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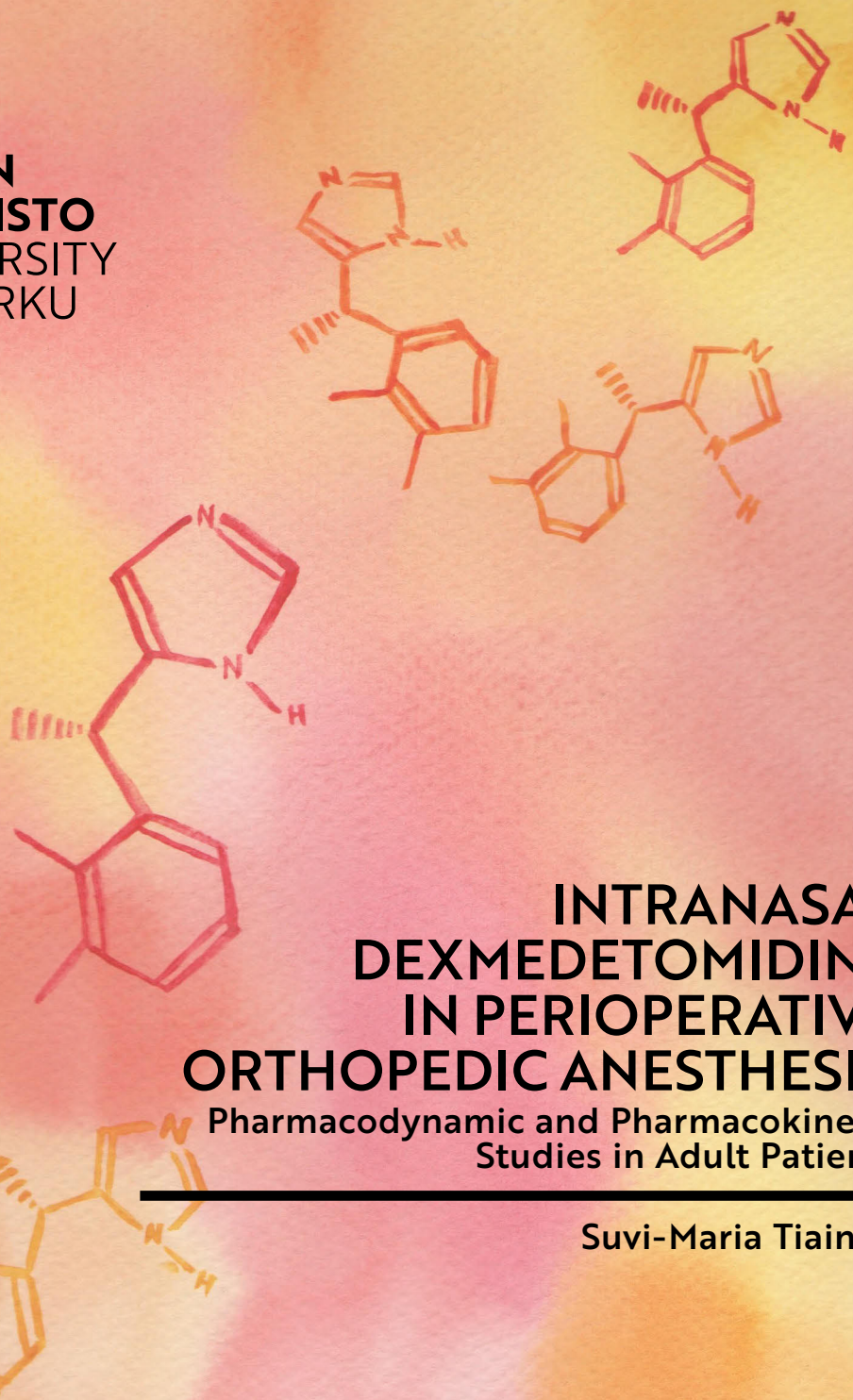

INTRANASAL DEXMEDETOMIDINE IN PERIOPERATIVE ORTHOPEDIC ANESTHESIA

Pharmacodynamic and Pharmacokinetic Studies in Adult Patients

Suvi-Maria Tiainen

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To my family

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ABSTRACT

Effective pain management is critical to ensure optimal recovery after orthopedic procedures, but postoperative pain remains an issue despite the use of multimodal analgesia. Alpha-2-agonist dexmedetomidine could be a valuable adjunct in orthopedic anesthesia due to its sedative, analgesic, anxiolytic, and antiemetic properties. Compared with other administration routes, intranasal administration of dexmedetomidine is advantageous due to favorable pharmacokinetics, noninvasiveness, and attenuated hemodynamic effects.

The present series examines intranasal dexmedetomidine as an adjunct in orthopedic anesthesia from different viewpoints. Specifically, we aim to characterize the effect of intranasally administered dexmedetomidine on postoperative pain and opioid consumption in patients undergoing total knee arthroplasty. We also aim to describe the population pharmacokinetics of intranasal dexmedetomidine on adult patients under general anesthesia for total joint arthroplasty and the effect of intranasal dexmedetomidine on perioperative hemodynamics, bleeding, and blood count; the feasibility of intranasal dexmedetomidine in treating postoperative restlessness, agitation, and pain in geriatric orthopedic patients are also evaluated.

Our results suggest that perioperative intranasal dexmedetomidine reduces postoperative pain and opioid consumption in patients undergoing total knee arthroplasty under general anesthesia, but the difference is not statistically significant in patients under spinal anesthesia. The bioavailability of intranasal dexmedetomidine was as good as observed in earlier studies, but the absorption half-time was longer than in prior pharmacokinetic investigations on adult subjects. The use of intranasal dexmedetomidine in geriatric orthopedic patients to treat postoperative restlessness, agitation, and pain seems feasible, but close observation of hemodynamic effects is warranted.

Our findings indicate that intranasal dexmedetomidine can be a safe and effective adjuvant in orthopedic surgery.

KEYWORDS: alpha2-agonist, dexmedetomidine, intranasal administration, multimodal pain management, orthopedic surgery, pharmacodynamics, pharmacokinetics

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TIIVISTELMÄ

Tehokas leikkauksenjälkeinen kivunhallinta on ratkaisevan tärkeää optimaalisen toipumisen varmistamiseksi. Käytössä olevista multimodaalisista kivunhallintamenetelmistä huolimatta leikkauksen jälkeinen kipu on edelleen usein haasteena ortopedisten toimenpiteiden jälkeen. Alfa-2-agonisti deksmedetomidiini voisi olla arvokas lisä ortopedisen anestesiaan sen rauhoittavien vaikutuksien, sekä kipua, ahdistusta ja pahoinvointia lievittävien ominaisuuksien vuoksi. Verrattuna muihin antoreitteihin deksmedetomidiinin intranasaalinen anto on edullista suotuisan farmakokinetiikan, kajoamattomuuden ja vähäisempien verenkiertovaikutusten vuoksi.

Tarkastelemme näissä tutkimuksissa intranasaalisen deksmedetomidiinin käyttöä apuaineena ortopedisessä anestesiassa eri näkökulmista. Erityisesti tarkoituksena on selvittää intranasaalisesti annetun deksmedetomidiinin vaikutusta postoperatiiviseen kipuun ja opioidien kulutukseen polviproteesileikkauksen jälkeen. Lisäksi tutkimme intranasaalisen deksmedetomidiinin farmakokinetiikkaa nukutetuilla aikuispotilailla, joille tehdään tekonivelleikkaus. Myös intranasaalisen deksmedetomidiinin vaikutusta perioperatiiviseen verenpaineeseen ja sykkeeseen, verenvuotoon ja verenkuvaan, sekä intranasaalisen deksmedetomidiinin käyttökelpoisuutta leikkauksen jälkeisen levottomuuden, kiihtyneisyyden ja kivun hoidossa geriatrisilla ortopedisilla potilailla arvioidaan.

Tuloksemme osoittavat, että perioperatiivisesti annosteltu intranasaalinen deksmedetomidiini vähentää leikkauksen jälkeistä kipua ja opioidien kulutusta potilailla, joille tehdään polven tekonivelleikkaus yleisanestesiassa, mutta ero ei ollut tilastollisesti merkitsevä, jos anestesiamuotona oli selkäydinpuudutus. Intranasaalisen deksmedetomidiinin biologinen hyötyosuus oli yhtä hyvä kuin aikaisemmissa aikuisilla koehenkilöillä tehdyissä farmakokineettisissä tutkimuksissa, mutta imeytymisen puoliintumisaika oli pidempi. Intranasaalisen deksmedetomidiinin käyttö iäkkäillä ortopedisilla potilailla leikkauksen jälkeisen levottomuuden, kiihtyneisyyden ja kivun hoitoon näyttää mahdolliselta, mutta verenkiertovaikutusten tarkka seuranta on perusteltua.

Tuloksemme osoittavat, että intranasaalinen deksmedetomidiini voi olla tehokas ja turvallinen apuaine ortopedisissä leikkauksissa.

AVAINSANAT: alfa2-agonisti, deksmedetomidiini, intranasaalinen annostelu, multimodaalinen kivunhoito, ortopedia, farmakodynamiikka, farmakokinetiikka

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Abbreviations

ASA	American Society of Anesthesiologists
BBB	blood-brain barrier
BMI	body mass index
bpm	beats per minute
CYP	cytochrome P450
CL	clearance
ECG	electrocardiogram
EDTA	ethylenediaminetetraacetic acid
ERAS	Enhanced Recovery After Surgery
F	relative bioavailability
FiO2	fraction of inspired oxygen
GABA	gamma-aminobutyric acid
ICU	intensive care unit
LIA	local infiltration analgesia
MAP	mean arterial pressure
MMA	multimodal analgesia
mRASS	modified Richmond Agitation Sedation Scale
NALT	nasal-associated lymphoid tissue
NIBP	non-invasive blood pressure
NMDA	N-methyl-D-aspartate
NSAID	non-steroidal anti-inflammatory drug
NTB	nose-to-brain
NRS	numeric rating scale
PACU	post-anesthesia care unit
PCA	patient-controlled analgesia
PK	pharmacokinetic
pK_a	acid dissociation constant
PNB	peripheral nerve block
PONV	postoperative nausea and vomiting
SD	standard deviation
SpO_2	peripheral arteriolar oxygen saturation

T_{ABS}	absorption half-time
TCI	target-controlled infusion
T_{LAG}	absorption lag time
TIVA	total intravenous anesthesia
THA	total hip arthroplasty
TJA	total joint arthroplasty
TKA	total knee arthroplasty
TRPV1	transient receptor potential cation channel subfamily V member 1
VAS-A	verbal analogue scale (anxiety)

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Suvi-Maria Seppänen, Ronja Kuuskoski, Keijo T. Mäkelä, Teijo Saari, Panu Uusalo. Intranasal Dexmedetomidine Reduces Postoperative Opioid Requirement in Patients Undergoing Total Knee Arthroplasty Under General Anesthesia. Journal of Arthroplasty, 2021; 3, 978–985.

II Suvi-Maria Tiainen, Brian Anderson, Ella Rinne, Aleksi Tornio, Marica Engström, Teijo Saari, Panu Uusalo. Absorption pharmacokinetics and feasibility of intranasal dexmedetomidine in patients under general anaesthesia. Acta Anaesthesiologica Scandinavica, 2024; 9, 1182–1191.

III Suvi-Maria Tiainen, Heta Heinonen, Atte Koskinen, Sanna Mäkelä, Ruut Laitio, Eliisa Löyttyniemi, Keijo Mäkelä, Teijo Saari, Panu Uusalo. Premedication with intranasal dexmedetomidine in patients undergoing total knee arthroplasty under spinal anaesthesia (TKADEX) – a prospective, double-blinded, randomised controlled trial. BJA Open, 2025; 13, 100382.

IV Suvi-Maria Tiainen, Atte Koskinen, Sanna Mäkelä, Ruut Laitio, Eliisa Löyttyniemi, Keijo Mäkelä, Carl-Olof Pirttikangas, Teijo Saari, Panu Uusalo. Effects of intranasal dexmedetomidine premedication on hemodynamics, oxygenation and bleeding in patients undergoing total knee arthroplasty under spinal anesthesia – a secondary analysis of a prospective, double-blinded, randomized controlled trial (TKADEX). *Manuscript.*

V Panu Uusalo, Suvi-Maria Seppänen, Mikko Järvisalo. Feasibility of Intranasal Dexmedetomidine in Treatment of Postoperative Restlessness, Agitation, and Pain in Geriatric Orthopedic Patients. Drugs & Aging, 2021; 38: 441–450.

1 Introduction

Many orthopedic procedures, such as total hip and knee arthroplasty, are associated with a considerable amount of pain (Gerbershagen et al. 2013). Success in postoperative pain management is a critical factor affecting postoperative outcomes, and failure in it may produce negative consequences such as chronic pain, prolonged hospital stay, and poor functional outcomes (Fletcher et al. 2015; Morrison et al. 2003). The prevalence of osteoarthritis is steadily increasing, and effective pain management is crucial to optimize patient care (Steinmetz et al. 2023). Although opioids have historically been the mainstay of postoperative analgesia, there has been a gradual but noticeable trend toward other analgesics as knowledge of opioid-related issues has grown (Roberts et al. 2024). Multimodal analgesia (MMA) combines pain medications that target different parts of the pain pathway. It aims to provide synergistic effects, resulting in more effective pain relief with fewer side effects. Because each analgesic component can be used at a lower dose, the risk of adverse effects associated with any single agent is reduced. One key goal of MMA is to minimize the need for opioid use. Highly selective alpha-2 agonist dexmedetomidine reduces opioid consumption (Chan et al. 2016; Uusalo et al. 2019; Donatiello et al. 2022); thus, it might be a promising addition to MMA of patients undergoing orthopedic surgeries.

Dexmedetomidine is best known as a sedative and is commonly used for sedation in intensive care units (ICU) and during different procedures. Originally the aim behind the development process of dexmedetomidine was to generate an effective premedication for surgical procedures (Kallio et al. 1989). However, for several years dexmedetomidine was used solely for sedation. Recently, the focus has expanded to other properties besides sedation, and the potential of dexmedetomidine as a premedication has been discovered anew. Official administration routes for dexmedetomidine are intravenous and sublingual (Precedex Approval Documents Abbot Laboratories 1999; Igalmi Product Label BioXcel Therapeutics 2022). Several other administration routes have been tested and intranasal administration of dexmedetomidine has especially become very popular (Iirola et al. 2011, Uusalo et al. 2019, van Hoorn et al. 2021). The intranasal route is a non-invasive, quick, and efficient way to administer medications, and hemodynamic alterations may be

attenuated compared to intravenous administration of dexmedetomidine (Iirola et al. 2011).

Previous studies show that intravenous dexmedetomidine reduces opioid consumption after orthopedic surgery (Donatiello et al. 2022), but administration through the intranasal route has not been researched in adults, except for total hip arthroplasty (THA) (Uusalo et al. 2019). Use of intranasal dexmedetomidine is gradually increasing, but knowledge of its pharmacokinetics is still limited. Since intranasal administration of dexmedetomidine during general anesthesia has been reported (Uusalo et al. 2019), further studies are essential to clarify its pharmacokinetics in such settings.

These studies examined how intranasal dexmedetomidine can be used as an adjunct for pain management in orthopedic surgery. We also studied the pharmacokinetics of nasally administered dexmedetomidine in anesthetized adult patients in the supine position and the effects of intranasal dexmedetomidine on hemodynamics and other perioperative parameters.

2 Review of the Literature

2.1 Anesthesia in Orthopedic Surgery

Orthopedic surgery usually aims to restore function, increase mobility and reduce pain. Unlike many other surgical specialties, orthopedic surgery is less about saving lives and more about improving the quality of life. This emphasis on enhancing day-to-day living presents certain challenges for anesthesiologists. Orthopedic surgery encompasses a broad spectrum of procedures—from minimally invasive procedures to major operations such as total joint arthroplasty (TJA) and spine surgery. It also includes elective and emergency surgeries. Anesthesiologists treating orthopedic patients must be adaptable and capable of performing a variety of anesthetic techniques, including general anesthesia, neuraxial anesthesia, and various blockades. The following section examines the challenges that orthopedic anesthesia presents for anesthesiologists, focusing on pain control in orthopedic procedures, especially in arthroplasty surgery.

2.1.1 Challenges in Orthopedic Anesthesia

The prevalence of osteoarthritis is continuously increasing, as is the number of arthroplasties performed (Steinmetz et al. 2023, Shichman et al. 2023). The rise in osteoarthritis has been mostly attributed to the aging population, but prevalence is also rising in younger patients because of obesity (Silverwood et al. 2015). Hip and knee arthroplasty are already the most frequent orthopedic surgeries in Finland, with nearly 30 000 primary arthroplasty procedures performed annually (THL 2024). Since osteoarthritis is becoming more common and utilizing TJA is bound to increase, optimizing of patient care is critical. Healthcare in Finland is already struggling to provide care for all patients, and the growing demand for arthroplasty surgery poses a significant challenge. One solution to managing growing treatment queues is to optimize patient care and reduce the time spent in the hospital since the postoperative ward's capacity is typically a bottleneck for the number of arthroplasties performed (THL 2024).

Adequate pain management is a significant challenge for anesthesiologists treating orthopedic patients. The need for efficient pain relief while avoiding side

effects and facilitating quick recovery is a delicate balance requiring careful consideration of numerous factors. Postoperative pain is a common problem after orthopedic surgery, that may have various negative consequences in the postoperative period, including persistent postoperative pain, delayed recovery, and worse functional outcomes (Raspopović et al. 2021; Fletcher et al. 2015). Patients coming to orthopedic procedures often already have long-lasting pain before the surgical operation, and pre-existing pain is a well-known risk factor for severe postoperative pain (Kalkman et al. 2003). Opioids have been the foundation of postoperative analgesia in orthopedic surgery due to their effectiveness in providing significant pain relief. There is growing concern over opioid use, although unlike in Northern America, there is no recognized "opioid crisis" in Europe. A recent study found that in Finland, postoperative pain was the most prevalent reason for opioid usage, accounting for 20% of total consumption (Keto et al. 2022). Opioid-sparing anesthesia approaches and the extreme approach of opioid-free anesthesia are examples of alternative solutions that have been developed due to growing knowledge of the possibility of opioid-related adverse effects. Although the usefulness of opioid-free anesthesia is a highly debated subject, MMA approaches are generally accepted to be beneficial (Chassery et al. 2024).

