV-PCA device but, with limited data, a meta-analysis was deemed inappropriate.

Bell and colleagues (2006) included 37 RCTs in a review of the efficacy of ketamine on acute postoperative pain. Of these, 22 investigated IV ketamine, either as an intraoperative infusion (11 studies), as a single bolus at wound closure (5 studies), as an intraoperative ketamine infusion followed by IV ketamine-morphine PCA (2 studies), or as ketamine administered solely in the postoperative period via morphine-PCA (4 studies). Due to high heterogeneity, Bell et al. omitted quantitative analysis of postoperative pain intensity after ketamine administration and did not conclude on ketamine's efficacy in reducing postoperative pain.

In 2011, Laskowski and others, aiming to limit heterogeneity, evaluated the role of IV ketamine in postoperative analgesia for adult and pediatric patients that had

undergone a surgical procedure under general anesthesia (Laskowski et al. 2011). For pain intensity, they reported only qualitative data, finding that ketamine was effective in 17 studies out of 47 in decreasing early pain scores (at 30 minutes). Twelve studies showed a significant decrease in late pain scores (24-72 h after IV ketamine administration. Additionally, the time to first analgesic request was significantly prolonged after IV ketamine, which they interpreted to mean better pain relief after ketamine administration.

Jouguelet-Lacoste and colleagues (2015) published a review of studies using exclusively IV administration of ketamine, distinguishing between different types of infusions (intraoperative, intraoperative + postoperative, or postoperative only). Some included studies were small with fewer than 10 participants per treatment arm (Edwards et al. 1993; Perrin and Purcell 2009), some had methodologically questionable aspects (such as placebo given by a different route than the study drug: Xie et al. 2003), while one study was an open-label trial (Urban et al. 2008). The authors did not provide quantitative data for ketamine's effect on pain intensity, but concluded that ketamine lowered postoperative pain scores, albeit with results less clear than for opioid consumption.

A recent review by Riddel and co-workers showed low-dose IV ketamine to decrease postoperative pain intensity significantly at 24 and 48 h after painful orthopedic surgery. Additionally, the time to first opioid dose was delayed after IV ketamine, indicating improved postoperative analgesia (Riddel et al. 2019). However, the studies in the review covered a variety of procedures, including shoulder arthroscopy, hip and knee arthroplasty, lumbar fusion surgery, anterior cruciate ligament surgery, and lower limb fracture repair, giving rise to significant heterogeneity.

In most studies included in our Cochrane review (Study I), initial postoperative pain intensities in the control group were below 4/10 cm on a Visual Analog Scale (VAS), indicating mild pain. This may explain the relatively modest decrease (approximately 20%) in postoperative pain scores. After a sensitivity analysis using only studies with higher initial pain intensity (VAS > 4/10 cm), there was some evidence that ketamine offered greater pain relief with higher background levels of pain. Clinically, that reflects circumstances where pain intensity is moderate or severe. These findings accord with those of Laskowski et al. (2011), who stated that the greatest efficacy of IV ketamine was in thoracic, upper abdominal and major orthopaedic surgery, i.e. in types of surgery likely to cause intense postoperative pain.

#### 6.1.1.1 S-ketamine's effect on postoperative pain after lumbar fusion surgery

We aimed to find out whether S-ketamine would be advantageous for patients undergoing lumbar fusion surgery. We first tested it as an

intraoperative infusion (Study II) but failed to show any long-lasting, statistically significant improvement in pain relief. Study III showed a beneficial effect in mean change of pain intensity at rest when S-ketamine was administered with oxycodone IV-PCA.

Our negative result for the effect of intraoperative ketamine infusion on postoperative pain after lumbar fusion surgery accords with the findings of Kim et al. (2013), but contradicts those of some other studies, which have reported beneficial effects for this mode of delivery on postoperative pain after spine surgery (Garg et al. 2006; Loftus et al. 2010; Nielsen et al. 2017; Yamauchi et al. 2008). However, a closer look at the aforementioned studies reveals that only Kim et al. (2013) and Nielsen et al. (2017) exclusively investigated patients undergoing lumbar fusion surgery. In other studies, populations comprised patients undergoing cervical, lumbar, or thoracic spine surgery (Yamauchi et al. 2008; Hadi et al. 2010), surgery with or without instrumentation (Loftus et al. 2010), and various back operations, such as microdiscectomy (Garg et al. 2006).

These studies were combined in a recent review by Pendi et al. (2018) which reported significantly lower pain scores at 6, 12, and 24 h after spine surgery, following ketamine administration. Some of the limitations were discussed above, one being the combining of different types of back surgery in different anatomical sites (cervical, thoracic, or lumbar spine), giving rise to heterogeneity. It might also be predicted that microdiscectomy would generate less pain than spinal fusion surgery. Second, it included both pediatric (Engelhardt et al. 2008; Pestieau et al. 2014) and adult patients. It is a reasonable speculation that, based on pharmacokinetics, the duration of the effect of ketamine is different in pediatric populations and furthermore the preoperative conditions (juvenile scoliosis and degenerative lumbar stenosis) are different. Additionally, one study (Nitta et al. 2013) was open-label and another had only women participants, making the results difficult to generalize (Song et al. 2013). This review also omitted two recent, large RCTs with intraoperative IV ketamine infusion (Loftus et al. 2010; Nielsen et al. 2017).

As for the large RCTs by Loftus et al. (2010) and Nielsen et al. (2017), these assessed patients receiving preoperative opioid medication. Previous opioid intake modulates pain perception, may cause OIH and opioid tolerance, while some patients may require larger opioid doses postoperatively. Apart from these, the other ketamine study in spinal surgery had < 50 participants per study arm (Kim et al. 2013).

Heterogeneity of the studies makes interpretation of the reviews and comparison of single studies difficult. There are several factors that need to be considered when evaluating the results. These include numbers of participants in studies, the dose of ketamine used and types of surgery. So far, previous data about S-ketamine's effectiveness in lumbar fusion surgery in opioid-naïve patient populations have not been fully established. As a large, randomized, double-blind placebo-controlled clinical trial, Study II offers new data on the feasibility of intraoperative IV S-ketamine on postoperative opioid consumption and pain after lumbar spinal fusion surgery in opioid-naïve patients.

In Study III, where S-ketamine was added to oxycodone IV-PCA, S-ketamine was beneficial in reducing pain at rest at 24 h after lumbar fusion surgery. A few reviews have previously focused on the effect of ketamine given via IV-PCA.

Based on 11 double-blind RCTs, Carstensen and Möller (2010) provided qualitative data on the efficacy of adjunct ketamine with an opioid PCA. They concluded that adjunct ketamine in opioid IV-PCA was superior to opioid IV-PCA alone for thoracic surgery. The effect was seen both in decreased pain intensity and in reduced cumulative morphine consumption. The effect for orthopedic and abdominal surgery was unclear.

Wang and colleagues assessed the addition of ketamine to morphine/hydromorphone PCA to treat postoperative pain (Wang et al. 2016). Based on data from 26 studies where ketamine was administered via PCA, they concluded that adjunct ketamine provided a small (< 1/10 cm pain reduction on a VAS) improvement in postoperative analgesia. Studies in the review were heterogeneous, with a variety of surgeries combined with general anesthesia, regional anesthesia, or sedation.

Assouline and others evaluated whether adjunct ketamine in opioid PCA would decrease pain intensity and cumulative opioid consumption (Assouline et al. 2016). Data retrieved from 9 RCTs showed that adjunct ketamine with opioid PCA decreased pain intensity by 32%. They combined studies on adults and children, which may limit the usefulness of this data.

Comparison of these reviews is again problematic since heterogeneity arises from: the different ketamine doses used in the studies; the different start times for the PCA device; the different anesthetic modes (general, regional, or sedation) for the surgeries; and from the choice of opioid used in the PCA device (fentanyl, hydromorphone, morphine, oxycodone, and

tramadol) (Carstensen and Möller 2010; Assouline et al. 2016; Wang et al. 2016). The choice of opioid may influence ketamine's efficacy, as there exist various interactions between NMDARs and MORs, as well as interaction and possible synergism between different mu-opioid agonists and ketamine (Garzon et al. 2012; Lilius et al. 2018).

There are few previous data on the effect of adjunct ketamine in opioid IV-PCA exclusively after lumbar fusion surgery in opioid-naïve patient populations. In most studies, pre-incisional boluses or intraoperative ketamine infusion has preceded the PCA administration (Pacreu et al. 2012; Yeom 2012), compromising the evaluation of the analgesic effect of IV-PCA administration of ketamine. In a homogeneous patient population with strictly standardized perioperative care, Study III demonstrated a significant mean change in postoperative pain intensity measured at rest at 24 h after lumbar spinal fusion surgery, when S-ketamine was added to an oxycodone IV-PCA in ratio 1:0.75 (oxycodone:S-ketamine).