Historically, patients stayed in the hospital for several weeks or even months after THA (Epstein et al. 1987). Now, advances in surgical techniques, anesthesia, and postoperative care have dramatically reduced hospital stays, allowing for the possibility of discharge on the same day the TJA is performed (Debbi et al. 2022). This shift towards rapid discharge benefits patients and the healthcare system, as it can reduce the risk of hospital-acquired infections, lower healthcare costs, and enable a quicker return to normal life (Jansen et al. 2020). Rapid discharge can be highly beneficial but poses challenges, particularly from an anesthesiologist's perspective. Enhanced Recovery After Surgery (ERAS) protocols have been developed to address these challenges by optimizing various aspects of perioperative care (Wainwright et al. 2020). Hypotension, pain, and postoperative nausea and vomiting (PONV) are the most frequent anesthesiologic causes of why rapid discharge fails (Shen et al. 2023; Gong et al. 2024). Optimized pain management is an important aspect of promoting swift rehabilitation, as effective pain management permits patients to move, and patients with controlled pain are likelier to adhere to rehabilitation programs. MMA, which involves using multiple methods to control pain, is often employed to minimize the side effects of any single analgesic technique (Lamplot et al. 2014).

In addition, the evolving patient population poses further challenges in orthopedic surgery. Many patients undergoing orthopedic surgery are elderly; this number will continue to rise in the coming decades. Older patients often present with frailty, polypharmacy, and multiple comorbidities—all of which increase their risk

for complications, including opioid-related side effects and the development of delirium. Reduced opioid-related side effects can improve recovery, facilitate earlier discharge, and maximize the use of resources. Besides the elderly, the rising number of obese patients undergoing orthopedic surgery provides challenges for anesthesiologists taking care of orthopedic patients. Obesity is associated with a higher risk of perioperative complications, such as a difficult airway and difficulties in providing neuraxial blocks. Overweight is also one known risk factor for increased postoperative pain severity (Basem et al. 2021).

Many orthopedic procedures are performed under neuraxial anesthesia. However, spinal anesthesia alone is often insufficient since patients are frequently nervous and request additional sedation. Conventionally used sedative medications carry a risk of severe side effects, such as delirium and respiratory depression. (Nolan et al. 2020; Athanassoglou et al. 2022). Numerous patients receive these medications, although little clinical evidence supports their use (Bucx et al. 2016). Anesthesiologists are tasked with the issue of balancing sedation so it is adequate while minimizing unwanted outcomes.

2.1.2 Pathophysiology of Pain in Orthopedic Surgery

Orthopedic surgery is associated with more intense postoperative pain than many other surgical specialties (Ekstein et al. 2011; Gerbershagen et al. 2013) and is one of the risk groups for persistent postoperative pain (Boko et al. 2024). TJA, in particular, has been identified as one of the most painful operations (Gerbershagen et al. 2013), with total knee arthroplasty (TKA) regularly causing more pain than THA (Pinto et al. 2016). The cause for more extreme acute postoperative pain following TKA compared to THA is unknown; however, more sophisticated joint mechanics, nerve involvement, and the intensity of rehabilitation have been suggested as possible explanations (Pinto et al. 2016). Extensive tissue damage and bone manipulation have been proposed as potential causes of significant postoperative pain in orthopedic procedures. The periosteum is densely innervated with nociceptors, which may correlate with high pain levels (Steverink et al. 2021). Postoperative pain may also be more intense because orthopedic patients often have pre-existing pain, such as pain from osteoarthritis. Pain following orthopedic surgery can be produced by a variety of factors, including inflammation, tissue trauma, and nerve compression or injury; therefore, it can be nociceptive, neuropathic, or inflammatory.

The transmission of pain in the nervous system can be divided into four stages: transduction, transmission, modulation, and perception (Figure 1). In peripheral tissues, nociceptors respond to a surgical stimulus (primary afferent neuron). Pain stimulus is then transmitted via A-delta and C fibers to the dorsal horn of the spinal

cord. After that, the pain impulse travels up the spinal cord in the lateral spinothalamic tract to the thalamus. Tertiary neurons carry the pain message from the thalamus to the cerebral cortex, where the actual sensation of pain arises in the sensory cortex (perception of pain). Pain modulation happens when inhibitory descending pathways block the activity of pain-transmitting nerves; however, modulation can also strengthen the sensation of pain. Interpreting pain also involves periaqueductal gray matter, the limbic system, and the basal ganglia.

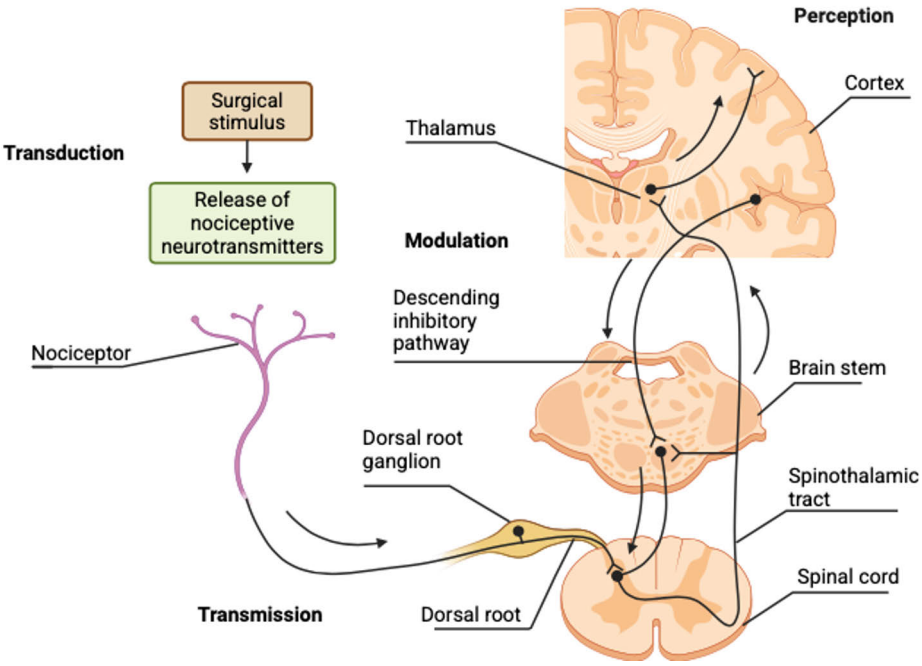


Figure 1. Pain pathways. Transduction: Nociceptor activation. Transmission: The pain message is transferred along neurons to the parts of the central nervous system whose activation leads to the sensation of pain. Modulation: modulation of pain in the central nervous system (CNS). Perception: the subjective feeling caused by the activation of pain-transmitting neurons. Modified from Lecturio: Pain: Types and Pathways. Created in BioRender.com

2.1.3 Multimodal Analgesia in Orthopedic Surgery

Many orthopedic patients continue to have disturbing postoperative pain, even with the use of extensive MMA. It has also been established that the effectiveness of analgesics may vary depending on the surgical procedure (Gray et al. 2005). Therefore, the search for better analgesics and their combinations, as well as

optimizing the pain management strategy in different procedures, ensues. The next section will look at the available components of MMA and some future prospects.

2.1.3.1 Opioids

The body produces endogenous opioids (endorphins, enkephalins, and dynorphins), which are important in regulating pain, mood, and other physiological functions. Exogenous opioids—drugs that exploit the natural opioid system—have been used for their analgesic effects for centuries. Although opioids are very effective analgesics, there is a danger of addiction, abuse, and overdose, besides other adverse effects. It has been estimated that over 125 000 people die annually due to opioid overdose, and non-fatal opioid overdoses are far more common than that, which has led to the term ”opioid crisis” (WHO 2023). Despite their questionable reputation, opioids remain an essential component of pain management and have their place as rescue analgesics in severe pain. Efforts are made to develop new opioids, such as mixed or biased opioid agonists, which could hopefully provide analgesia with fewer side effects.

Opioid receptors are found all over the body, but mostly in the central and peripheral nervous systems. The most common types of opioid receptors are mu (μ), kappa (κ), and delta (δ). All the most commonly used opioids in perioperative settings, like morphine, fentanyl, and oxycodone, are agonists of the mu-receptor. Most opioid side effects, including respiratory depression, opioid tolerance, opioid-induced hyperalgesia, constipation, PONV, dependency, and misuse risk, are also caused by the activation of mu-receptors (Loh et al. 1998). Opioids produce their analgesic effects presynaptically by blocking the release of pain neurotransmitters and postsynaptically by causing hyperpolarization, consequently increasing the required action potential to generate nociceptive transmission. Analgesic effects of opioids are elicited by central opioid receptors while many of the side effects are caused by the activation of peripheral opioid receptors; thus, peripherally acting opioid receptor antagonists can mitigate some of the adverse effects.

Intrathecal opioids have been used to provide analgesia in arthroplasty surgery. They provide analgesic benefits but increase the risk of side effects. Due to side effects, their use is not recommended routinely in arthroplasty guidelines (Lavand’homme et al. 2022; Anger et al. 2021).

2.1.3.2 Paracetamol

Paracetamol (acetaminophen) is a widely used analgesic, and although its analgesic effect is modest, it is a recommended first-line component of MMA due to its low cost and risk (Lavand’homme et al. 2022; Anger et al. 2021). Besides the analgesic

effect, paracetamol is also antipyretic. Despite its long and widespread use, paracetamol's analgesic mechanism of action is still unknown. However, it is assumed to involve cyclooxygenase inhibition (Lee et al. 2007). Another explanation is that paracetamol is a prodrug, with the analgesic activity coming from the metabolite AM404, which produces analgesia by activating Transient receptor potential cation channel subfamily V member 1 (TRPV1) (Mallet et al. 2010). Paracetamol is primarily metabolized in the liver; therefore, its use is contraindicated in severe hepatic impairment. Adverse effects are uncommon when paracetamol is administered in the therapeutic range. Hepatotoxic NAPQI (N-acetyl-p-benzoquinone imine) is a byproduct of paracetamol metabolism, and there is a risk of liver injury if paracetamol is used over the recommended dose or for patients with decreased hepatic function.

2.1.3.3 Non-steroidal Anti-inflammatory Drugs

Non-steroidal anti-inflammatory drugs (NSAID) are a group of drugs that inhibit the enzyme cyclooxygenase (COX) and prostaglandin production (Vane 1971). Besides analgesic effects, they also have antipyretic and anti-inflammatory effects. NSAIDs can be divided by their selectivity as specific COX 2 inhibitors and nonspecific inhibitors of COX 1 and COX 2 (Cryer and Feldman 1998). Commonly used NSAIDs in orthopedic anesthesia include nonselective ibuprofen and ketoprofen, as well as COX-2 selective etoricoxib, among others. NSAIDs have become essential components of MMA, but their potential side effects limit their use. The inhibition of COX-1, which protects the stomach lining, can cause gastric irritation, ulcers, and gastrointestinal bleeding. NSAIDs also inhibit thromboxane (TXA2) synthesis, resulting in decreased platelet aggregation and impaired coagulation. Renal dysfunction is another possible side effect, and NSAIDs can cause various types of kidney injury. COX-2 inhibitors have a distinct side effect profile compared to nonselective inhibitors The gastrointestinal side effects are reduced because they do not inhibit COX 1. However, they promote thrombosis by inhibiting prostacyclin (PGI2), increasing the risk of heart attacks (Kearney et al. 2006). In orthopedic anesthesia, it has been a topic of interest and continuing debate whether NSAIDs interfere with bone healing. Prolonged use or high doses might be associated with delayed union of fractures, but short-term use is generally considered safe (Borgeat et al. 2018).

2.1.3.4 Other Adjuvants

Glucocorticoids can be used as an adjunct in perioperative MMA. Besides the opioid-sparing effect, glucocorticoids are beneficial since they effectively reduce

PONV. The analgesic effects of glucocorticoids likely stem from their anti-inflammatory properties: They reduce inflammation and inhibit prostaglandin synthesis (Lewis, Campbell, and Johnson 1986). Dexamethasone has a long half-life and is the most extensively researched adjuvant glucocorticoid. However, its superiority over other glucocorticoids remains under debate as a small number of studies limit the literature; therefore, no comparisons between different glucocorticoids can be made. Side effects of glucocorticoids include hyperglycemia, risk of infection, and delayed wound healing (Herbst et al. 2020; Dostal et al. 1990). The optimal dosage and frequency of corticosteroids remain unclear. The adverse effects are typically not a concern, at least with modest dosages (6–12 mg of intravenous dexamethasone). The efficacy of glucocorticoids as an analgesic adjunct appears to be dose-dependent; in arthroplasty surgery, even high-dose glucocorticoids (up to 25mg of intravenous dexamethasone equivalents) can be employed (Nielsen et al. 2022). Despite concerns about side effects, high doses of glucocorticoids also seem to be generally well-tolerated (Jørgensen et al. 2017). It has been proposed that repeated glucocorticoid doses might provide additional benefits in arthroplasty surgery (Lei et al. 2020; Li et al. 2019).

Gabapentinoids derive their name from their structural similarity to gamma-aminobutyric acid (GABA), but despite what one might think from their name, they do not bind to GABA receptors (Jensen et al. 2002). The mechanism of action for analgesia is not well understood, but they act on voltage-gated Ca^{2+} channel subunit α2δa in the dorsal root ganglion and inhibit the release of various neurotransmitters (Chen et al. 2018), as well as modulate descending pathways (Hayashida et al. 2007). Gabapentinoids have well-established analgesic properties in neuropathic pain, but their role in postoperative pain is unclear. Oversedation, respiratory depression, and postoperative pulmonary complications are some of the adverse effects of gabapentinoids, especially when combined with postoperative opioids (Myhre et al. 2016). Although gabapentinoids have been shown to decrease pain, they are not currently advised as an adjunct in MMA after arthroplasty surgery because of the increased incidence of adverse effects (Anger et al. 2021).

N-methyl-D-aspartate (NMDA)-antagonist ketamine is widely used in pain management and can be especially useful in patients with high opioid tolerance or chronic pain (Nielsen et al. 2017). In addition to NMDA-antagonism (MacDonald et al. 1987), ketamine interacts with μ opioid, GABA, and muscarinic acetylcholine receptors (Durieux 1995; Wang et al. 2017; Pacheco et al. 2014). Ketamine has undesirable side effects, such as hallucinations and increased risk for postoperative delirium, which limit its use. Low-dose ketamine appears to be beneficial in spine surgery (Yamauchi et al. 2008; Garg et al. 2016). However, the evidence for ketamine use in arthroplasty is more mixed, with conflicting results on its efficacy (Adam et al. 2005; Tan et al. 2019)

Perioperative administration of intravenous lidocaine and intravenous magnesium ($MgSO_4$) have been suggested as a nonopioid components of MMA. The analgesic mechanism of intravenous lidocaine is not completely understood, but it does not appear to include sodium channels, as when used in local anesthesia. It has been suggested that lidocaine may not be effective in arthroplasty surgery (Fletcher et al. 2008), but it might be effective in spine surgery (Farag et al. 2013). Intravenous lidocaine has a narrow therapeutic window and the possibility for severe side effects like local anesthetic systemic toxicity (LAST). Unlike lidocaine, magnesium has a broad therapeutic index. Magnesium has analgesic effects because it acts as an antagonist of NMDA receptors in the central nervous system and may prevent central sensitization (Harrison et al. 1985; Woolf et al. 1991). In a recent study, intraoperative magnesium infusion significantly reduced postoperative pain after TKA (Xu et al. 2024)

2.1.3.5 Local Anesthesia

Local infiltration anesthesia (LIA) refers to injecting local anesthetics directly into the surgical site, which the surgeon applies during the operation. Adjuncts like adrenaline or ketorolac can also be used (Andersen et al. 2013). LIA is safe and effective and does not produce motor blockade; therefore, it is unsurprising that it has become a common practice in TJA; several guidelines recommend its use (Anger et al. 2021; Lavand'homme et al. 2022). The advantages of LIA are evident in patients undergoing TKA, while its efficacy in THA has been a debated subject, and the old ERAS guidelines did not recommend using LIA in THA (Wainwright et al. 2020). However, the updated recommendations encourage using LIA in THA (Anger et al. 2021).

Peripheral nerve blocks (PNB) can be an effective part of MMA after arthroplasty surgery, but their use may be limited in some cases due to the potential for impaired motor function and delayed mobilization. PNBs can be performed with a single shot or with continuous infusion through a catheter. After TKA, femoral nerve block or adductor canal block are theoretically possible PNB techniques. Femoral nerve block compromises motor function and is hence not the ideal choice. However, adductor canal block, which inhibits the sensory branch of the femoral nerve, is advised for postoperative pain control following TKA (Lavand'homme et al. 2022). For postoperative pain management after THA, several PNB methods have been suggested, but they all possess some degree of risk for motor block. If PNB is used in THA patients, a fascia iliaca block is recommended (Anger et al. 2021).

Epidural analgesia is very successful in treating postoperative pain in arthroplasty surgery. However, its adverse effects, such as limb weakness, make it unsuitable in today's fast-paced arthroplasty procedures. It has almost completely

been replaced by LIA and PNB techniques. However, it still retains its place in more complex cases like revision surgery and patients with severe chronic pain.

2.1.3.6 Emerging Analgesic Agents

Drugs in development for MMA target different parts of the pain pathway and supplement the existing ones, offering alternative or additional mechanisms of action for pain treatment.

Transient receptor potential cation channel subfamily V member 1 (TPRV1) receptors are located on nociceptors and in the central nervous system. TRPV1 antagonists are a promising new group of drugs for treating postoperative pain, as TRPV1 plays a role in pain transmission and regulation. The best-known TRPV1-acting drug is agonist capsaicin, which causes TRPV1 desensitization and can consequently alleviate pain. Capsaicin is not used in postoperative pain but in chronic pain conditions. Vocacapsaisin—a prodrug of capsaicin—effectively reduced postoperative pain and opioid consumption in a trial with patients undergoing bunionectomy, and the effect was long-lasting (Shafer et al. 2024). TRPV1 antagonist—intra-articular resiniferatoxin—is being tested in clinical trials to treat pain in patients with knee osteoarthritis (Iadarola et al. 2018).

Voltage-gated sodium channels NaV 1.7, 1.8, and 1.9 are predominantly located on nociceptors, and their blockers are one emerging option for postoperative analgesia. Voltage-gated sodium channels (NaV) play a key role in pain transmission because their opening causes depolarization, allowing the pain signal to travel further from nociceptors. NaV 1.8 blocker VX-548 effectively reduced postoperative pain after bunionectomy in a phase II trial (Jones et al. 2023).