A 20 to 30% reduction is typically considered clinically important in postoperative pain (Farrar et al. 2000; Lee et al. 2003; Olsen et al. 2017). Based on previous reviews (Schmid et al. 1999; Subramaniam et al. 2004; Elia and Tramér 2005; Bell et al. 2006), perioperative ketamine offers moderate decreases in postoperative pain intensity although the opioid-sparing effect is greater.

It may be argued that different thresholds for minimal clinically important differences in pain may apply for different patient populations. For example, higher baseline pain intensity might require greater pain reduction to experience benefit from a treatment. Another question is, what is the tolerable pain level for an individual patient? It may be unrealistic to expect a totally pain-free state after major trauma following surgery such as instrumented lumbar spinal fusion (a deep longitudinal skin incision, extensive tissue trauma following lumbar nerve root decompression, transpedicular screw fixation, while ensuring hemostasis with a bipolar sealer). Based on the clinical studies (Studies II and III), S-ketamine added to an oxycodone IV-PCA provided better pain relief after lumbar fusion surgery than administration via intraoperative IV infusion.

IV-PCA is a means for patients to titrate their analgesic consumption to a level where pain intensity is tolerable. Thus, PCA oxycodone consumption

### 6.1.2 OPIOID-SPARING EFFECT AFTER INTRAVENOUS KETAMINE ADMINISTRATION

The minimal clinically important difference in postoperative opioid consumption has not been clearly defined, but typical values range from 20% to 40% (Loftus et al. 2010; Nielsen et al. 2017; Thybo et al. 2019; Laigaard et al. 2021). From a pragmatic viewpoint, a meaningful reduction in postoperative opioid consumption would be such reduction that would result in a decreased number of opioid-related adverse effects or would reduce the risk of development of opioid tolerance or susceptibility to OIH.

In Study II, where S-ketamine was administered as intraoperative infusion, we aimed at a 30% reduction in postoperative oxycodone consumption. In Study III, where S-ketamine was given with oxycodone IV-PCA, the target reduction in oxycodone consumption was 20%.

The Cochrane review (Study I) revealed a 19% reduction in postoperative opioid consumption after perioperative IV ketamine administration at both 24 and 48 h, compared with controls. Greater reductions in postoperative opioid consumption were seen in thoracic, orthopedic and major abdominal surgery, a finding similar to that of Laskowski et al. (2011). In Study II, intraoperative IV S-ketamine infusions decreased oxycodone consumption significantly during the PACU stay when compared to patients receiving control treatment (placebo), but not later during the 48-h study period.

Most reviews report an opioid sparing effect for IV ketamine. Both Elia and Tramér (2005) and Bell and colleagues (2006) have reported approximately 16 mg lower opioid consumption at 24 h after IV ketamine administration. Elia and Tramér have translated this as 27-47% reduction when compared to those patients who did not receive ketamine. Jouguelet-Lacoste and colleagues (Jouguelet-Lacoste et al. 2015) have calculated that IV low-dose ketamine reduces opioid consumption by 40% (the limitations of the review by Jouguelet-Lacoste et al. were discussed above). Pendi and colleagues (2018) reported a significantly decreased mean difference in morphine consumption up to 24 h when ketamine was used for patients undergoing spine surgery but, as stated above, the studies in this review are heterogeneous as to localization in the spine and type of surgery.

Laskowski (2011) and Riddel (2019) give standard mean differences (SMD) and report changes of –1.741 and -0.82, respectively. Both assess these reductions to be statistically significant.

As for ketamine administration in conjunction with opioid IV-PCA, the opioid-sparing effect ranged from 28 to 60% (Assouline et al. 2016; Carstensen and

Möller 2010). Based on absolute values (reduction in mg) reported by Wang and colleagues (2016), adjunct ketamine in opioid IV-PCA reduces cumulative morphine consumption at 24 to 72 h by 5 to 20 mg. In contrast, Subramaniam and colleagues (2004) found the effect of ketamine added to morphine PCA to be unclear, while Elia and Tramér (2005) concluded that IV-PCA with ketamine and morphine did not improve postoperative analgesia.

With Study III, we demonstrated an oxycodone-sparing effect after lumbar spinal fusion surgery, when S-ketamine was added to oxycodone IV-PCA in ratio 1:0.75 (oxycodone:S-ketamine).

The use of mean analgesic consumption as a measure of analgesic efficacy has been criticized because the distribution of analgesic consumption is not Gaussian but skewed, with a minority of patients consuming the majority of the analgesics (Moore et al. 2011). However, it is commonly used as an outcome measure in clinical pain studies and is often the only metric available, enabling comparison and summary of clinical studies in meta-analyses. Additionally, opioid use after surgery is associated with adverse events that may compromise mobilization, rehabilitation, and patient satisfaction, making recording (and reporting) of analgesic consumption meaningful. Changes in opioid consumption can therefore serve as a feasible measure of analgesic efficacy. Additionally, the use of IV-PCA can be seen as a means for each patient to titrate their analgesic consumption to a level where their pain intensity is tolerable. Thus, PCA oxycodone consumption can be regarded as the true analgesic measure for postoperative pain relief.

The discrepancy between postoperative reductions in opioid consumption and pain intensity (i.e. significant in opioid consumption but not in pain intensity) after ketamine administration may also be explained by ketamine's ability to attenuate neural activity in structures responsible for processing the affective component (unpleasantness) of pain (Sprenger et al. 2006; Robu and Lavand'homme 2019). Ketamine may serve here as a dissociative analgesic that disrupts nociceptive input before it reaches somatosensory association areas. Clinically, this might be observed as better toleration of pain with reduced need to self-administer opioid via the PCA device. This would result in significantly reduced opioid consumption despite insignificant differences in reported postoperative pain intensity following both ketamine and placebo administration.

## 6.2 EFFECT OF DIFFERENT KETAMINE DOSES ON ANALGESIC OUTCOMES

There are a few attempts in published research to define the relationship between optimal ketamine dose and postoperative analgesic efficacy. Suzuki and colleagues (1999) administered three different doses of IV ketamine as a single bolus before the end of various outpatient surgical operations. They found that 75 μg/kg and 100 μg/kg doses of ketamine, given together with morphine, reduced total morphine consumption by 40% and decreased pain scores by 35% postoperatively. However, they recorded pain intensity only for the first postoperative hour and the amount of analgesic needed during Phase 1 of recovery, so the clinical relevancy of these results is questionable.

Aqil et al. (2011) tested analgesic efficacy of different ketamine doses on patients undergoing septorhinoplasty. In their study, a single bolus of racemic ketamine, 1 mg/kg or 1.5 mg/kg, at induction of anesthesia was beneficial in delaying the time to first analgesic request in the PACU and reducing postoperative ketoprofen requirement.

Bornemann-Cimenti and colleagues (2016) could not find any difference in postoperative pain intensity after major abdominal surgery when they administered S-ketamine, either as low dose (0.25 mg/kg bolus at induction followed by a continuous infusion of 0.125 mg/kg/h for 48 h) or as minimal dose (no initial bolus, continuous infusion of S-ketamine 0.015 mg/kg/h from the beginning of surgery up to 48 h postoperatively). Both doses were of comparable effectiveness, and were significantly more effective than placebo, in reducing postoperative opioid consumption.

Most reviews have found no evidence of a relationship between the dose of ketamine and analgesic efficacy (Elia and Tramér 2005; Laskowski et al. 2011; Assouline et al. 2016). Bell and colleagues found that there seemed to be no increased morphine-sparing effect when ketamine doses exceeded 30 mg/24 h (Bell et al. 2006). Wang and colleagues concluded that a meta-regression did not detect a significant relationship between ketamine doses and pain scores (Wang et al. 2016).

The selection of doses in the clinical studies reported in this thesis was based upon the fact that the analgesic effect of ketamine is achieved via low-dose administration. Typical analgesic doses of ketamine range between 0.15 and 0.5 mg/kg for bolus administration and 0.15 and 1.2 mg/kg/h for continuous infusion (Schmid et al. 1999; Subramaniam et al. 2005; Elia and Tramér 2005; Bell et al. 2006; Laskowski et al. 2011; Jouguelet-Lacoste et al. 2015; Peltoniemi et al. 2016). Analgesia produced by ketamine occurs at plasma concentrations of 100 to 160 ng/ml (Clements et al. 1981; Mion and Villevieille 2013).

In Study II, we chose a dose of 0.12 mg/kg/min for the first intervention group, at the lower limit of the dose range mentioned above. We speculated that a five-fold difference between the S-ketamine infusion rates would reveal a possible dose dependency, and then used a dose

of 0.6mg/kg/min for the other intervention group. Previous studies report using ketamine infusions for up to 48 h (Jouguelet-Lacoste 2015) and even 72 h after surgery (Hayes et al. 2004) but, due to practical constraints and local hospital practice, we restricted S-ketamine administration to just the intraoperative period.