2.2 Dexmedetomidine

2.2.1 Alpha2-receptors and Their Agonists

2.2.1.1 Adrenergic Receptors

Adrenergic receptors mediate the effects of endogenous catecholamines, such as noradrenaline and adrenaline, as well as a variety of medications. They are part of a large G-protein (guanine nucleotide-binding proteins) coupled receptor superfamily. Adrenoceptors are divided into two main groups: alpha (α) and beta (β). Alpha-adrenergic receptors are divided into α1 and α2 -receptors. Subclassification to α1 and α2 receptors was originally based on the anatomical localization of receptors. Later, it became obvious that classification could not be based solely on location as

both receptors are found pre- and postsynaptically. Instead of localization, the relative potency of selective agonists and antagonists is the basis for the current classification. Human α2 receptors are further divided into three subtypes: α2A, α2B, and α2C (Bylund et al. 1994). Affinity for agonists and antagonists is used to divide the various kinds of α2 receptors. The existence of the fourth α2-receptor subtype, α2D, was suspected for some time, but later, it was discovered to be rather a species variation of the α2A subtype, not an actual subtype (Aantaa et al. 1995). Nine human adrenergic receptors have been identified (α1A, α1B, α1D, α2A, α2B, α2C, β1, β2, and β3) (Bylund et al. 1994).

2.2.1.2 Localization and Functions of Alpha-2 Receptors

Alpha-2 receptors are distributed ubiquitously in the body and are in the nervous system, platelets, and various organs (McCune et al. 1993; Hoffman et al. 1982)—presynaptically, postsynaptically, and extrasynaptically. Alpha-2 autoreceptors regulate the release of noradrenaline and adrenaline by negative feedback and participate in various physiological functions. Alpha-2 heteroreceptors can control the exocytosis of a variety of other neurotransmitters such as dopamine and serotonin (Scheibner et al. 2001; Bücheler et al. 2002).

All α2 isoreceptors (α2A, α2B, α2C) have actions in common and individual effects. Significant regional variations exist in the density of different receptor subtypes (McCune et al. 1993); depending on receptor type and location, they regulate different physiological responses. Endogenous agonists noradrenaline and adrenaline bind to all three subtypes with identical affinity, whereas exogenous agonists all differ in selectivity. The exact physiological activities of these receptors and their therapeutic potential are still mostly unclear, although they have been extensively studied in animal models. The α2A-subtype is the dominant subtype in the central nervous system and probably responsible for most of the traditional actions of α2-adrenergic receptor agonists: sedation and analgesia (Hunter et al. 1997), as well as antihypertensive and bradycardic effects (MacMillan et al. 1996). The α2B subtype regulates the contraction of vascular smooth muscle (Link et al. 1996), and the α2C subtype affects sensory processing, cognition, the output of the adrenal medulla, and locomotor activity (Scheinin et al. 2001). However, this division is an oversimplification; the actual impact is more complex than that. Some functions require synergistic action of more than one receptor subtype, and some actions are controlled by counteracting α2-receptor subtypes.

2.2.1.3 Alpha-2 Agonists

Several medications activate alpha-2 receptors, so-called exogenous alpha-2 agonists. Alpha-2 agonists are used to treat a variety of conditions such as hypertension, attention deficit hyperactivity disorder (ADHD), bipolar disorder, schizophrenia, spasticity, opioid dependence, and alcohol withdrawal. The most common alpha-2 agonists in clinical practice are clonidine, tizanidine, and dexmedetomidine. Table 1 presents different alpha2-agonists in clinical use.

Table 1. Clinical indications of different alpha2-agonists in clinical use.

Drug	**Indication**	**Administration routes**	**Comments**
Dexmedetomidine	ICU sedation and procedural sedation Agitation in bipolar disorder or schizophrenia	Intravenous Sublingual	Sublingual formulation is not approved in Europe
Clonidine	Hypertension Drug withdrawal ADHD	Intravenous Intramuscular	
Tizanidine	Spasticity	Peroral	
Methyldopa	Hypertension	Peroral Intravenous	Not in use in Finland
Lofexidine	Hypertension Opioid withdrawal	Peroral	Not in use in Finland
Guanfacine	ADHD Hypertension	Peroral	Off-label use: PTSD, anxiety
Guanabenz	Hypertension	Peroral	Not in use in Finland
Xylazine	Veterinary anesthesia	Peroral Inhalation Intravenous Intramuscular Subcutaneous	

Author's own drawing.

Clonidine is considered the prototype alpha2-agonist, which is the reference against which all other alpha-agonists are measured. Dexmedetomidine has an α2:α1 selectivity ratio of 1620:1, making it eight times more selective than clonidine (selectivity ratio 220:1). Dexmedetomidine has no significant subtype selectivity,

but α2A-receptor and α2C-receptor affinity is higher compared to clonidine (Fairbanks et al. 2009). Dexmedetomidine is a far more potent sedative than clonidine due to its enhanced specificity for the alpha-2 adrenoreceptors, particularly for the α2A subtype. Clonidine's sedative impact is reduced due to the activation of central α1-adrenoceptors, counterbalancing the sedative α2 effects.

Entirely subtype-selective alpha-2 ligands are not yet available, but some have partial selectivity. Creating subtype-selective medications may lead to more focused action and fewer side effects. As some alpha2-receptor-mediated functions involve two or more isoreceptors, non-subtype-selective α2-receptor agonists may still retain their position even if specific subtype-selective agonists are developed.

2.2.2 History of Dexmedetomidine, Present Indications, and Off-label Use

Dexmedetomidine is still considered a new sedative, although it is well over 30 years old. Farmos Pharma originally developed dexmedetomidine in Turku, Finland. Initially, the intention was to develop a new drug for premedication (Kallio et al. 1989), but the new drug molecule, MPV 785, was observed to have a strong sedating effect, ultimately leading to pursuing it commercially as a sedative. Dexmedetomidine was first used in humans in 1987 when tested on healthy volunteers (Scheinin et al. 1987). The first studies were conducted with a racemate, but early on, its development was focused on the active isomer: dexmedetomidine (MPV 1440). A racemic mixture—medetomidine—is still used in veterinary medicine and as a marine antifouling substance. After the Food and Drug Administration's (FDA's) approval, commercial use of dexmedetomidine started in the United States in 1999. In Europe, dexmedetomidine was not approved until 2011 because of the European Medicines Agency's demand that dexmedetomidine had to be compared to other sedatives first. Non-inferiority studies MIDEX and PRODEX (Jakob et al. 2012) were conducted; after this, marketing authorization was granted in Europe.

Now, the official indications for intravenous dexmedetomidine in Europe are sedation of intubated and mechanically ventilated patients in the ICU and perioperative sedation of non-intubated patients (Product Label Dexdor Orion Pharma 2016). Recently, the FDA also approved using dissolving sublingual formulation for the acute treatment of agitation associated with schizophrenia or bipolar disorder (Preskorn et al. 2022), but European authorities have not yet granted permission for this indication.

Off-label use refers to using medicine for purposes other than those indicated in the marketing authorization. This can include use for a different indication, in a different patient population, or via an alternative delivery route. Off-label use of

dexmedetomidine for different indications and through various administration routes is exceedingly common, especially with pediatric patients (van Hoorn et al. 2021). Intranasal administration of dexmedetomidine has gained interest in adult patients as well. Over the past few years, research on using intranasal administration of dexmedetomidine has grown substantially (Figure 2). *Chapter 2.2.8, New Clinical Applications for Dexmedetomidine*, further discusses the off-label use of dexmedetomidine for new application prospects.

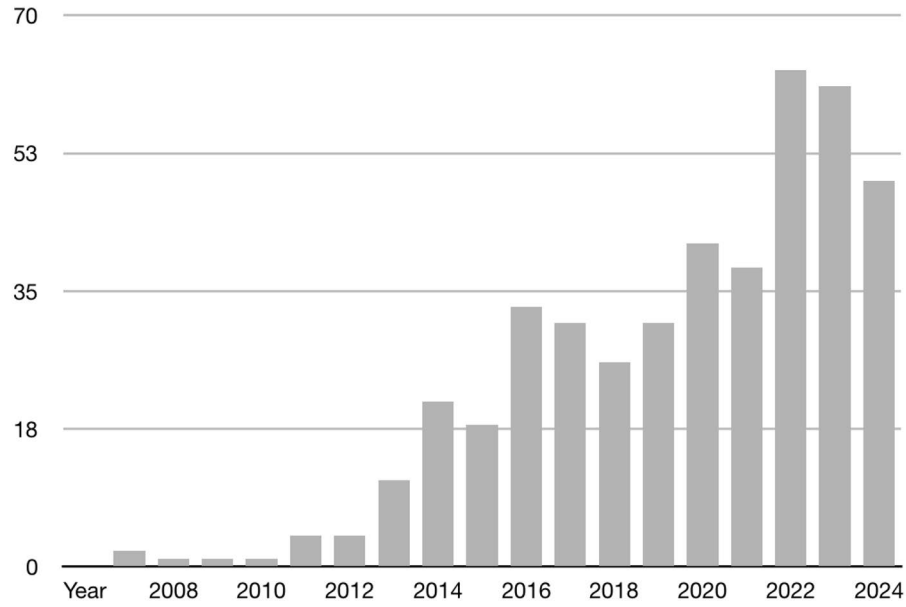


Figure 2. Studies on intranasal dexmedetomidine from 2007 to 2024. Search terms used: "intranasal dexmedetomidine". Modified from Pubmed 11/2024.

2.2.3 Pharmaceutical Aspects of Dexmedetomidine

Dexmedetomidine is an imidazole derivative and belongs to the class of organic compounds known as o-xylenes. It is a chiral compound (S-enantiomer), and its stereoisomer (R-enantiomer) is levomedetomidine. The racemic mixture of these enantiomers is called medetomidine. Dexmedetomidine is considered the active isomer, whereas levomedetomidine is usually regarded as inactive (MacDonald et al. 1991). However, levomedetomidine is constituted as a weak inverse agonist (Jansson et al. 1998); at high dosages, levomedetomidine may decrease the sedative and analgesic properties of dexmedetomidine (Kuusela et al. 2001). Figure 3 presents

the chemical formulas of the two enantiomers, dexmedetomidine and levomedetomidine.

The chemical formula of dexmedetomidine is $C_{13}H_{16}N_2$. The molecular weight of dexmedetomidine is 200,28 g/mol. Dexmedetomidine is freely soluble in water. Dexmedetomidine has a pKa of 7.1 and a logP of 2.8. Dexmedetomidine hydrochloride concentrate is a clear and colorless solution with a pH between 4.5 and 7.0. (Pubchem)

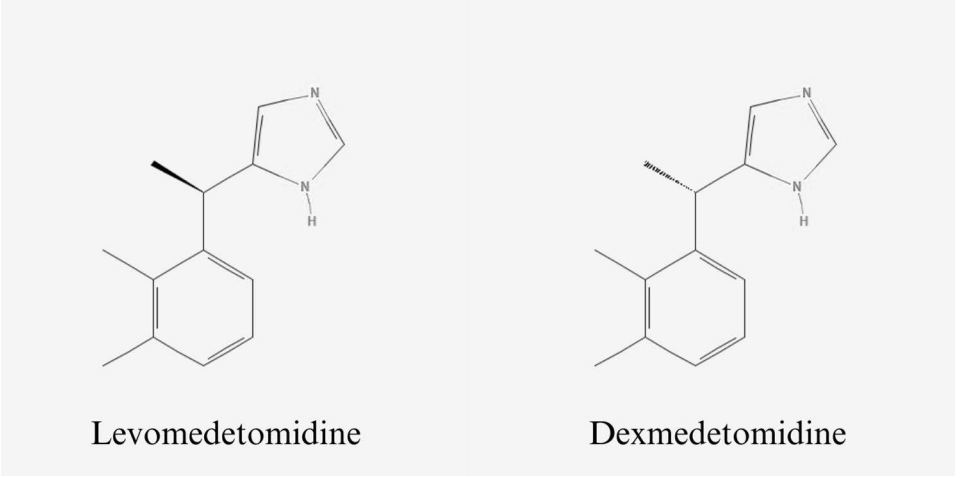


Figure 3. Chemical formula of medetomidine enantiomers: levomedetomidine and dexmedetomidine. Modified from Pubchem.

2.2.4 Pharmacokinetics of Dexmedetomidine

Dexmedetomidine exerts linear pharmacokinetics when infused in the recommended dose (0,2–1,4 μg/kg/h intravenously) and does not accumulate with normal liver function (Välitalo et al. 2013). However, nonlinear pharmacokinetics apply when plasma concentrations exceed 2 ng/l (Alvarez-Jimenez et al. 2022).

Several population pharmacokinetic (PopPK) models have been published to characterize the pharmacokinetics of intravenous dexmedetomidine; based on pooled pediatric and adult data, a universal pharmacokinetic model was developed (Morse et al. 2020). Most studies have used a two-compartment model (Venn et al. 2002; Iirola et al. 2012), but a three-compartment model has also been used (Alvarez-Jimenez et al. 2022; Hannivoort et al. 2015).

Body size and hepatic function strongly influence dexmedetomidine pharmacokinetics. Plasma albumin and cardiac output are thought to affect the apparent volume of distribution and clearance (CL). Obese people have a reduced size-normalized clearance of dexmedetomidine (Cortínez et al. 2015), but obesity

does not influence dexmedetomidine clearance when administered according to lean body mass (Rolle et al. 2018). Dexmedetomidine has a high hepatic extraction ratio, and liver blood flow is observed to substantially affect dexmedetomidine clearance (Dutta et al. 2000). Dexmedetomidine reduces cardiac output in a dose-dependent manner, which lowers liver blood flow (Dutta et al. 2000). In patients with hepatic impairment, the mean elimination half-life of dexmedetomidine is significantly prolonged (Cunningham et al. 1999). Hypoalbuminemia (e.g., due to malnutrition, burn injury, or nephrotic syndrome) may lead to prolonged effects, as there is an increased unbound fraction of dexmedetomidine in plasma (Iirola et al. 2012). However, one study found that although pharmacokinetic alterations occurred in individuals with modest hypoalbuminemia, pharmacodynamics (blood pressure, heart rate, and sedation) were unaffected (Zhang et al. 2015).

Studies on the impact of other patient features besides size and hepatic function on dexmedetomidine pharmacokinetics have yielded inconclusive results. It has been disputed whether sex affects the pharmacokinetics of dexmedetomidine (Alvarez-Jimenez et al. 2022). Ethnicity has not been observed to have a significant effect, but alterations in pharmacokinetics due to ethnicity cannot be completely ruled out (Kurnik et al. 2011). Age does not appear to influence dexmedetomidine pharmacokinetics, but clearance of dexmedetomidine is reduced in the elderly (Iirola et al. 2012). Thus, sedative effects are more pronounced in older adults and dose adjustment is advisable.

2.2.4.1 Absorption

The bioavailability of dexmedetomidine has been studied using several delivery routes, although only intravenous and sublingual routes are officially approved. Dexmedetomidine has been administered via oral, intramuscular, subcutaneous, intranasal, transdermal, intratechal, epidural, perineural and intra-articular routes, as well as in inhaled form (Chamadia et al. 2020; Scheinin et al. 1993; Uusalo et al. 2018; Iirola et al. 2011; Kivistö et al. 1994; Abdel-Ghaffar et al. 2018; Al-Metwalli et al. 2008, Mo et al. 2023, Liu et al. 2022, Liu et al. 2024).

Dexmedetomidine is well absorbed through the oral and nasal mucosa, and administration via intranasal or buccal routes results in high bioavailability (65% and 82%, respectively) (Iirola et al. 2011, Anttila et al. 2003). Much interindividual variation exists in intranasal administration (Iirola et al. 2011). Bioavailability following intramuscular or subcutaneous injection is also high (104% and 81%, respectively) (Uusalo et al. 2018; Dyck et al. 1993, Scheinin et al. 1992). The oral route has very poor bioavailability (16%) due to extensive first-pass metabolism in the liver (Anttila et al. 2003). Table 2 presents the comparison of dexmedetomidine pharmacokinetics across different administration routes.

In clinical practice, the intranasal route is probably the most popular extravascular route, although use via subcutaneous administration is also quite common. Pharmacokinetics of intranasal dexmedetomidine have been previously evaluated in both adults (Iirola et al. 2011; Kuang et al. 2022; Li et al. 2018; Yoo et al. 2015; Wu et al. 2022) and pediatric patients (Miller et al. 2018; Grogan et al. 2023; Wang et al. 2019; Uusalo et al. 2020).

Table 2. Comparison of dexmedetomidine pharmacokinetics across different administration routes.

Administration route	**Bioavailability (F)**	**Time to reach maximum concentration (T_{MAX})**	**Elimination half-life ($t_{1/2}$)**	**Reference**
Intravenous	100%	0.17 (0.08–0.17) h	2.17 ± 0.42 h	Uusalo et al. 2018 Anttila et al. 2003
Sublingual	72%	2 h	2.8 h	Igalmi Product Label BioXcel Therapeutics 2022
Intramuscular	104% (96–112%)	1.7 ± 1.8 h	2.5 ± 0.6 h	Anttila et al. 2003
Intranasal	65% (35–93%)	0.63 (0.25–1) h	1.92 (1.65–2.42) h	Iirola et al. 2011
Subcutaneous	81% (49–97%)	0.25 (0.25–4) h	3.8 (0.89) h	Uusalo et al. 2018
Oral	16% (12–20%)	2.2 ± 0.5 h after a lag-time of 0.6 ± 0.3 h	1.2 ± 0.3 h	Anttila et al. 2003
Buccal	82% (73–92%)	1.5 ± 0.2 h after a lag-time of 0.13 ± 0.04 hours	1.9 ± 0.5 h	Anttila et al. 2003
Transdermal	51%	N/A	5.6 h	Kivistö et al. 1994

Author's own drawing. Data are shown as mean ± standard deviation, or median and range

2.2.4.2 Distribution

Dexmedetomidine is rapidly distributed after intravenous administration, with a distribution half-life of about 6 min. The onset of action after intravenous injection is about 15 min when a loading dose is used, whereas intranasal administration results in a slower onset of action, and the anticipated effect can be seen about 30 min after intranasal administration (Yuen et al. 2010).

Dexmedetomidine is highly lipophilic. It binds highly to plasma proteins (about 94%), mainly in albumin and, to a lesser extent to α1-acid-glycoprotein.