In studies assessing the effect of ketamine as an adjunct to opioid-PCA, the typical opioid:ketamine ratio has varied between 1:0.5 to 1:2.5 (Carstensen and Möller 2010; Assouline et al. 2016; Wang et al. 2016), with racemic ketamine being most often used. In Study III, we chose oxycodone:S-ketamine ratios of 1:0.25, 1:0.5, and 1:0.75, aiming to investigate whether there existed a dose-response relationship in the different S-ketamine dosing regimens. We chose doses that were roughly half of the racemic ketamine doses used in the previous studies, because S-ketamine is known to be twice as potent as the racemate (Peltoniemi et al. 2016).

After lumbar spinal fusion surgery, both 0.12 mg/kg/h and 0.6 mg/kg/h intraoperative IV S-ketamine doses were successful in decreasing oxycodone consumption significantly in the PACU but not later during the initial 48 h study period. Postoperative pain intensity was significantly lower at 4 h after both ketamine doses, compared with placebo, but the effect was temporary.

Adjunct S-ketamine with oxycodone IV-PCA in a ratio 1:0.75 mg (a bolus containing oxycodone 1 mg/ml + S-ketamine 0.75mg/ml) resulted in 25% decrease in oxycodone consumption at 24 h after lumbar fusion surgery. Lower S-ketamine doses added to an oxycodone IV-PCA did not show a significant oxycodone-sparing effects at 24 h. The oxycodone:S-ketamine ratio 1:0.75 in a PCA device resulted in a beneficial effect in mean change of pain intensity at rest during the 24 h after lumbar fusion surgery.

## 6.3 THE EFFECT OF TIMING OF DOSING OF S-KETAMINE ON POSTOPERATIVE OPIOID CONSUMPTION AND PAIN INTENSITY

In Study I, we evaluated studies with pre-incisional and postoperative ketamine administration. At 24 h, there was no evidence of a difference in opioid consumption or pain intensity between administrations; at 48 h after surgery, postoperatively administered ketamine was more effective in reducing opioid consumption than pre-incisional. As for pain intensity, at 48 h after surgery, there was no significant differences between pre-incisional and postoperative ketamine administration.

Study II showed no beneficial effect of intraoperative IV S-ketamine administration on opioid consumption or postoperative pain after lumbar fusion surgery, whereas S-ketamine added to oxycodone IV-PCA in Study III, i.e., postoperatively, reduced opioid consumption and improved analgesia after such surgery.

Ketamine's active metabolite, norketamine, could in part underlie the effect of timing of dosing on ketamine's analgesic efficacy. In addition to ketamine's analgesic action per se, norketamine's analgesic potency is about 20-30% that of ketamine. Norketamine is slowly eliminated, persisting more than 5 h after ketamine administration (Malinovsky et al. 1996). This accords with the findings of Studies II and III, where the effect of intraoperatively administered S-ketamine vanished after 4 h, whereas postoperative dosing by IV-PCA both improved analgesia and decreased oxycodone consumption at 24 h after lumbar fusion surgery.

## 6.4 TOLERABILITY OF PERIOPERATIVE IV KETAMINE AND S-KETAMINE

### 6.4.1 CENTRAL NERVOUS SYSTEM ADVERSE EVENTS

Hallucinations, dizziness, confusion, nightmares, visual disturbances, and diplopia are adverse events often associated with ketamine use. These adverse events are linked with NMDAR antagonism by ketamine and, in part, with inhibition of nicotinic and muscarinic receptors in cholinergic neurons in the prefrontal cortex (Mion and Villevieille 2013). However, CNS adverse events are likely to be dose-dependent and, when using subanesthetic ketamine doses, their occurrence is rare.

In the Cochrane review (Study I), 52 out of 130 studies reported CNS adverse events; 12 did not report CNS adverse events at all; the remaining 53 studies reported that no CNS adverse events occurred in either study group. Combining these groups, 5% of patients receiving ketamine and 4 % of patients receiving control treatment experienced CNS adverse events, indicating low incidence of CNS adverse events after ketamine administration. The percentage of participants withdrawing from the study because of CNS adverse events was 0.2 for those receiving ketamine and 0.1 for those receiving control treatment.

Hallucinations (one participant saw her husband in different colors!), disorientation, and accommodation disturbances were the most common CNS adverse events in Study II, but the rate of CNS adverse events among participants treated with ketamine was not significantly different than for control participants. Occurrence of any CNS adverse event was 11% in the control group and 7% and 5% in the groups receiving intraoperative S-ketamine infusion. Unpleasant dreams were experienced often when S-ketamine was administered postoperatively by oxycodone IV-PCA (Study III). However, the groups showed no difference in this regard, and the incidence did not change after changing to PCA with oxycodone only at 24 h, implying that this effect was unrelated to ketamine. No participants in the clinical studies (Studies II and III) were withdrawn due to CNS adverse events.

The results showing good tolerability of low-dose IV ketamine and S-ketamine in Studies I-III are consistent with previous studies (Subramaniam et al. 2004; Elia and Tramér 2005; Bell et al. 2006; Assouline et al. 2016; Wang et al. 2016). Only Laskowski et al. (2011) reported an increased risk of hallucinations and nightmares following ketamine administration.

### 6.4.2 POSTOPERATIVE NAUSEA AND VOMITING (PONV)

Nausea and vomiting are common adverse effects of postoperative opioid analgesia. Reducing PONV is one incentive for utilizing ketamine as an adjunct analgesic in the perioperative setting. The clinical studies (Studies II and III) failed to show any decrease in the occurrence of PONV after intraoperative or postoperative S-ketamine administration. On the other hand, intraoperative S-ketamine infusion, or adjunct S-ketamine in the oxycodone IV-PCA did not seem to increase the risk for PONV, either. Both clinical studies were designed to detect a difference in primary outcomes, and thus the power analyses were based on detecting a difference in postoperative opioid consumption. Thus, the failure in Study III to find a correlation between the beneficial effect of adjunct S-ketamine in oxycodone IV-PCA in reducing 24 h oxycodone consumption and a decreased occurrence of PONV could be simply due to a lack of power.

We combined a large body of data in the Cochrane review (Study I), analyzing 95 studies (5965 participants) providing data on nausea and vomiting. We found that IV ketamine treatment reduced PONV from 27% with placebo to 23% with ketamine. The number-needed-to-benefit (NNTB) to prevent one episode of PONV with perioperative intravenous ketamine administration was 24. The effect size is smaller than has been reported previously (Bell et al. 2006; Laskowski et al. 2011).

## 6.5 LIMITATIONS

This thesis has some limitations, and these will now be discussed. The literature review (Study I) included many small studies which may have given rise to heterogeneity in analyses. Small studies may overestimate treatment effects (Deschartres et al. 2013; Gavaghan et al. 2000, Nüesch et al. 2010; Sterne et al. 2002) but they nevertheless provide much of the current data available on the use of perioperative IV ketamine. To mitigate heterogeneity, several subgroup and sensitivity analyses were conducted, addressing such factors as type of surgery, initial pain intensity in control groups (studies with higher pain intensity), and study size.

Challenges with Study II were associated with the study setting, as it was a prospective RCT. First, there were more withdrawals than anticipated and yet, with 189 participants, this trial is

the largest study assessing the effectiveness of intraoperative IV S-ketamine on postoperative pain and opioid consumption after lumbar fusion surgery in opioid-naïve adults.

Second, when designing Study II, the power analysis was calculated with a two-sample t-test, if the 48-h oxycodone consumption would follow a normal distribution. When analyzing the results, we found that this did not hold and so had to use the Mann-Whitney U-test, weakening the power of the analysis.

Third, results for secondary outcomes in Studies II and III must be interpreted with caution because initial power analyses were based on the primary outcomes. On the other hand, results for adverse events (CNS and PONV) were consistent with previous studies (Assouline et al. 2016; Bell et al. 2006; Wang et al. 2016) and were also very similar to those found in our Cochrane review (Study I), where a large body of data was retrieved from several sources, with consistent results. Additionally, though the significant reduction in postoperative oxycodone consumption achieved by oxycodone:S-ketamine ratio 1:0.75 in Study III did not correlate with a reduction in opioid-related side effects, this could be a secondary consequence of a lack of power.

## 6.6 STRENGTHS

The Cochrane review (Study I) was performed using strict methodological and reporting standards, aiming to minimize bias, to maximize transparency, and to improve the accuracy of the available data (McKenzie et al. 2013; Starr et al. 2009). The overall judgement of outcome quality was moderate, except for adverse events, where the quality of evidence was judged as high because of a consistent effect found over a large body of data.

Studies II and III are large randomized, double-blind, placebo-controlled clinical studies evaluating the effect of different dosing regimens of IV S-ketamine on postoperative opioid consumption, postoperative pain, and occurrence of adverse events, after lumbar spinal fusion surgery. Study II is the largest randomized study conducted on this topic.