2.2.4.3 Metabolism

Dexmedetomidine is metabolized in the liver to inactive metabolites. Since the metabolism of dexmedetomidine occurs mainly in the liver, caution should be used when administering dexmedetomidine to patients with hepatic dysfunction; lowering the dose, depending on the degree of impairment, may be necessary. Metabolism of dexmedetomidine occurs via glucuronidation, hydroxylation, N-methylation, and oxidation -reactions. Hydroxylation of dexmedetomidine is mediated by cytochrome P450 (CYP) enzymes, primarily CYP2A6 and, to a lesser extent, CYP1A2, CYP2C19, CYP2D6, and CYP2E1. N-glucuronidation accounts for approximately one-third of dexmedetomidine metabolism and is mediated by UGT2B10 and UGT1A4 (Precedex Approval Documents Abbot Laboratories 1999)

Metabolites of dexmedetomidine are N-methyl-dexmedetomidine, N-methyl dexmedetomidine O-glucuronide, 3-hydroxydexmedetomidine and 4-[(S)-1-(2,3-dimethylphenyl)ethyl]-1,3-dihydroimidazol-2-one(H-3). All metabolites of dexmedetomidine are inactive. Clinically significant quantities of chiral inversion do not occur (Precedex Approval Documents Abbot Laboratories 1999).

2.2.4.4 Excretion

Dexmedetomidine has a short elimination half-life (approximately 2 hours +/- 0.4 hours) (Anttila et al. 2003) compared to clonidine, which has a much longer elimination half-life (about 8 hours, +/- 2 hours) (Keränen et al. 1978). The elimination half-life of dexmedetomidine is slightly prolonged in critically ill patients (3.7 hours) (Iirola et al. 2011), and especially in severe hepatic impairment, elimination half-life has been reported to be significantly prolonged (3.3 hours, 5.4 hours and 7.5 hours in Child-Pugh A, B, and C, respectively) (Cunningham et al. 1999). In healthy adult volunteers, dexmedetomidine clearance ranges between 0.6 and 0.7 L/min (Dyck et al. 1993; Talke et al. 2018).

Dexmedetomidine is mainly excreted in the urine as inactive metabolites, with only a small amount in feces (95% and 4%, respectively). Within the expected therapeutic range, dexmedetomidine clearance is nearly constant, but it has been suggested that at high plasma concentrations, clearance is reduced (Alvarez-Jimenez et al. 2022). Impairment in kidney function has little influence on the pharmacokinetics of dexmedetomidine but may prolong the sedative effect because of decreased plasma protein binding (De Wolf et al. 2001).

2.2.4.5 Pharmacokinetic Interactions

Due to metabolism mediated by CYP enzymes, dexmedetomidine may, theoretically, be susceptible to pharmacokinetic interactions. However, previous studies have reported only a few interactions. The sponsor did not expect noteworthy pharmacokinetic interactions, as half-maximal inhibitory values (IC50) for dexmedetomidine against multiple CYP isoforms were relatively high in preclinical studies; in clinical practice, dexmedetomidine concentrations in plasma are substantially lower (Precedex Approval Documents Abbot Laboratories 1999). Nevertheless, dexmedetomidine concentrations in the liver seem to be much higher than plasma concentrations; therefore, interactions may occur. Anticonvulsants that induce CYP enzymes (e.g., phenytoin and carbamazepine) can increase the clearance of dexmedetomidine (Flexman et al. 2014).

Dexmedetomidine is not only a substrate of CYP enzymes but an inductor and inhibitor of numerous CYP enzymes. Dexmedetomidine induces CYP1A2-, CYP2B6-, CYP2C8-, CYP2C9- and CYP3A4-enzymes and inhibits CYP2B6-enzyme in vitro -studies (Precedex Approval Documents Abbot Laboratories 1999). In theory, dexmedetomidine could affect the metabolism of various medications metabolized by these enzymes. Interaction with tacrolimus, which is metabolized via CYP3A4, has been described. Tacrolimus plasma concentrations were increased 4-fold with concomitant administration of dexmedetomidine on a pediatric liver transplant patient (Stiehl et al. 2016). Otherwise, studies of CYP enzyme-mediated drug interactions are lacking, and clinical relevance remains unknown.

2.2.5 Pharmacodynamics of Dexmedetomidine

2.2.5.1 Sedative Effects

Unlike other sedative agents, dexmedetomidine mimics the endogenous sleep pathway (Nelson et al. 2003). Its clinical effect resembles non-rapid eye movement (NREM) sleep, and the EEG pattern during dexmedetomidine sedation looks similar to stage II sleep (Mason et al. 2009). In comparison to other sedatives, dexmedetomidine has been proposed to produce more restorative sleep because it provides more natural-like sedation (Sanders et al. 2011). Dexmedetomidine produces a state of cooperative sedation, where the patient's capacity to communicate with medical staff is sustained, and patients are easily aroused by light stimuli (Venn et al. 1999).

A key location for the sedative effects of alpha-agonists is the major wakefulness-promoting nucleus of the brain, locus coeruleus, which is in the pons in the brain stem and contains one of the largest densities of α2-adrenoceptors (Probst et al. 1984). Dexmedetomidine acts on central pre- and postsynaptic α2-receptors in locus coeruleus,

and binding to these α2-receptors causes inhibitory noradrenergic neurons to activate, suppressing noradrenaline release (Nacif-Coelho et al. 1994). By reducing noradrenaline release, dexmedetomidine activates the sleep-promoting ventrolateral preoptic nucleus, which releases sleep-promoting neurotransmitters GABA and galanin (Nelson et al. 2003). This suppresses histamine release from the tuberomammillary nucleus, orexin release from the perifornical area, serotonin release from the dorsal raphe nucleus, acetylcholine from laterodorsal tegmental nuclei, and pedunculopontine tegmental nuclei (Sherin et al. 1998). Suppression of these wakefulness-promoting neurotransmitters facilitates the transition into sleep. Figure 4 summarizes the sedative mechanism of dexmedetomidine related to endogenous sleep pathways.

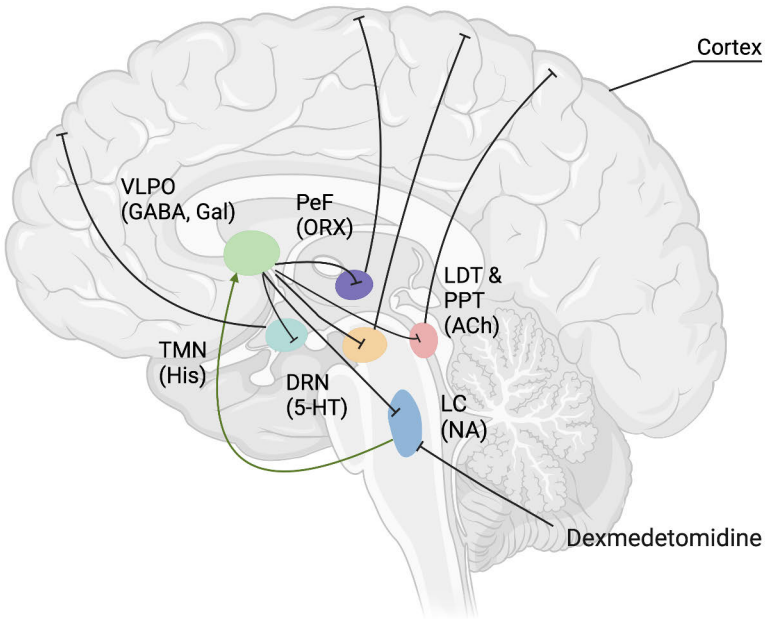


Figure 4. Sedative mechanisms of dexmedetomidine related to endogenous sleep pathways. Dexmedetomidine suppresses noradrenaline (NA) release from locus coeruleus (LC) and activates the ventrolateral preoptic nucleus (VLPO) to release sleep-promoting GABA and galanin (Gal). Wakefulness-promoting neurotransmitters are suppressed: histamine (His) from tuberomammillary nucleus (TMN), orexin (ORX) from perifornical area (PeF), serotonin (5-HT) from dorsal raphe nucleus (DRN) and acetylcholine (ACh) from laterodorsal tegmental nuclei and pedunculopontine tegmental nuclei (LDT & PPT). Suppression of wakefulness-promoting neurotransmitters facilitates the transition to sleep. Author's own drawing. Created in BioRender.com.

The sedative effect of dexmedetomidine is dose-dependent. In healthy volunteers, plasma concentrations over 0.2 ng/ml are associated with significant and rousable sedation (Hall et al. 2000), whereas plasma values exceeding 1.9 ng/mL are thought to cause profound sedation (Ebert et al. 2000).

2.2.5.2 Respiratory Effects

Unlike conventional sedatives, respiratory depression will unlikely occur with dexmedetomidine (Belleville et al. 1992). Dexmedetomidine improves hypoxic pulmonary vasoconstriction (Xia et al. 2015), reduces intrapulmonary shunt (Wang et al. 2022), and increases lung compliance (Hasanin et al. 2018). However, dexmedetomidine dampens chemoreflexes and reduces hypercapnic and hypoxic ventilation (Lodenius et al. 2016).

Dexmedetomidine's impact on pulmonary arterial pressure is inconclusive; it is thought to have no effect or to decrease pulmonary arterial pressure. Some evidence shows that dexmedetomidine may be a feasible option for patients with existing pulmonary hypertension (Shinohara et al. 2010; But et al. 2006). The mechanism of action could be sympatholysis and a decrease in circulating catecholamines, subsequently leading to indirect action on pulmonary vascular resistance.

Limited data exists about the bronchodilator effects of dexmedetomidine. Activation of α2-receptors relaxes bronchial smooth muscle, leading to attenuation and prevention of bronchoconstriction in animal studies (Groeben et al. 2004). Dexmedetomidine may also reduce airway hyperresponsiveness (Xiao et al. 2023; Zhou et al. 2023).

2.2.5.3 Cardiovascular Effects

Dexmedetomidine has a biphasic effect on blood pressure: At low plasma concentrations, dexmedetomidine causes bradycardia and hypotension; at higher plasma concentrations, vasoconstriction and hypertension occur (Ebert et al. 2000). Two subtypes of α2-receptors mediate the two stages of blood pressure response. Activation of peripheral α2B -adrenergic receptors produces the initial vasoconstriction, leading to hypertension (Link et al. 1996). Activation of α2A-receptors produces hypotension and reflex bradycardia due to reduced sympathetic tone (MacMillan et al. 1996). The hemodynamic effects are dose-dependent (Ebert et al. 2000) and more prevalent when a loading dose is used due to a temporary high plasma peak (Ickeringill et al. 2004). It has been reported that extravascular dosing may lead to attenuation of hemodynamic alterations since plasma peak after administration remains lower (Uusalo et al. 2018; Chamadia et al. 2020; Iirola et al. 2011).

Heart rate decreases as a response to vasoconstriction after dexmedetomidine administration. Reductions in heart rate are usually minor, and a typical decrease in heart rate is 15%–20% from the baseline (Ebert et al. 2000; Colin et al. 2017). Significant bradycardias are still possible; even asystole has been reported (Takata et al. 2014). Depending on the definition, the incidence of bradycardia after dexmedetomidine administration has been reported to vary between 10% and 40%,

(Riker et al. 2009; Jakob et al. 2012). Dexmedetomidine-induced bradycardia does not usually require intervention but responds to anticholinergic medication. Caution is advised when used for patients with a slow resting heart rate or pre-existing bradycardia and advanced heart block is a contraindication for dexmedetomidine.

Dexmedetomidine does not reduce stroke volume, but it lowers heart rate, resulting in decreased cardiac output. However, since peripheral vascular resistance is reduced and venous return to the heart is improved, dexmedetomidine may ultimately maintain cardiac output. Systolic and diastolic cardiac function are unaffected by dexmedetomidine (Lee et al. 2015). Dexmedetomidine also reduces myocardial oxygen demand (Lawrence et al. 1996).

Dexmedetomidine's impact on cardiac conduction is controversial. Dexmedetomidine suppresses sinus and atrioventricular nodal function (Hammer et al. 2008), which can lead to dose-dependent prolongation of the PR interval. Because dexmedetomidine decreases heart rate, it belongs to drugs that may prolong QT-interval. However, many studies show that dexmedetomidine actually decreases corrected QT-interval (QTc) in rabbits (Tsutsui et al. 2012) and in adults and children undergoing surgery (Kim et al. 2016; Görges et al. 2019). Dexmedetomidine has been linked to the reduced occurrence of arrhythmias in several clinical investigations. Dexmedetomidine seemingly reduces ventricular arrhythmias (Chrysostomou et al. 2011) but does not affect postoperative atrial fibrillation incidence (Turan et al. 2020). In acquired LQT2, dexmedetomidine may be antiarrhythmic and prevent torsade de pointes (Ellermann et al. 2021).

2.2.5.4 Gastrointestinal Effects

Studies on dexmedetomidine's impact on the digestive system have shown conflicting results. Conversely, dexmedetomidine inhibits gastric emptying (Iirola et al. 2011). However, other studies have concluded that dexmedetomidine improves bowel motility after surgery and facilitates recovery (Chen et al. 2016; Li et al. 2019; Lu et al. 2021). Dexmedetomidine enhances peristaltic movement by reducing sympathetic tone via acting on central alpha2-adrenergic receptors (Cho et al. 2015). Another explanation is that dexmedetomidine reduces opioid consumption, thus improving gastrointestinal motility. The effect on the gastrointestinal tract is possibly dose-dependent; adverse effects occur with higher doses, whereas low-dose dexmedetomidine seemingly has favorable gastrointestinal effects. Dexmedetomidine also helps protect the intestine from mucosal damage during cardiac bypass in animal studies (Jia et al. 2022).

Like other alpha2-agonists, dexmedetomidine inhibits salivation. Alpha2-receptor stimulation inhibits the secretory response of salivary glands (Kaniucki et al. 1984).

Dexmedetomidine reduces PONV (Jin et al. 2017). Although the exact mechanisms causing antiemesis are still unknown, it has been hypothesized that antiemesis is due to reduced opioid and anesthetic use. Elevated sympathetic tone and catecholamine release may contribute to the emergence of PONV (Jenkins et al. 1971). Another theory is that antiemesis is consequential to the modulation of neurotransmitters (dopamine and 5HT release) (Hopwood et al. 2001; Whittington et al. 2006).

2.2.5.5 Analgesic Effect

How dexmedetomidine suppresses pain has not been fully elucidated, and whether dexmedetomidine has a true analgesic effect has been questioned. It has been claimed that the analgesic effect seen after dexmedetomidine administration could merely result from altered perception and reduced anxiety. One study showed that the analgesic properties of dexmedetomidine could be neutralized by giving the alpha2-antagonist atipamezole (Siegenthaler et al. 2020), pointing to the analgesic effect being α2 dependent; however, the possibility that dexmedetomidine also works through some α2 independent mechanisms to provide analgesia cannot be ruled out completely. All three subtypes of α2-receptors play some role in controlling pain perception, but the analgesic efficacy of dexmedetomidine is thought to be mainly mediated by the α2A-adrenoceptor subtype (Malmberg et al. 2001). In addition to its effects on pain modulation, dexmedetomidine may affect pain perception and improve pain management by reducing inflammation. The analgesic effect of dexmedetomidine is dose-dependent. One study revealed a ceiling effect for analgesic efficacy at dosages exceeding 0.5 μg/kg (Jaakola et al. 1991); however, another study found a dose-dependent response with plasma concentrations ranging from 0.5 to 8.0 ng/ml (Ebert et al. 2000).

How dexmedetomidine causes analgesia is hypothesized to involve several sites in the pain pathway: central, spinal, and peripheral. Noradrenaline is a key neurotransmitter involved in pain modulation, mainly in the descending inhibitory regulation of pain. The primary noradrenergic brain structure, locus coeruleus (LC), is thus an important modulator of nociceptive transmission and one of the sites from which descending inhibitory noradrenergic routes to the spinal cord dorsal horn originate. Dexmedetomidine depolarizes locus coeruleus and indirectly stimulates the descending inhibitory noradrenergic pathways, leading to increased spinal noradrenaline release (Guo et al. 1996). The dorsal horn of the spinal cord is the main location for dexmedetomidine-mediated analgesia. Stimulation of presynaptic α2-receptors reduces the release of neurotransmitters like substance P and glutamate, decreasing the transmission of pain signals to the central nervous system (Kuraishi et al. 1985). Also, dexmedetomidine may directly hyperpolarize postsynaptic spinal neurons. Additionally, the interplay between α2-adrenoceptors and cholinergic

interneurons leading to increased acetylcholine (ACh) release is suggested to be an analgesic mechanism at the level of the spinal cord (Hayashida et al. 2010). Alpha-2 adrenergic receptors are co-localized with TRPV1 in the dorsal root ganglia, and it has been proposed that their suppression may also contribute to the analgesic action of dexmedetomidine (Lee et al. 2020). Although peripheral α2-receptor activation may cause a decrease in neurotransmitter release, it has also been proposed that the mechanism behind peripheral analgesia with alpha2-agonists is primarily about a decreased inflammatory response (Lavand'homme et al. 2003). Figure 5 summarizes the proposed analgesic mechanisms of dexmedetomidine.

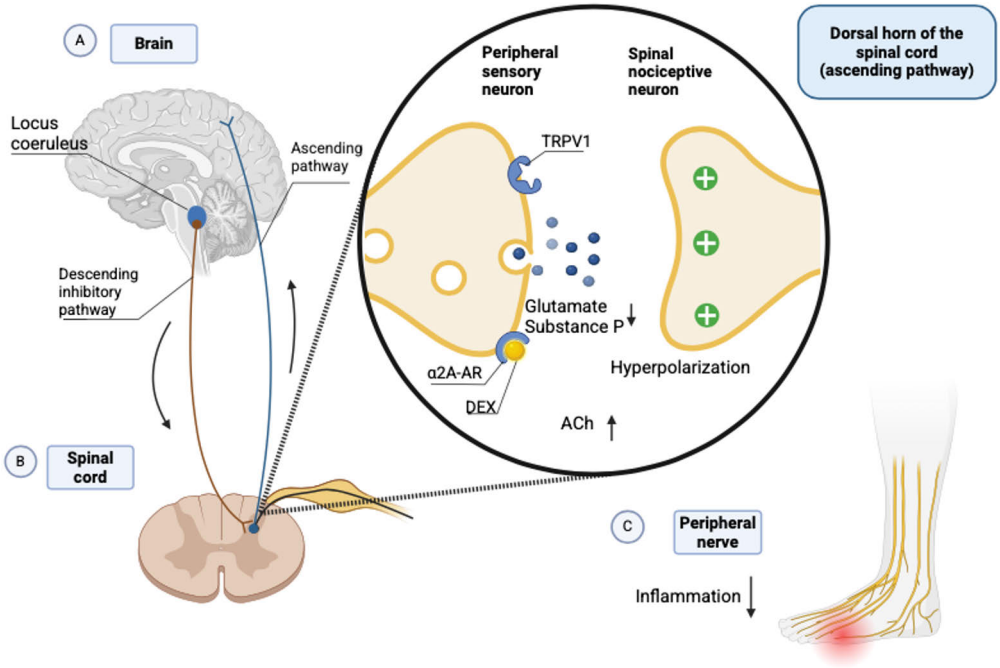


Figure 5. Proposed analgesic mechanisms of dexmedetomidine. A) Dexmedetomidine activates the locus coeruleus in the brain, stimulating inhibitory descending noradrenergic pathways. B) In the dorsal horn of the spinal cord, dexmedetomidine decreases neurotransmitter release and hyperpolarizes neurons, reducing pain transmission to the central nervous system. Additional effects involve interactions with cholinergic neurons and TRPV1 receptors. C) Peripherally, dexmedetomidine's analgesic effect may result from reduced inflammation. Abbreviations: DEX; dexmedetomidine, α2-AR; α2-adrenergic receptor, ACh; acetylcholine, TRPV1; transient receptor potential cation channel subfamily V member 1. Author's own drawing. Created in BioRender.com

2.2.5.6 Other Effects

Dexmedetomidine may affect blood glucose levels. Pancreatic β cells are regulated by α2A adrenoreceptors, and alpha agonists directly inhibit insulin secretion.