Lumbar spinal fusion surgery often causes severe postoperative pain (Gerbershagen et al. 2013), hence the need to assess the feasibility of analgesic adjuvants in this setting to provide better pain relief and reduce opioid consumption. Both studies represent real clinical settings, as participant recruitment was not limited to a certain ASA classification, which could have resulted in selection bias. Additionally, the patient population is homogeneous in study groups, consisting of adult men and women of all ages, undergoing posterolateral lumbar spinal fusion. Indeed, there exist few studies assessing the analgesic effect of adjunct ketamine exclusively after lumbar spinal fusion surgery.

The beneficial effect of adjunct IV ketamine in reducing postoperative opioid consumption and pain in the opioid-tolerant patient population after lumbar fusion surgery is well established (Loftus et al. 2010; Nielsen et al. 2017; Nielsen et al. 2018; Boenigk et al. 2019) but the effect in the opioid-naïve population has been less evident. It is recognized that patients with previous opioid intake have altered pain perception and may require higher opioid doses postoperatively. Based on clinical experience, most patients undergoing spinal fusion surgery in Finland are opioid-naïve. Therefore, the applicability of the results in the previous studies is limited. Studies II and III offer clinically feasible data on the role of adjunct ketamine exclusively after spinal fusion surgery.

# 7.

# CONCLUSIONS

Based on the findings in this thesis, the conclusions are as follows:

1.
Perioperative IV ketamine offers a moderate decrease in postoperative pain intensity and opioid consumption in adult patients undergoing any type of surgery under general anesthesia. The effect is seen at 24 h postoperatively and decreases over time. Ketamine is probably more effective in situations with a higher background level of pain (Study I). For opioid-naïve patients, the analgesic effect of intraoperative IV S-ketamine after lumbar fusion surgery is only temporary (Study II).

2.
The data on a possible dose-response relationship are preliminary. There seems to be no difference in the effect of different dosing regimens on postoperative pain and oxycodone consumption when S-ketamine is administered intraoperatively as a continuous infusion during lumbar fusion surgery (Study II).

3.
When S-ketamine is administered as an adjunct via oxycodone IV-PCA after lumbar fusion surgery, the effective oxycodone:ketamine ratio for improving analgesia and reducing oxycodone consumption is 1:0.75 (Study III).

4.
The ideal timing of dosing of ketamine is in the postoperative period (Studies I, II and III). This may be due to the analgesic effect of ketamine per se but also due to its active metabolite, norketamine, that possesses some analgesic potency.

5.
Low-dose IV ketamine and S-ketamine are well-tolerated: they do not increase the risk of CNS adverse events or PONV when used as adjunct analgesics in the perioperative period (Studies I, II and III). Perioperative IV ketamine reduces the occurrence of PONV to a small extent (Study I).

# 8.

# FUTURE ASPECTS

The role of adjunct ketamine in situations with higher levels of pain warrants more research. However, studies should recruit a homogeneous patient population and be adequately powered so that the data derived from these could be utilized in clinical practice. Patient subgroups that might benefit from ketamine's opioid-sparing effect should be investigated. These include, for example, the elderly, and individuals who are sensitive to opioid-induced adverse events. Further, knowing of ketamine's ability to suppress the affective component of pain, it would be interesting to test ketamine on an enriched patient population with known psychological risk factors for higher postoperative pain. This would help to target ketamine at those who are likely to benefit from ketamine's analgesic and opioid-sparing effect.

Future studies pursuing the optimal opioid:S-ketamine ratio should initiate testing from 1:0.75 upward. This could be combined with a pharmacokinetic testing to characterize the dose-concentration-effect relationship.

Finally, acknowledging the various interactions between NMDARs and MORs, as well as between different μ-opioid agonists and ketamine (Lilius et al. 2018), assessing coadministration of ketamine with different opioids in a clinical setting would be of the utmost interest.

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# APPENDIX I

Two review authors (ECVB and ET) independently determined eligibility by reading the abstract of each study identified by the search. Studies that clearly did not satisfy the inclusion criteria were eliminated and full copies of the remaining studies were obtained. Two review authors (ECVB and ET), independently read and selected relevant studies and, in the event of disagreement, a third author adjudicated (VK). We did not anonymise the studies in any way before we assessed studies for inclusion. PRISMA flow chart was created as recommended in Chapter 6 of the Cochrane Handbook for Systematic Reviews of Interventions.

### DATA EXTRACTION AND MANAGEMENT

Two review authors (ECVB and ET) independently extracted data using a standard form and verified for agreement before entry into Review Manager 5 (RevMan 5 (Review Manager 2014)). We collected characteristics of the included studies in sufficient detail to populate a table of 'Characteristics of included studies' in the full review. The results are summarized and interpreted in the 'Effects of interventions' section.