However, dexmedetomidine's effect on blood glucose is not that straightforward, as dexmedetomidine decreases cortisol levels, and attenuated stress response may lead to reduced blood glucose levels. Dexmedetomidine also reduces insulin resistance and may improve glucose homeostasis (Yun et al. 2016). Dexmedetomidine reduces intraocular pressure (Kim et al. 2015) by decreasing the production of aqueous humor and increasing its outflow.

Dexmedetomidine reduces postoperative shivering (Lamontagne et al. 2019) by suppressing vasoconstriction and reducing the shivering threshold (Talke et al. 1997). Some evidence shows that dexmedetomidine might influence body temperature. Dexmedetomidine has been linked to increased body temperature, and hyperthermia associated with dexmedetomidine administration has been reported (Grayson et al. 2017; Kruger et al. 2017; Grayson et al. 2021).

Polyuria is possible but is reportedly a quite a rare side-effect with dexmedetomidine administration, although several case reports exist (Chen et al. 2020; Pratt et al. 2013). Central (deficiency of antidiuretic hormone secretion) and nephrogenic diabetes insipidus (lack of antidiuretic hormone function in kidneys) may influence the pathophysiology, and non-antidiuretic hormone-dependent mechanisms have also been suggested. Hypokalemia has been identified as a possible but rare side effect of dexmedetomidine. The incidence of hypokalemia is seemingly higher in pediatric patients (Chrysostomou et al. 2014).

It has been suggested that dexmedetomidine may have anticonvulsant effects, but studies on the subject are controversial. In animal studies, dexmedetomidine reduced the seizure threshold (Miyazaki et al. 1999), but a heightened seizure threshold after dexmedetomidine administration has also been observed (Whittington et al. 2002). Dexmedetomidine has been proposed as a potential antidepressant (Liu et al. 2024). The etiology of depression could at least be partially linked to alpha-2 receptors in the central nervous system (Landau et al. 2015); therefore, α2 agonists could be a reasonable treatment option.

Dexmedetomidine seemingly possesses organoprotective effects on a variety of organs. Increasing evidence shows that dexmedetomidine protects at least kidney, lung, brain, heart, and liver tissues in vitro and in vivo (Okada et al. 2007; Gu et al. 2011; Wang et al. 2014; Zhu et al. 2020; Lv et al. 2021). Dexmedetomidine reduces the concentration of various immunological factors, implying that dexmedetomidine can reduce perioperative inflammation and protect immune function (Wang et al. 2019). Since dexmedetomidine is structurally an imidazole compound, it could have an inhibitory effect on cortisol synthesis. Short-term sedation with dexmedetomidine does not inhibit cortisol synthesis (Venn et al. 2001), but the effects of long-term infusion are unknown.

It has been hypothesized that dexmedetomidine might promote cancer recurrence and metastasis (Lavon et al. 2018). Due to α2 adrenoreceptors in breast cancer tissue,

the effects following breast cancer surgery are particularly concerning. Studies on the subject are inconclusive, and further studies are needed to draw definitive conclusions.

2.2.5.7 Pharmacodynamic Interactions

Dexmedetomidine has an anesthetic-sparing effect and reduces the consumption of sevoflurane, thiopental, and propofol (Sharma et al. 2017; Buhrer et al. 1994; Dutta et al. 2019). Dexmedetomidine has a synergistic effect with opioids and has an opioid-sparing effect when used perioperatively (Chan et al. 2016).

Co-administration of β-blockers could increase the hypotensive and bradycardic effects of dexmedetomidine. Calcium channel blockers may reduce the effects of dexmedetomidine on heart rate and blood pressure (Precedex Approval Documents, Abbot Laboratories 1999).

2.2.6 Pharmacogenomics of Dexmedetomidine

Genetic polymorphisms may explain, at least partly, the observed heterogeneity in responsiveness to dexmedetomidine. In general, genetic variations in metabolizing enzymes, transporters, or pharmacological targets may play a role in responding to different medications.

The CYP-mediated part of dexmedetomidine metabolism is mainly mediated by CYP2A6. Various polymorphisms have been discovered but so far, most do not seemingly affect dexmedetomidine clearance or sedative effect (Kohli et al. 2012; Wang et al. 2018). One study found that CYP2A6 polymorphism influences the metabolic rate of dexmedetomidine and is connected with sensitivity to sedative effects, whereas GABRA2 (gamma-aminobutyric acid receptor) polymorphism is associated with reductions in the heart rate (Fang et al. 2022).

UDP-glucuronosyl transferases (UGTs) are the second most important metabolic pathway after CYP enzymes and significantly affect the metabolism of many drugs. Dexmedetomidine is metabolized by UGT1A4 and UGT2B10 (Kaivosaari et al. 2008), but insufficient evidence exists about UGT polymorphisms and their clinical relevance regarding dexmedetomidine metabolism.

Genetic differences in alpha-2 receptor subtypes may also influence response to dexmedetomidine. Mutations in α2 adrenoreceptor coding genes (ADRA2A, ADRA2B, ADRA2C) may produce a receptor with lower affinity to dexmedetomidine, or even entirely inoperative receptors. ADRA2A gene polymorphism may weakly influence response to dexmedetomidine. In one study variants were more hypotensive and in another study, polymorphism weakly decreased sedative response (Yağar et al. 2011; Kurnik et al. 2011).

2.2.7 Contraindications and Adverse Effects of Dexmedetomidine

Contraindications for dexmedetomidine use are hypersensitivity to the active substance, advanced heart block (grade 2 or 3) unless paced, uncontrolled hypotension and acute cerebrovascular conditions (Precedex Approval Documents Abbot Laboratories 1999).

The most common adverse effects after dexmedetomidine administration are hemodynamic alterations, including bradycardia (vagomimetic action), hypotension, and transient hypertension (Precedex Approval Documents Abbot Laboratories 1999). Hypotension and bradycardia are greatest approximately one hour after commencing intravenous infusion (Bloor et al. 1992). Prolonged administration of dexmedetomidine leads to the upregulation of alpha2-receptors and withdrawal symptoms, including agitation, headaches, and hypertensive crisis, are possible if the infusion is stopped abruptly (Haenecour et al. 2017). In some cases, sedation can also be considered an unwanted side effect.

Dexmedetomidine has a broad safety spectrum; overdose is usually the due to administration error (Tiainen et al. 2024). Dexmedetomidine overdose may lead to bradycardia, hypotension, hypertension, excess sedation, respiratory depression, or cardiac arrest. Atipamezole, an α2-adrenoceptor antagonist, is a theoretically possible antidote, but studies on human subjects are limited (Karhuvaara et al. 1991; Scheinin et al. 1998). Currently, atipamezole is approved only for veterinary use as a reversal agent for medetomidine and dexmedetomidine.

Intranasal dexmedetomidine has been generally well tolerated, and studies have not demonstrated any adverse effects specific to the intranasal administration route. Potential side effects are the same as those associated with intravenous use, including hemodynamic effects, which may be more pronounced in elderly patients (Xu et al. 2022, Barends et al. 2020). Local irritation may occur in nasal mucosa, but this is usually mild and recedes quickly.

2.2.8 New Clinical Applications of Dexmedetomidine

In the European Union, dexmedetomidine has marketing authorization only for sedation in ICU and procedural sedation. In the USA, agitation in schizophrenia or mania are also indications. Dexmedetomidine is a versatile drug and has broad application prospects besides these. Off-label use of dexmedetomidine with different administration routes and new clinical applications is growing rapidly. Over the last few years, several off-label uses for dexmedetomidine have been researched, including as adjuvant to MMA (Donatiello et al. 2022), an adjuvant to nerve blocks (Rocans et al. 2022), in the prevention and treatment of delirium (Djaijani et al. 2016), in the treatment of depression (Liu et al. 2024), as an adjuvant in electroconvulsive therapy (Subsoontorn et al. 2021), in the treatment of alcohol

withdrawal (Rayner et al 2012), in organoprotection (Zhang et al. 2021), and as a glymphatic enhancer (Lilius et al. 2019). The next chapter reviews some possible new clinical applications for dexmedetomidine.

2.2.8.1 Adjuvant to Nerve Blocks

Adjuvants to local anesthetics are generally used to provide better, longer-lasting postoperative analgesia. Dexmedetomidine has a synergistic effect with local anesthetics and can be used as an adjunct to enhance the effect of regional as well as central blocks, shortening the onset of block and prolonging the duration of analgesia (Kang et al. 2018; Kanazi et al. 2006). Proposed underlying mechanisms behind this phenomenon include local vasoconstriction, activation of α2 receptors on nerves, or blockade of hyperpolarization (Brummett et al. 2011). A direct central effect on the locus coeruleus has also been suggested (Guo et al. 1996).

Adjuvant dexmedetomidine has been administered via intrathecal, epidural, intravenous, intra-articular, and perineural routes (Rocans et al. 2022; Kang et al. 2018; Al-Metwalli et al. 2008; Liu et al. 2017; Bi et al. 2020). The best administration route has not been established. Perineural and intravenous administration of dexmedetomidine successfully prolong the length of PNBs, but perineural administration appears to be slightly more effective (Abdallah et al. 2016). Intranasal dexmedetomidine administration has not been researched, but at least in theory, it could similarly prolong blocks to other administration routes.

2.2.8.2 Delirium

Over the last few years, delirium has been a hot topic in dexmedetomidine research (Chen et al. 2024). How dexmedetomidine reduces delirium remains unclear, but it has been proposed that the mechanism could be multifactorial—as the pathophysiology of delirium itself. One theory is that dexmedetomidine acts by reducing sedative drug consumption since GABAergic medications have been identified as a risk factor for developing delirium (Pandharipande et al. 2006). Another theory is enhanced sleep quality and a lighter sedation level after dexmedetomidine administration since the disturbed circadian rhythm has been identified as a contributing factor in delirium pathogenesis. Dexmedetomidine reduces opioid consumption, improves pain control, and alleviates anxiety—all of which can lower delirium risk (Morrison et al. 2003). Dexmedetomidine may also act as a glymphatic enhancer since it has been proposed that malfunction of the glymphatic system may play a role in developing delirium (Ren et al. 2021).

Studies evaluating the prevalence of delirium and other unfavorable neurocognitive outcomes in the ICU show that dexmedetomidine has favorable

effects (Pandharipande et al. 2007; Skrobik et al. 2018). Dexmedetomidine has also been extensively researched for preventing delirium in perioperative settings, but there is still significant debate in this area. Evidence exists for (Su et al. 2016) and against (Deiner et al. 2017; Turan et al. 2020) prophylactic dexmedetomidine for delirium prevention. Possible explanations for conflicting results include patient population, timing of medication, and surgery type (cardiac surgery/non-cardiac surgery). Substantial heterogeneity among studies and significant differences in defining postoperative delirium exists.

Besides preventing delirium, dexmedetomidine has been proposed as a possible treatment for delirium. One study found that dexmedetomidine was feasible as a rescue drug when haloperidol provided an inadequate response (Carrasco et al. 2016). In a recent Cochrane review, of all examined drugs, dexmedetomidine was the only one associated with a shorter duration of delirium. Dexmedetomidine reduced the duration of mechanical ventilation, and the ICU stay was shorter (Burry et al. 2019). Dexmedetomidine may also be feasible for managing terminal delirium (Thomas et al. 2021).

2.2.8.3 Withdrawal Symptoms and Drug Overdose

Dexmedetomidine can be used as an adjunct to benzodiazepine therapy to alleviate alcohol withdrawal symptoms (Rayner et al. 2012). However, as dexmedetomidine does not affect the underlying pathophysiology of alcohol withdrawal syndrome, it should not be the sole medication administered. While the debate on dexmedetomidine's usefulness is ongoing, the American Society of Addiction Medicine (ASAM) guideline already recommend using dexmedetomidine to control autonomic hyperactivity and anxiety not responding to treatment with benzodiazepines ("The ASAM Clinical Practice Guideline on Alcohol Withdrawal Management" 2020).

Opioid withdrawal symptoms have been treated with dexmedetomidine, which has also been used to facilitate weaning from opioids (Finkel et al. 2005), aid in weaning off cocaine (Maccioli 2003), and been successfully used as part of the treatment regime for several different drug overdoses such as anticholinergic toxidrome syndrome (Gee et al. 2015), methamphetamine overdose (Lam et al. 2017), hypertensive crisis induced by cocaine (Kontak et al. 2013), delirium after cannabis ingestion (Leikin et al. 2017), and intoxication from dextromethorphan and ecstasy (Tobias 2010). Dexmedetomidine is a particularly good choice when agitation is the most alarming symptom after substance abuse.

2.2.8.4 Pain Management

Various studies have demonstrated that dexmedetomidine has an opioid-sparing effect (Donatiello et al. 2022; Chan et al. 2016). Stimulation of α2-adrenoceptors is

thought to enhance the antinociceptive effect of opioid receptors, and the synergistic effect is suggested to happen at the level of the spinal cord (Ouyang et al. 2012). It has been postulated that the opioid-sparing impact might be greater in male patients (Li et al. 2016). The analgesic-sparing effect of dexmedetomidine lasts much longer than the elimination half-life would lead to assume (Ge et al. 2016). Some studies have also suggested that dexmedetomidine may be effective in preventing or managing opioid-induced hyperalgesia (Belgrade et al. 2010). Numerous animal studies have concluded that dexmedetomidine has an analgesic effect also on neuropathic pain (Lin et al. 2018; Xu et al. 2022).

2.2.8.5 Glymphatic Enhancer

One possible use for dexmedetomidine is as a glymphatic enhancer. The glymphatic system is a recently discovered system for waste removal from the central nervous system (Iliff et al. 2012). The word "glymphatic" is a combination of the words "glial" and "lymphatic". Dexmedetomidine enhances glymphatic transport (Lilius et al. 2019). Apart from waste management, this system helps in the brain-wide dispersion of chemicals crucial for normal brain function. Normally, the glymphatic system is active during natural sleep (Xie et al. 2013). Alterations in glymphatic cerebrospinal fluid flow have been linked to several neurological diseases. Pathophysiology of neurodegenerative diseases such as Parkinson's and Alzheimer's diseases may involve the glymphatic system (Zhu et al. 2010; Ding et al. 2021). The glymphatic system is also impaired after acute brain injuries (Gaberel et al. 2014; Li et al. 2020). Drugs that can increase glymphatic clearance are hypothesized to attenuate neurodegeneration and are, therefore, a possible therapeutic target for managing neurodegenerative disorders. Dexmedetomidine is proposed to enhance the glymphatic flow and improve the absorption of intrathecally administered medications by activating the glymphatic system (Lilius et al. 2019).

2.3 Intranasal Administration of Medications

Intranasal medication administration has raised significant interest during the last few years. In 2023, the global nasal medication delivery technology market was estimated to be worth USD 76.9 billion and has been forecasted to grow considerably during the next few years (Predecence Research 2024).

Antihistamines and corticosteroids for rhinitis or nasal decongestants for cold symptoms are a few examples of intranasal medications intended for local effects. Besides local effects, intranasal drug administration can also achieve systemic effect or target the central nervous system. Many intranasal medications already exist for systemic delivery, including treatments for pain (Borland et al. 2007), antiepileptic drug delivery

(Thakker et al. 2013), vaccinations (Nichol et al. 1999), and hormone therapies (Hemelaar et al. 2006; Banks et al. 2009). Numerous other medications for nasal delivery are under development, with potential applications in areas such as neurodegenerative diseases (Novak et al. 2019) and cancer (Ullah et al. 2020), among others.

2.3.1 Anatomy and Physiology of Intranasal Administration

The nasal cavity, extending from the nostrils to the pharynx, is the uppermost part of the respiratory tract. The nasal cavity ends in posterior apertures called choanae, which are the entrance to the nasopharynx. A cartilaginous wall, the nasal septum, divides the nasal cavity into two compartments. The main functions of the nasal cavity are to humidify and warm air, provide a sense of olfaction, drain paranasal sinuses, and protect against pathogens.

The nasal cavity is divided into three regions: vestibular, respiratory, and olfactory. Table 3 presents the characteristics of these regions, and Figure 6 shows their locations.

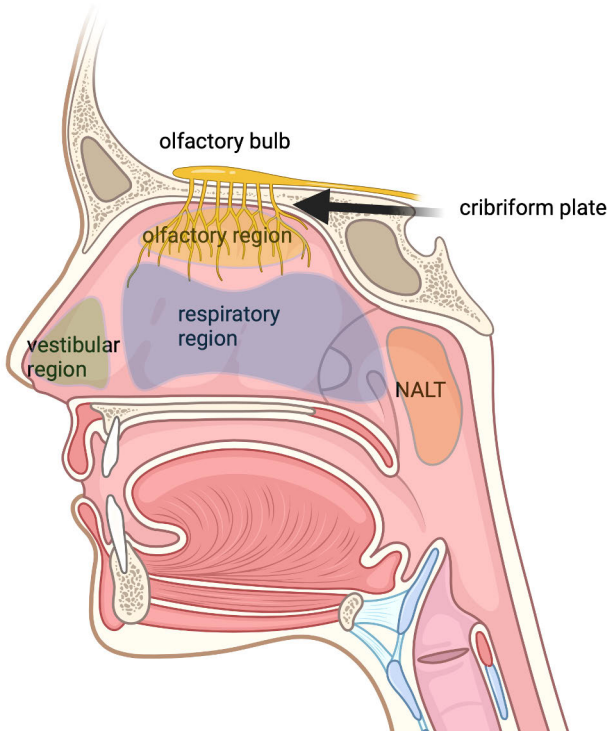


Figure 6. Nasal regions. The respiratory region is important for absorbing intranasal medications. The olfactory region is the target for drugs aimed at NTB transport. NALT is the target for intranasally administered vaccines. Abbreviations: NTB; nose-to-brain, NALT; nasal-associated lymphoid tissue. Modified from Gänger et al. 2018. Created in BioRender.com.

The nasal vestibule is the frontmost portion of the nasal cavity. The vestibular region comprises stratified squamous epithelium, sebaceous glands, and keratinized epithelial cells with nasal hair. Nasal hair (i.e., cilia) filters and retains large particles from inhaled air. The surface area of the vestibular region is small.

The respiratory region is on the lateral walls of the nasal cavity. The combination of large surface area and high vascularization make the respiratory region an important area for drug absorption into the systemic circulation. Absorption from the nasal mucosa bypasses the hepatic first-pass metabolism, leading to good bioavailability compared to oral administration. The respiratory epithelium consists of pseudostratified columnar epithelial cells, goblet cells, basal cells, and mucous and serous glands. Goblet cells secrete mucus, forming a protective layer for respiratory mucosa. Ciliated cells move the mucus toward the nasopharynx (mucociliary clearance). Three bony structures known as turbinates or conchae project medially from the lateral wall of the nasal cavity.

The olfactory region is atop the nasal cavity. It has a small surface area and is quite hard to reach. This region consists of non-ciliated, pseudostratified columnar epithelium, olfactory nerve cells, and supporting cells (sustentacular cells). Part of the ethmoid bone is the cribriform plate; the olfactory bulb is directly above it. The cribriform plate has apertures that allow the passage of olfactory nerves into the nasal cavity, meaning the central nervous system is directly exposed at this site.

Table 3. Characteristics of the nasal regions.

Nasal region	Cells	Surface area
Vestibular region	stratified squamous epithelium, keratinized epithelial cells with nasal hair	≈ 0.6 cm2
Respiratory region	columnar non-ciliated cells columnar ciliated cells goblet cells basal cells	≈ 130 cm2
Olfactory region	sustentacular cells olfactory cells basal cells	≈ 15 cm2

Modified from Pires et al. 2009.

The desired area for drug deposition depends on whether the intended effect is local, or systemic or if the target is specifically the central nervous system. The olfactory region is the main targeted absorption area of drugs aimed for nose-to-brain

(NTB) transport (Thorne et al. 1995). The target location for intranasal vaccines is the nasal-associated lymphoid tissue (NALT) (Wu et al. 1997).

The nasal cavity receives innervation via branches of two cranial nerves: trigeminal (CN V) and olfactory nerves (CN I). The trigeminal nerve divides into three branches. The two upper branches, the ophthalmic nerve (V_1), and the maxillary nerve (V_2) innervate the nose and nasal cavity. The olfactory nerve (CN I) enters the nasal cavity through openings in the cribriform plate. Figure 7 presents the innervation of the nasal cavity.

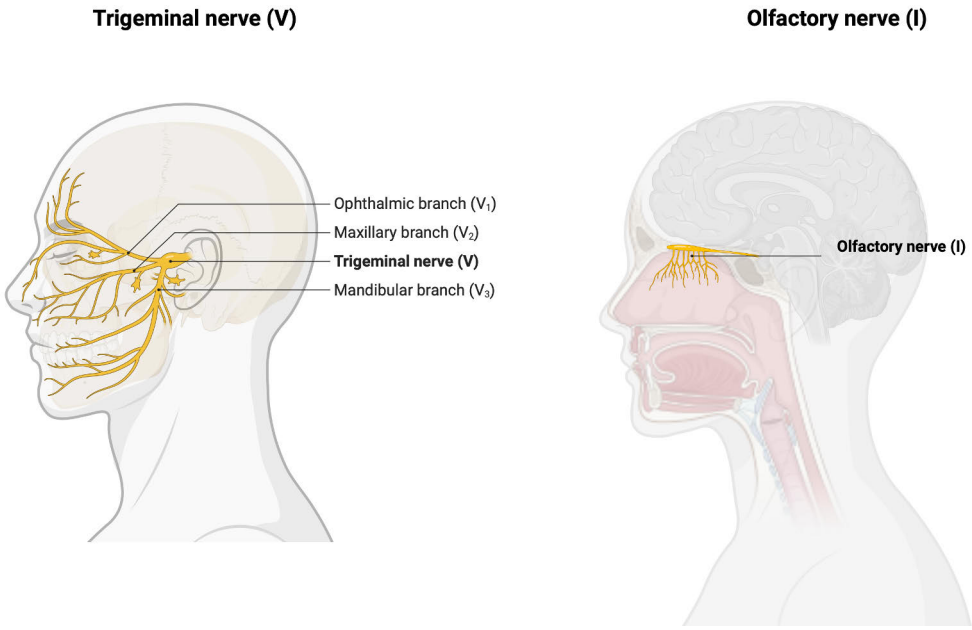


Figure 7. Innervation of the nasal cavity. The nasal cavity receives innervation via two cranial nerves: the olfactory nerve (CN I) and two upper branches of the trigeminal nerve (CN V): the ophthalmic nerve (V1) and the maxillary nerve (V2). Author's own drawing. Created in BioRender.com.

The nasal cavity has a very rich vascular supply. Blood vessels to the nose arise from the branches of internal and external carotid arteries. Veins of the nasal cavity run parallel to arteries and ultimately merge into the pterygoid plexus, facial vein, or cavernous sinus. These veins enter the systemic circulation, bypassing hepatic portal veins.

2.3.2 Advantages of Intranasal Administration

Intranasal administration has several advantages over other administration routes. Bolus dosing is convenient; administration is easier compared to intravenous administration and even possible for self-administration by patients. Furthermore, a sterile technique is not required. Needle-free administration is important for pediatric patients and adults who fear needles. Moreover, there is no risk of needle injuries and transmission of blood-borne diseases for the staff, even if the patient is uncooperative. The intranasal route is a good alternative, when intravenous access is unachievable (i.e., burn victims and small children) and a good alternative to the oral route in case of nausea and vomiting or dysphagia.

Intranasal administration offers favorable pharmacokinetics when hepatic first-pass metabolism is avoidable, resulting in short onset of action and high systemic bioavailability. A growing body of evidence supports the theory of medication delivery directly from the nose to the brain (Crowe et al. 2018). Increased central nervous system availability and reduced systemic exposure could result in fewer side effects. Conventional vaccines induce mucosal immunity poorly, but nasal administration provides a direct contact site for vaccines and can produce mucosal immunity (van der Ley et al. 2021).

2.3.3 Limitations of Intranasal Administration

Although intranasal administration is advantageous in many ways, it has limitations. The main limitation is that the intranasal administration route does not apply to all medications, at least not without techniques that enhance drug absorption. Lipophilic, small molecular weight medications (like dexmedetomidine) are adequately absorbed, but big hydrophilic molecules (like glycopyrrolate) are not.

Another drawback is the uncertainty about whether the drug will reach its intended target. Because the conditions inside the nose can alter (congestion, nosebleed, etc.), the quantity of absorption can fluctuate, and delivery can be unpredictable. Contraindications for intranasal administration are relative and related to friable nasal mucosa, including patients with neutropenia or a high risk of bleeding.

2.3.4 Intranasal Administration to Target Brain

The blood-brain barrier (BBB) is a physiological barrier guarding the central nervous system from harmful substances. While the BBB protects the central nervous system, it also hinders some beneficial medications from reaching their target. The BBB can be crossed by molecules that meet certain requirements, such as being lipid-soluble, electrically neutral at physiological pH, having a molecular weight below 500 Da,

and exhibiting a partition coefficient between 0.5 and 6.0. Only about 2% of small drug molecules can pass the BBB in therapeutic amounts. Dexmedetomidine is one example—a small, lipophilic drug that crosses the BBB readily (Precedex Approval Documents Abbot Laboratories 1999).

If medications could penetrate the BBB more efficiently and reach their target in the central nervous system, several difficult-to-treat neurogenerative diseases could be treated or even cured. Forcing BBB to open is one method of gaining access. Several methods can force the BBB open: osmotically with mannitol (Rapoport et al. 1972) or with MR-guided focused ultrasound (MRgFUS) (Abrahao et al. 2019). Other methods, such as RMP-7 and regadenoson (Bartus et al. 1996; Jackson et al. 2016), have also been studied, but their efficacy is questionable. Disruption of the BBB is quite effective, but not without consequences. Possible complications include seizures, brain damage, or even death (Elkassabany et al. 2008). Intranasal administration may be a feasible, noninvasive option to achieve drug transmission into the central nervous system without tampering with the BBB integrity. Intranasal administration might bypass the BBB and lead to even higher brain bioavailability than after intravenous administration.

Although the precise mechanisms underlying intranasal drug delivery to the central nervous system are unknown, NTB delivery pathways are thought to include the olfactory and trigeminal pathways (Thorne et al. 2004), as well as the perivascular space, lymphatic system, and cerebrospinal fluid. Neuronal pathways for NTB transport include the olfactory and the trigeminal pathways. The olfactory pathway starts from the olfactory area, where olfactory neurons are located. Drug molecules can enter olfactory nerve endings and move via them to the olfactory bulb. Similarly, drugs can be transported along the trigeminal nerve branches to reach the brain. The ophthalmic branch of the trigeminal nerve, which innervates the upper anterior nasal segment, and the maxillary branch, which innervates most of the respiratory mucosa, are involved in transport. Moreover, intranasally administered compounds can cross the BBB indirectly to reach the brain via systemic circulation and the lymphatic system. Rich vasculature in the nasal cavity allows rapid absorption to the systemic circulation. The medications may enter the systemic circulation through the lymph nodes and finally reach the brain. Figure 8 illustrates the pathways involved in NTB transport.

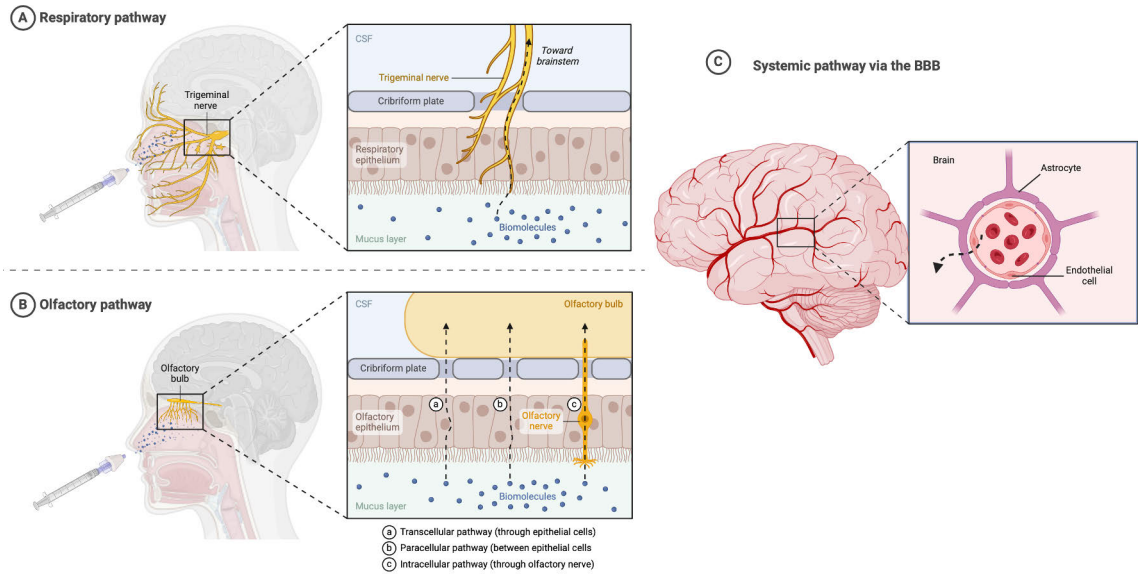


Figure 8. Pathways of NTB transport. A) Trigeminal pathway. B) Olfactory pathway C) Systemic pathway via BBB. The systemic pathway is only accessible to small and lipophilic molecules because this pathway requires crossing the BBB. Modified from Jeong et al. 2023. Created in BioRender.com.

2.3.5 Factors Affecting Intranasal Administration

Several factors may influence the efficacy of intranasal administration. Elements that should be considered include characteristics of the drug, patient-related factors, and characteristics of the delivery system. Because the regions of interest within the nasal cavity for local and systemic delivery differ from those for central nervous system delivery, drug delivery may be improved by selectively targeting the drug to its preferred site using the optimal combination of head position, formulation, and delivery device.

2.3.5.1 Characteristics of Drug

The physicochemical properties of the drug and its formulation affect how well the drug is absorbed from the nasal cavity. Drug-related factors that might influence intranasal drug administration are acid base dissociation constant (pK_a), partition coefficient, polarity, size, and degree of lipophilicity (log P). The nonionized drug fraction is more permeable than the ionized one. Furthermore, the pH of the drug may affect absorption. The average pH of the nasal cavity is 6.3 (Washington et al. 2000). The nasal mucosa may be irritated if the pH of the drug is too high or too low, which may affect drug permeation. Lipophilic molecules easily cross nasal epithelium, whereas absorption of hydrophilic drugs is generally poor. Large

molecules are poorly absorbed, and those with a molecular weight of over 1000 Daltons have a low bioavailability (McMartin et al. 1987). The formulation's viscosity may influence droplet size and nasal deposition, affecting the efficacy of nasal administration.

2.3.5.2 Patient-related Factors

Conditions that increase nasal secretions (rhinitis, common cold) may impede drug absorption from the nasal mucosa. Sinonasal diseases, such as nasal polyps, could also interfere with drug distribution or absorption. Vasoconstrictor or vasodilator medications affect nasal blood flow, causing variation in the absorption of substances at this location. Environmental factors such as temperature and humidity can also affect intranasal administration efficacy.

The interaction between the cilia and the mucus layers (mucociliary clearance) and the phase of the nasal cycle influence drug absorption after intranasal administration. Drug bioavailability following nasal delivery is inversely correlated with nasal mucociliary clearance. Illnesses or medications can alter the rate of mucociliary clearance. The nasal cycle also influences mucociliary clearance: The patent nostril has faster clearance times (Soane et al. 2001). Physiological factors affecting the nasal cycle include posture, estrogen levels, exercise, and age. About 80% of adults have a nasal cycle, which is rare in older persons (>70 years) (Mirza et al. 1997). Nasal obstruction may be more evident in the supine position (O'Flynn 1993).

Structural features of the nose and anatomical anomalies, such as a deviated nasal septum, or aberrant nasal turbinates can affect drug deposition. The dimensions of the nasal cavity increase with age and are generally larger in males than females (Samoliński et al. 2007). Anatomical differences in nasal cavity vasculature may affect the rate of intranasal absorption.

2.3.5.3 Nasal Drug Delivery Devices

Characteristics of the administration device are one important factor affecting the efficacy of intranasal drug delivery. A wide variety of nasal drug delivery devices exist, such as pipettes, squeeze bottles, and various spray pumps. A mucosal atomization device (MAD) is frequently used in clinical practice to administer medications intranasally. Devices differ concerning delivery accuracy, dose reproducibility, emitted particle size, velocity of emitted droplets, plume angle, and pattern of disposition. The desired area for drug deposition determines which administration device is optimal for each situation. Atomizers have been postulated to provide a superior effect compared to drops and sprays (Moffa et al. 2019). Precise

dosing is nearly impossible with drops, and the distribution of drops depends on gravity. The administration technique also has an impact; proper usage of the chosen delivery device plays a key role in intranasal drug administration.

The patient's position and head orientation must be considered when administering drugs intranasally. Posture considerably impacts the deposition of intranasal medications (Merkus et al. 2006). The patient's position affects some administration devices more than others. The MAD Nasal™ atomizer has been advertised to atomize in any position. According to some studies, the head position impacts medication distribution in the nasal cavity even when using the MAD Nasal™ atomizer (Habib et al. 2013). Different head positions may cause deposition in different areas of the nasal cavity. Administration in a supine position prevents dripping out of the nose; however, the medicine may drip into the nasopharynx. For instance, administration in the supine position using a spray bottle atomizer led to an overdose in one study (Goldhammer et al. 2017).

It has been proposed that the administration angles in the sagittal and coronal planes are critical when optimizing drug deposition (Figure 9). Since individual variation in the anatomy of the nasal cavity is great, it has been suggested that using patient-specific administration angles rather than fixed administration angles might be advantageous (Warnken et al. 2018).

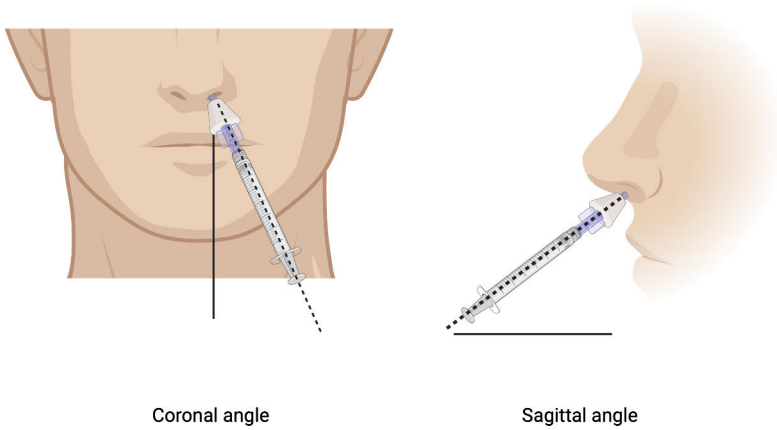


Figure 9. Spray angle in coronal and sagittal plane with mucosal atomization device (MAD). Author's own drawing. Created with Biorender.com.

The amount of liquid that can be dosed is limited, as the nasal cavity has limited absorption capability. If the emitted dose volume is high, part of the medication may be lost via anterior or posterior runoff. The optimal volume of intranasally administered medications is quite a poorly studied subject. The ideal volume has

been reported to be less than 0.2–0.3 ml in studies; however, in practice, volumes between 0.3 and 0.5 ml are simpler to administer than very small doses (Tsze et al. 2017). Splitting the dose in half to both nostrils doubles the available mucosal surface area. Low administration volume may also be more comfortable for patients. Formulations with higher concentrations allow smaller total volumes.

Atomizer dead space should be considered. For example, the MAD Nasal™ atomizer has a dead space of approximately 0.1 ml, which is small but may be significant when small volumes are administered. An air bubble technique can be utilized to compensate for atomizer dead space, ensuring the complete dose is delivered.

3 Aims

The present series of studies was designed and conducted to enhance knowledge on the perioperative use of intranasal dexmedetomidine in the anesthetic care of orthopedic patients.