### ASSESSMENT OF RISK OF BIAS IN INCLUDED STUDIES

Two review authors (ECVB and ET), independently assessed risk of bias for each study, using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2017), and adapted from those used by the Cochrane Pregnancy and Childbirth Group. We resolved any disagreements by discussion. A 'Risk of bias' table was completed for each included study using the 'Risk of bias' tool in RevMan 5 (Review Manager 2014).

We assessed the following for each study.

- Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process, e.g., random number table; computer random number generator); unclear risk of bias (method used to generate sequence not clearly stated). We excluded studies using a non- random process (e.g., odd or even date of birth; hospital or clinic record number).

- Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the methods as: low risk of bias (e.g., telephone or central randomization; consecutively numbered, sealed, opaque envelopes); unclear risk of bias (method not clearly stated). We excluded studies that did not conceal allocation (e.g., open list or randomization based on an individual's ID-number).

- Blinding of participants and personnel (checking for possible performance bias). We assessed the methods used to blind study participants and personnel from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study states that it was blinded and describes the method used to achieve blinding, e.g., matched in appearance); unclear risk of bias (study states that it was blinded but does not provide an adequate description of how it was achieved). We considered studies that were not double-blind to have high risk.

- Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study states a clear statement that outcome assessors were unaware of treatment allocation, and ideally describes how this was achieved); unclear risk of bias (study states that outcome assessors were blind to treatment allocation but lacks a clear statement on how it was achieved). We excluded studies where outcome assessment was not blinded.

- Incomplete outcome data (checking for possible attrition bias due to the amount, nature, and handling of incomplete outcome data). We assessed the methods used to deal with incomplete data as: low risk (10% or fewer of participants did not complete the study or used 'baseline observation carried forward' analysis, or both); unclear risk of bias (used 'last observation carried forward' analysis, number of participants that were excluded from the study were not reported); high risk of bias (used 'completer' analysis or inconsistency between article text and tables).

- Selective reporting (checking for reporting bias). We recorded reporting bias, such as failing to report a planned outcome. We assessed whether primary and secondary outcome measures were pre-specified and whether these were consistent with those reported. We assessed the methods as: low risk of bias (all predefined outcomes were reported); unclear risk of bias (insufficient information of some outcomes, e.g., only P values were reported); high risk of bias (predefined outcomes were not reported or outcomes that were not predefined were reported.

- Size of study (checking for possible biases confounded by small size). We assessed studies as being at low risk of bias (200 participants or more per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); high risk of bias (fewer than 50 participants per treatment arm).

### ASSESSMENT OF HETEROGENEITY

Two review authors (ECVB and ET) independently assessed the clinical homogeneity of the studies. In case of discrepancy, we consulted a third review author (VK). The I2 statistic (Higgins 2003) was used as described in the Cochrane Handbook for Systematic Reviews of Interventions and addressed the sources of heterogeneity as appropriate.

### QUALITY OF THE EVIDENCE

Three review authors (RAM, ECVB and VKK), independently rated the quality of the evidence for each outcome using the GRADE system (GRADE 2004), and the guidelines provided in Chapter 12.2 of the Cochrane Handbook for Systematic Reviews of Interventions.

The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias), to assess the quality of the body of evidence for each outcome. The GRADE system uses the following criteria for assigning grade of evidence:

- high: we are very confident that the true effect lies close to that of the estimate of the effect.
- moderate: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
- low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

We decreased the GRADE rating by one (−1) or two (−2) if we identified:

- serious (−1) or very serious (−2) limitation to study quality.
- important inconsistency (−1);
- some (−1) or major (−2) uncertainty about directness;
- imprecise or sparse data (−1);
- high probability of reporting bias (−1).

Factors that would decrease the quality level of a body of evidence were:

- limitations in the design and implementation of available studies suggesting high likelihood of bias.
- indirectness of evidence (indirect population, intervention, control, or outcomes).
- unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses).
- high probability of publication bias;
- imprecision beyond that expected from small studies.

# AUTHOR'S NOTE

This study was carried out at the Department of Anesthesiology, Intensive care and Pain Medicine of Helsinki University Hospital and University of Helsinki during the years 2013-2021. While much of the clinical research was feasible to do along with the clinical work (as well as during maternity leave and on family vacations), I appreciate the financial support I received from The Finnish Society of Anesthesiologists, The Finnish Association for the Study of Pain, Gust. Rud. Idman Foundation of the Finnish Medical Society Duodecim and The Finnish State funding for university-level Health Research.

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