The aims of the sub-studies were as follows:

1. To evaluate the effect of intranasally administered dexmedetomidine on postoperative opioid consumption in patients undergoing TKA under general anesthesia (Study I).
2. To characterize the population pharmacokinetics of intranasal dexmedetomidine administration on anesthetized adult patients in the supine position (Study II).
3. To investigate if preoperatively given intranasal dexmedetomidine is an effective analgesic adjuvant for treating postoperative pain in patients undergoing TKA under spinal anesthesia (Study III).
4. To determine the effect of premedication with intranasal dexmedetomidine on perioperative hemodynamics, bleeding, hemoglobin and thrombocytes in patients undergoing TKA (Study IV).
5. To investigate the feasibility of intranasal dexmedetomidine in treating postoperative restlessness, agitation, and pain in geriatric orthopedic patients (Study V).

4 Materials and Methods

All studies were conducted at Turku University Hospital: two at TYKS ORTO Hospital and two at TYKS Salo Hospital. Prospective data collection occurred from 2021 to 2023; retrospective data was retrieved from 2017 to 2020.

4.1 Study Designs and Eligibility Criteria (Studies I–V)

Altogether, 315 subjects were enrolled in these studies, all of whom were adult patients scheduled for orthopedic surgery (knee arthroplasty, hip arthroplasty, shoulder arthroplasty, laminectomy, hip fracture). Table 4 presents the characteristics of the studies.

Table 4. Characteristics of studies.

STUDY NRO	**I**	**II**	**III-IV**	**V**
Name of the study	**PROTEDEX2**	**INDEX**	**TKADEX**	**INDEXWARD**
Study design	Retrospective register-based case-control study	Prospective open-label pharmacokinetic study	Prospective double-blinded randomized controlled trial	Retrospective register-based study
Number of enrolled participants	150	32	110	23
Type of surgery	TKA	TKA, THA	TKA	Any orthopedic procedure
Type of anesthesia	General anesthesia (TIVA)	General anesthesia (TIVA)	Spinal anesthesia	Postoperative period, any type of anesthesia

Author's own drawing. Abbreviations: TKA; total knee arthroplasty, THA; total hip arthroplasty, TIVA; total intravenous anesthesia.

Study I (PROTEDEX2) was a retrospective register-based case-control study. Patients were identified retrospectively using Turku University Hospital's electronic

patient record system and data were obtained from it and anesthesia reports. We included patients who had undergone unilateral TKA at Turku University Hospital in the Salo unit. We collected data from 150 patients, 75 patients in each group: the dexmedetomidine (DEX) group and the control (CTRL) group. The inclusion criteria were that the patient had to be scheduled for primary unilateral TKA under total intravenous anesthesia (TIVA), be classified as American Society of Anesthesiologists (ASA) 1–2, age 35–80, and weigh between 50kg and 100 kg. Exclusion criteria were recent or ongoing illness affecting absorption, distribution, metabolism, excretion, or response to the study drug, clinically significant abnormal findings in laboratory screening or physical examination, use of opioids before surgery, use of other adjuvant analgesics (e.g., ketamine, gabapentinoids, clonidine, or tricyclic antidepressants), and spinal or inhalational anesthesia.

Study II (INDEX) was a prospective open-label pharmacokinetic study. We aimed to recruit 30 patients for Study II. The study population consisted of patients coming to elective unilateral THA or TKA under general anesthesia at Turku University Hospital in the Salo unit. Inclusion criteria were that the patient had to be scheduled for primary unilateral THA or TKA under general anesthesia, age 35–80, weigh between 50kg and 100 kg, be classified as ASA 1–3, be fluent in Finnish and give written informed consent. Exclusion criteria included intolerance to the study drug or related compounds and additives, opioid use before surgery, use of other adjuvant analgesics (e.g., ketamine, gabapentinoids, clonidine, or tricyclic antidepressants), participation in any other study concomitantly or within one month before the entry into this study, disease or condition affecting the ability to give written informed consent, recent or ongoing illness affecting absorption, distribution, metabolism, excretion, or response to the study drug, history of cardiac issues (e.g. valvular insufficiency, severe left ventricular dysfunction), or abnormal ECG rhythm (bradycardia < 50/min, 2nd- or 3rd-degree AV-block, pacemaker), low preoperative blood pressure (<110 mmHg), clinically significant abnormal findings in physical examination or laboratory screening, pregnancy or breastfeeding, use of drugs or natural products known to cause enzyme induction or inhibition, and spinal anesthesia.

Study III (TKADEX) was a prospective, double-blinded, randomized controlled trial. Study IV was a secondary analysis of Study III. Patient recruitment for Studies III and IV occurred at TYKS ORTO Hospital between May 2022 and September 2023. Patients coming to elective unilateral TKA under spinal anesthesia were recruited. Altogether, 110 patients were enrolled, with 55 in each group (DEX and CTRL groups). The inclusion criteria included the patient being scheduled for elective unilateral TKA under spinal anesthesia, age 35–80, weigh between 50kg and 100 kg, classified as ASA 1–3, be fluent in Finnish and give written informed consent. The exclusion criteria included intolerance to the study drug or related

compounds and additives, disease or condition affecting the patient's ability to give written informed consent, recent or ongoing illness affecting absorption, distribution, metabolism, excretion, or response to the study drug, history of cardiac issues (valvular insufficiency, severe left ventricular dysfunction) or abnormal ECG rhythm (bradycardia < 50/min, 2nd- or 3rd-degree AV-block, pacemaker), low preoperative blood pressure (<110 mmHg), opioid use before surgery, use of other adjuvant analgesics (e.g., ketamine, gabapentinoids, clonidine, or tricyclic antidepressants), participation in any other study concomitantly or within one month before the entry into this study, clinically significant abnormal findings in physical examination or laboratory screening, pregnancy or breastfeeding, use of drugs or natural products known to cause enzyme induction or inhibition, and intolerance to NSAIDs.

Study V (INDEXWARD) was a retrospective register-based study. Eligible patients were identified, and patient data were extracted from the anesthesia reports and the patient database of Turku University Hospital. We included patients age > 70 years who had undergone orthopedic surgery and received intranasal dexmedetomidine (100μg) postoperatively in a postoperative intermediate care unit. We acquired data from all eligible patients treated during one year. Inclusion criteria were orthopedic surgery between November 2019 and November 2020, receiving a single dose of intranasal dexmedetomidine 100 μg postoperatively for postoperative restlessness, agitation, or pain and age >70 years. Exclusion criteria included patients with contraindications for administration of dexmedetomidine, patients with unstable hemodynamics and respiration, patients receiving other sedatives for delirium or agitation within 6 h before or after dexmedetomidine administration, patients requiring vasoactive agents at the time of or 6 h before dexmedetomidine administration, and patients with insufficient recordings of hemodynamic and respiratory parameters.

4.2 Dexmedetomidine Dosing (Studies I–V)

In all sub-studies, dexmedetomidine (Dexdor®100 μg/ml, Orion Pharma, Espoo, Finland) was administered intranasally using an LMA MAD Nasal™ device (Teleflex MAD Nasal, NC, USA) attached to a syringe. Figure 10 illustrates an intranasal administration using the MAD Nasal™ device and syringe.

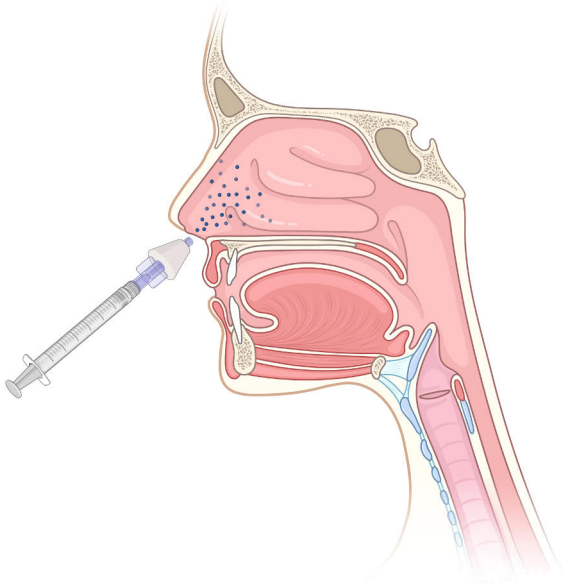


Figure 10. Intranasal administration of medication using the MAD Nasal™ device and syringe. Author's own drawing. Created in BioRender.com.

In Studies I and II, adult patients undergoing arthroplasty surgery under general anesthesia were scheduled to receive 100 µg of intranasal dexmedetomidine shortly after induction of anesthesia. All patients in the studies weighed between 50kg and 100 kg; therefore, the dexmedetomidine dosage varied from 1 to 2 µg/kg. Administration of dexmedetomidine was done according to local protocol within 5 min of inducing anesthesia. At the time of administration, patients were in the supine position and under general anesthesia, with a laryngeal mask in place. Registered nurses who had received training in the administration method performed the drug administration.

In Studies III and IV, adult patients undergoing TKA under spinal anesthesia were scheduled to receive intranasal dexmedetomidine 1 µg/kg (volume 0.5–1 ml) or an equivocal amount of placebo (saline) approximately 30–60 min before anticipated anesthesia induction according to randomization. A member of the research team (senior anesthesiologist) performed the dexmedetomidine administration with the patient in the semi-recumbent position.

In Study V, adult patients received 100 µg intranasal dexmedetomidine at the postoperative intermediate care ward to treat postoperative pain, agitation, or restlessness. Dexmedetomidine administration was performed with the patient in the semi-recumbent position. Registered nurses who had received training in the administration method performed drug administration.

4.3 Blood Sampling (Study II)

In Study II, venous blood samples were obtained to determine dexmedetomidine concentrations. For this, a second peripheral venous cannula was placed in the contralateral antecubital vein to facilitate the collection of blood samples. We aimed to obtain two venous blood samples during the assumed absorption phase i.e., within the first 20 min after drug administration, another two samples during the assumed distribution phase i.e., within 30–60 min after drug administration, and one sample during the assumed elimination phase i.e., within 60–240 min after drug administration. Blood samples were obtained at six time points: immediately before the administration of dexmedetomidine (baseline) and thereafter at 5, 15, 45 min, 1 h, and 4 h. Samples were collected into EDTA tubes and placed on ice. A 5–10 min variation in sampling times was allowed. Actual sampling times were recorded and used in the data analysis. Plasma was separated by centrifuge using 4800 rpm at +4°C. Plasma was frozen at -20…-40°C immediately after separation; the samples were later stored at −70°C until analysis.

4.4 Analysis of Dexmedetomidine Concentrations in Plasma (Study II)

In Study II, dexmedetomidine plasma concentrations were measured at the Department of Pharmacology, Drug Development and Therapeutics, University of Turku, using a validated liquid chromatographic/mass spectrometric method. The sample analysis system included a Sciex ExionLC™ AD HPLC instrument and a Sciex QTrap 6500+ triple quadrupole mass spectrometer (AB Sciex LP, Concord, ON, Canada). A Gemini C18 analytical column (150 x 2.0 mm, particle size 5 µm) and precolumn from Phenomenex (Torrance, CA, USA) were used for separation. Positive Turbo Ion Spray (TIS) ionization was used for mass spectrometric detection, using multiple reaction monitoring (MRM) mode. The lower limit of quantitation (LLOQ) was 0.05 ng/ml.

4.5 Pharmacokinetic Analysis (Study II)

The assessment of absorption parameters (absorption half time [T_{ABS}], absorption lag time [T_{LAG}], relative bioavailability [F]) necessitated combining time-concentration data from Study II with data from earlier intravenous administration studies. Intranasal dexmedetomidine concentration data collected in this study were combined with previously published intravenous dexmedetomidine time-concentration measurements (Rolle et al. 2018; Potts et al. 2009; Talke et al. 2018; Cortínez et al. 2015; Hannivoort et al. 2015)

Dexmedetomidine pharmacokinetics were described using two-compartment pharmacokinetic (PK) models with first-order elimination. The clearance (CL), volume of distribution (V1, V2), and intercompartmental clearance (Q2) parameters were used to parameterize the model. Allometric theory was applied to measure size-related variations in PK parameters. The absorption rate constant (k_a), represented as an absorption half-time (T_{ABS}), was modeled using a depot compartment.

Nonlinear mixed effects models (NONMEM 7.5 ICON Development Solutions, USA) with first-order conditional estimation and convergence criteria set to three significant digits were used to estimate population parameters. ADVAN13 TOL=9 of NONMEM was used in the first-order conditional interaction estimate method to estimate the population mean parameters between-subject variance and residual variance.

PK parameters (e.g., CL, Q2, V1, V2) were allometrically scaled to an adult body size with a standard weight of 70 kg. An exponential model for random effect variables was used to account for population parameter variability (PPV). This assumes a log-normal distribution and prevents parameter estimates from being less than biologically realistic. Proportional and additive residual errors were used to model residual unidentified variability (RUV). For data, the between-subject variability (RUV,i) of the RUV was also assessed.

Model selection was also based on parameter plausibility and prediction-corrected visual predictive checks plots. Internal evaluation of the model was conducted using prediction-corrected visual predictive checks and bootstrap methods. These provided the means to evaluate parameter uncertainty. Altogether, 100 bootstrap replications were used to estimate parameter means and confidence intervals.

4.6 Analysis of Pharmacodynamic Effects (Studies I–V)

4.6.1 Assessment of Hemodynamic and Respiratory Effects (Studies I–V)

Hemodynamic measures (heart rate [HR], mean arterial pressure [MAP], noninvasive blood pressure [NIBP]) and respiratory effects (peripheral arterial oxygen saturation [SpO2]) were monitored in all sub-studies. In Study I, measurements were taken before surgery, during incision, an hour after anesthetic induction, at wound closure, and in the postoperative anesthesia care unit (PACU) an hour after surgery. In Study II, parameters were recorded immediately before the administration of dexmedetomidine and at 5, 10, 15, 30, and 45 min, and 1, 2, 3, and 4 h after dexmedetomidine administration. In Studies III and IV, parameters were

monitored and recorded at baseline (before administration of dexmedetomidine or placebo), at 5-minute intervals during the operation, and at 15-minute intervals in the PACU. In Study V hemodynamic measurements were taken before dexmedetomidine administration (baseline) and every hour for the next 5 hours.

4.6.2 Assessment of Opioid-sparing Effects (Studies I, III, V)

Postoperative opioid consumption was recorded in Studies I, III, and V. Opioid consumption was documented until discharge, or up to 48 hours after operation whichever occurred first. Opioids were converted to oral morphine equivalents (OME). Significant postoperative opioid use reduction was defined as >20% or 20mg–30 mg. In Study V, cumulative opioid consumption was assessed 0–6 hours before and 0–6 hours after dexmedetomidine dosing.

4.6.3 Assessment of Anxiolytic Effects (Study III)

The severity of preoperative anxiety was evaluated using the verbal analogue scale anxiety (VAS-A) perioperatively in Study III (Facco et al. 2013). Also, the need for additional sedatives (midazolam and fentanyl) was documented.

4.6.4 Patient Satisfaction (Study III)

In Study III, all study participants were telephoned approximately a month after the operation to inquire about their satisfaction with pain management after surgery. Patients were asked to evaluate their satisfaction at three different time points: in the PACU, the postoperative ward, and at home. Patients were also asked to rate pain management in general. Patients were asked to rate their satisfaction on a five-point Likert scale (5=extremely satisfied, 4=somewhat satisfied, 3=neutral, 2=somewhat dissatisfied, 1=extremely dissatisfied).

4.7 Safety and Adverse Events (Studies I-V)

In prospective Studies, II, III, and IV, objective or subjective adverse events and the treatments used to treat them were documented in the case report form (CRF). In retrospective Studies, I and V, objective or subjective adverse events were gathered from the patient database and anesthesia reports.

Study I defined bradycardia as HR lower than 50 beats per minute (bpm) and severe bradycardia as HR lower than 40 bpm. Hypertension was defined as systolic blood pressure over 160 mmHg, and hypotension was defined as systolic blood pressure lower than 90 mmHg.

In Study II, bradycardia, hypotension, respiratory issues, and other medication responses that occurred within 4 hours after the administration of dexmedetomidine were identified as adverse events of relevance. Bradycardia, including atropine treatment, was defined as an HR below 40 bpm. MAP less than 65 mmHg despite a sufficient fluid bolus or vasoactive medicine was considered hypotension. Any allergic responses or local symptoms associated with intranasal medication delivery were considered additional drug reactions.

Study III/IV defined bradycardia as HR lower than 50 bpm and severe bradycardia as HR lower than 40 bpm. Hypertension was defined as systolic blood pressure over 150 mmHg, and hypotension was defined as systolic blood pressure lower than 90 mmHg.

In Study V, adverse events included bradycardia (HR < 40 bpm), hypotension (MAP < 65 mmHg for more than one hour or any MAP < 60 mmHg), excessive sedation (modified Richmond Agitation Sedation Scale, mRASS < −3), hypoxia (SpO2 < 92%), hypoventilation (RR < 10/min or < 8/min if baseline RR was < 10/min), nausea, or vomiting within 6 hours of dexmedetomidine administration. Serious adverse events included loss of consciousness or the requirement for intubation, assisted breathing, or vasopressor infusion.

4.8 Statistical Analysis (Studies I–V)

4.8.1 Study Hypotheses and Outcomes (Studies I–V)

Our hypothesis in Study I was that patients undergoing TKA under general anesthesia would need fewer opioids after intraoperative intranasal dexmedetomidine administration. Our primary outcome measure was the cumulative number of opioids administered to the patients in morphine-equivalent doses. Secondary outcomes were MAP and HR values recorded during the perioperative period, incidence of PONV, intraoperative entropy levels, length of PACU time, and length of hospital stay.

In Study II, we hypothesized that intranasal dexmedetomidine is well absorbed in anesthetized adult patients in the supine position. C_{max} and T_{max} of intranasally administered dexmedetomidine were the main outcome variables.

In Study III, our primary hypothesis was that premedication with intranasal dexmedetomidine lowers postoperative pain levels and opioid consumption after TKA performed under spinal anesthesia. We also hypothesized there would be fewer opioid-related side effects, patients would be more satisfied after dexmedetomidine administration, and that intranasal administration would lead to stable intraoperative hemodynamics. Our primary outcome measure was postoperative pain, which was measured using the numerical rating scale (NRS). Our secondary aims were to

measure the requirement for postoperative opioids and intraoperative sedatives, the incidence of PONV, 30-day patient satisfaction, and hemodynamic adverse effects.

In Study IV, the primary outcomes were perioperative hemodynamics and peripheral oxygen saturation. The secondary outcomes were intraoperative blood loss and perioperative changes in hemoglobin and platelets and incidence of intraoperative bradycardia, tachycardia, hypotension and hypertension. We hypothesized that premedication with intranasal dexmedetomidine reduces intraoperative heart rate and blood pressure and thus may reduce intraoperative bleeding. We hypothesized that intranasal dexmedetomidine does not affect respiratory parameters.

In Study V, our primary outcome measures were to assess the changes in MAP, HR, RR, and SpO2, from the baseline value within 5 h of dexmedetomidine administration, cumulative opioid consumption 6 h before and 6 h after dexmedetomidine dosing, and mRASS at dexmedetomidine administration as well as the lowest value of mRASS within the following 4 h of dexmedetomidine dosing. Secondary outcomes were the FiO2 levels during dexmedetomidine administration, the time between operation and dexmedetomidine administration, and the time to mobilization following dexmedetomidine administration. We hypothesized that intranasal dexmedetomidine may affect hemodynamics and opioid consumption but not respiratory parameters.

4.8.2 Sample Size Calculations (Studies I–V)

No prior data was available to inform a sample size calculation in Study I. Therefore, we pragmatically chose the sample size based on previous experience with similar studies (Uusalo et al. 2019). We gathered 75 patients in each group (totaling 150 patients) and evaluated the statistical power achievable with the planned sample sizes by calculating confidence intervals.

Study II used a sparse sampling scheme, and a non-linear mixed effects modeling approach was used. Due to their complexity, traditional power calculations may not directly apply to nonlinear mixed effects models. The key challenge with these models is that the calculation of statistical power is more complex than linear models due to the non-linearity and the incorporation of fixed and random effects. Therefore, we used simulation-based methods (Berkeley Madonna) to determine the sample size needed using prior data (Iirola et al. 2011; Li et al. 2018). This ensures the analysis has adequate power to detect the effects of interest while accounting for the intricacies of the model structure. We aimed to recruit 30 patients for Study II. To prepare for dropouts due obvious sample hemolysis during the study, two additional patients were recruited.

In Study III, sample size calculations were made with NRS (pain) as the primary outcome. To establish a 30% decrease from 5.0 to 3.5 in NRS ratings (a clinically meaningful difference) (Laigaard et al. 2021), using a level of significance of p = .05 and a power of 90%, we count that fifty-one (51) patients per group and a total of 102 patients would be required. Altogether, 110 patients were planned to be enrolled and randomized, with 55 in each group and an allowance for eight dropouts.

Study IV was a secondary analysis of Study III, and no sample size calculations were performed.

In Study IV all eligible patients during one year were identified and included. The sample size was not calculated due to this study's preliminary nature.

4.8.3 General Statistics (Studies I–V)

The analyses were performed with JMP Pro 13.0 for Mac (SAS Institute Inc., Cary, NC, USA) and the IBM SPSS Statistics version 24 (IBM Corp., Armonk, NY, USA).

In Study I, the Shapiro–Wilk test was employed to evaluate the normality assumptions. The Wilcoxon rank-sum test was used to evaluate non-normally distributed data, while the Student's t-test was used to compare the groups with normally distributed data. Chi-square analysis was employed to evaluate nominal data. A two-tailed p-value of < .05 was considered statistically significant.

In Study II, only pharmacokinetic modeling was performed, not general statistics.

In Study III, the Shapiro–Wilk test was used to evaluate the normality assumptions. The Student's t-test was used to compare groups with normally distributed data, while non-normally distributed data was tested using the Wilcoxon rank-sum test. The nominal data were tested using chi-square analysis. A Fischer's exact test was used to evaluate patient satisfaction, which was measured using the Likert scale. P-values < .05 (two-tailed) were considered statistically significant. When the normality assumption was unmet, the results were expressed as mean values with standard deviations (SD) or medians with interquartile ranges (IQR).

Study IV used the Shapiro–Wilk test (p > .05), which was employed to evaluate the normality assumptions together with visual evaluation. To determine if the mean changes over time for hemodynamic variables varied between the DEX and CTRL groups, linear mixed models for repeated measurements were employed. Group (between-subject factor), time (within-subject factor), and group by time interaction were all included in the model. The model also took sex and age into account. Compound symmetry covariance structure was fitted to the data. For degrees of freedom, Kenward-Roger correction was applied. Normality assumption was checked with studentized residuals. Student's t-test was used for normally distributed

variables and the Wilcoxon rank-sum test for skewed data. Association between two categorical variables were tested using chi-square analysis.

In Study V, normality assumptions were evaluated using the Shapiro–Wilk test. The Wilcoxon rank-sum test was used to test non-normally distributed data, whereas the Student's t-test was used to compare groups with normally distributed data. A chi-square analysis was used to examine the nominal data. Two-tailed $p < .05$ was considered as statistically significant.

4.9 Ethical Considerations (Studies I–V)

The investigations described during this study were conducted according to the revised Declaration of Helsinki of the World Medical Association and ICH GCP guidelines for good clinical trial practice. When applicable, the study protocols, patient information and informed consent forms were submitted for approval to the Ethics Committee of the Hospital District of Southwest Finland and to the Finnish Medicines Agency.

Intranasal dexmedetomidine has been safely administered in several earlier studies. Although intranasal administration of dexmedetomidine is off-label, it has been widely adopted in clinical practice. The doses of intranasal dexmedetomidine used in Studies I–V were based on previous studies (Iirola et al. 2011; Lu et al. 2016; Wu et al. 2016).

Studies I and V were retrospective register-based studies that had no impact on patient care. Permission from the Ethics Committee was not sought; permission was obtained from Turku CRC (Clinical Research Center).

The Ethics Committee of the Hospital District of Southwest Finland and the Finnish National Agency for Medicines approved the study protocols of prospective Studies II–IV. Trials were registered before patient enrollment at clinicaltrials.gov and in the EudraCT database. Written informed consent was obtained from all study subjects for prospective Studies II–IV. All patients received information regarding the discomforts and potential risks related to the study and had time to decide on participation. A qualified anesthesiologist and anesthetic nurse always monitored the safety and well-being of the patients.

In Study II, there was no change to the customary local practices because intranasal dexmedetomidine had been routinely given to patients undergoing arthroplasty surgery at the Turku University Hospital in the Salo Unit from 2017 onward. Patients were already under anesthesia when the intravenous cannula for taking blood samples was inserted; therefore, the patient experienced no further pain.

The employed doses of dexmedetomidine in Studies II–IV were not expected to have any marked effects on respiration and blood oxygen saturation. The dose of intranasal dexmedetomidine (1–2 μg/kg) was predicted to lead to lower

dexmedetomidine plasma concentrations, hemodynamic effects, and sedative effects than intravenous administration. Minor temporary reductions in blood pressure and concurrent drops in heart rate were expected to occur, but it was considered unlikely that these effects would be symptomatic in supine patients.

5 Results

5.1 Study Subjects (Studies I–V)

After dropouts, data from altogether 302 patients were analyzed. Table 5 presents the characteristics of study subjects.

Table 5. Characteristics of study subjects.

STUDY NRO	**I**	**II**	**III-IV**	**V**
Name of the study	**PROTEDEX2**	**INDEX**	**TKADEX**	**INDEXWARD**
Number of participants[3]	150	28	101	23
Age (years)[1]	DEX 66 (8) CTRL 68 (8)	66,8 (7.3)	DEX 68 (6.0) CTRL 66.5 (7.9)	79.9 (7.5)
BMI (kg/m2)[1]	DEX 27.9 (3.3) CTRL 28.9 (4.1)	28,6 (4.4)	DEX 28.7(3.6) CTRL 29.2 (4.2)	28.1 (5.2)
Sex (Male/Female)[3]	DEX 23/52 CTRL 23/52	9/19	DEX 10/39 CTRL 11/41	11/12
Weight-adjusted dexmedetomidine dose (μg/kg)[1]	1.30 (0.19)	1.22 (0.15)	1.00 (0.04)	1.31 (0.25)
Actual dexmedetomidine dose (μg)[2]	100 μg	100 μg	80 μg (70–90)	100 μg

Author's own drawing. Age, BMI, and weight-adjusted dexmedetomidine dose expressed as [1]mean and standard deviation, as [2]median and interquartile range or [3]number. Abbreviations: BMI, body mass index; CTRL, control group; DEX, dexmedetomidine group.

5.2 Analgesic and Opioid-sparing Effect of Dexmedetomidine (Studies I, III, V)

The analgesic and opioid-sparing effects of dexmedetomidine were studied in Sub-studies I, III, and V.

In Study I, intranasal dexmedetomidine administered during operation reduced opioid requirement in patients undergoing TKA under general anesthesia. The DEX group had a significantly lower 48-hour postoperative opioid requirement compared to the CTRL group (- 28.5 mg, 95% CI 12–47 mg, p <.001). The cumulative opioid dose differed significantly between groups at all time points (2, 12, 24, 36 h, and 48h postoperatively) (p <.001) (Figure 11).

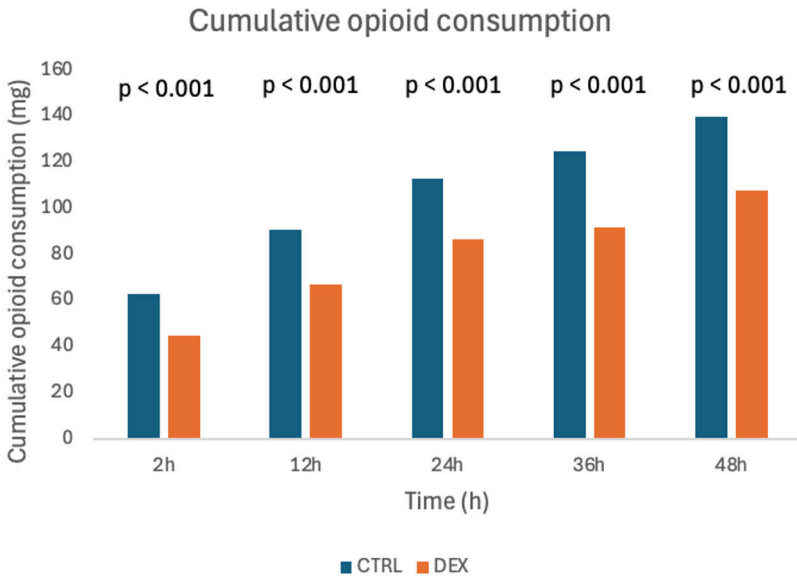


Figure 11. Cumulative postoperative opioid requirement in Study I. Cumulative postoperative opioid requirements of dexmedetomidine (DEX) and control (CTRL) groups, measured as oral morphine equivalents (OME). Values are given as median. Modified from Original Publication I.

In Study III, patients in the DEX group had lower NRS scores at 3 hours compared to the CTRL group (p = .037). Also, $NRS_{AUC0\text{-}24h}$ was lower in the DEX group than in the CTRL group (p = .011) (Figure 12). There was a trend toward lower cumulative opioid consumption in the DEX group, but the difference was not statistically significant. There was no difference between intraoperative fentanyl consumption (p = .398).

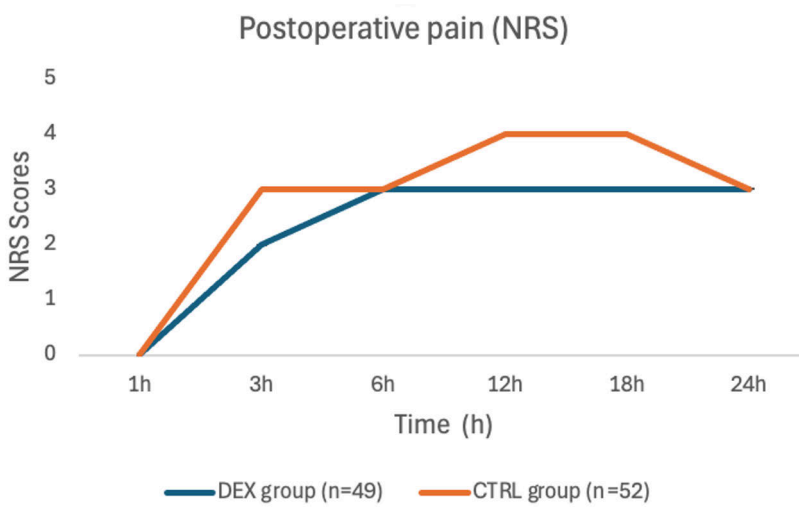


Figure 12. Postoperative pain in Study III. Postoperative pain in Study III presented as NRS scores in dexmedetomidine (DEX) and control (CTRL) groups. Values are given as median. Modified from Original Publication III.

In Study V, the cumulative 6 h opioid consumption was significantly reduced after dexmedetomidine administration compared with that before dexmedetomidine (median difference − 0.24 mg/kg; 95% CI − 0.63 to 0.02; p = .005). The reduction in opioid consumption was negatively associated with age (p = .01), but not with sex, weight, body mass index (BMI), or the weight-adjusted dexmedetomidine dose. HR was negatively correlated with cumulative opioid consumption following dexmedetomidine administration (β = .596; p = .02; $\log_e$ opioid consumption).

5.3 Anxiolytic Effect of Dexmedetomidine (Study III)

The anxiolytic effect of dexmedetomidine was studied in Study III. The change in preoperative anxiety levels, assessed by VAS-A ratings, from baseline (before the time of drug administration) to the moment before spinal anesthesia, did not differ between the groups (p = .20). Patients in the DEX group required less additional intraoperative midazolam (mg) (p = .033). The median dose in the DEX group was 1 mg (IQR 1–2 mg), while the CTRL group received 2 mg (IQR 1–3 mg). In the CTRL group, 94% of patients (48/51) required midazolam for sedation, whereas 82% of patients in the DEX group (40/49) requested extra sedation (p = .14).

5.4 Pharmacokinetics of Intranasal Dexmedetomidine after Intranasal Administration in Adult Patients under General Anesthesia (Study II)

Pharmacokinetics of intranasal dexmedetomidine were studied in Study II. Thirty-two subjects were recruited, but four were excluded due to incomplete or hemolyzed samples. Altogether, 168 plasma samples were collected from 28 subjects. The dose of intranasal dexmedetomidine administered for all patients was 100 μg and the median weight-adjusted dose of dexmedetomidine was 1,22 μg/kg.

In the pooled dexmedetomidine PK analysis, 2284 dexmedetomidine concentrations were amenable to modeling, including 168 drug concentrations from the 28 participants administered intranasal dexmedetomidine. A two-compartment PK model was used to describe the concentration profiles. Allometric scaling of the pharmacokinetic parameters using total body weight was included in the final model. Using differential equations in Berkeley Madonna™ modeling and simulation software (Robert Macey and George Oster of the University of California Berkeley, USA), time-concentration profiles were simulated (1000 replications) for nasal dexmedetomidine 100 μg with current parameter values.

After intranasal administration, a mean C_{MAX} of 0.273 μg/L was achieved at a T_{MAX} of 98 min. Concentrations were sustained around this C_{MAX} for over 2 hours (Figure 13). The relative bioavailability of dexmedetomidine was 80% (95% CI 75 to 91%). Table 6 compares the pharmacokinetic parameters of intranasal dexmedetomidine for anesthetized adult patients with earlier studies.

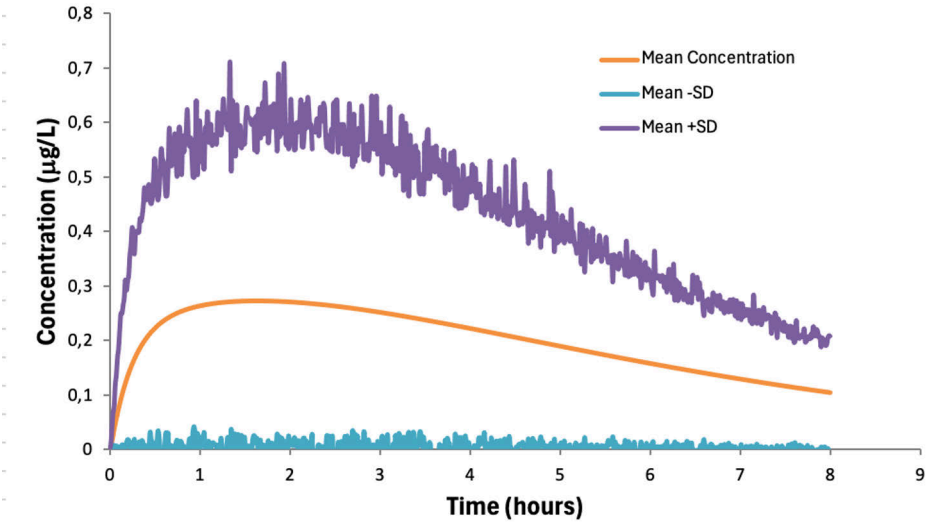


Figure 13. Plasma concentration-time curve of intranasal dexmedetomidine in Study II. Concentrations of intranasally administered 100 µg dexmedetomidine. Modified from Original Publication II.

Table 6. Pharmacokinetic parameters after administration of intranasal dexmedetomidine for anesthetized adult patients (Study II) compared with earlier studies.

Parameter	Current study	Li et al. 2018		Wu et al. 2022	Kuang et al. 2022	Iirola et al. 2011	Yoo et al. 2015
Administration method and solution	Nasal atomizer	Nasal atomizer	Nasal drops	Nasal drops	Specialized nasal spray	Spray pump, highly concentrated veterinary solution	Spray pump, highly concentrated veterinary solution
Patient population	Patients undergoing TKA/THA	Healthy adults	Healthy adults	Patients undergoing tympanoplasty	Healthy adults	Healthy men	Healthy men
Number of subjects analyzed	28	8	8	14	12	6	6
F (%)	80	40,6	40.7		85	65	82
T_{MAX} (min)	98	47.5	60	13.2	30	30	30
C_{MAX} (ng/ml^{-1})	0.273	0.28	0.25		0.556	0.34	0.314
ka (h^{-1})	0.424	0.855	0.725				0.94

Modified from Original Publication II. F = bioavailability, T_{MAX} = time to reach maximum concentration, C_{MAX} maximum concentration, ka = absorption rate constant.

5.5 Hemodynamic and Respiratory Effects (Studies I–V)

Hemodynamic effects were evaluated in all sub-studies, whereas respiratory effects were evaluated in Studies IV–V. Bradycardia and hypotension were more frequent in patients who received dexmedetomidine, but in general, the hemodynamic effects were mild, and intranasal dexmedetomidine was well-tolerated.

In Study I, postoperative MAP was lower in patients in the DEX group ($p < .001$), but higher in the DEX group during wound closure ($p < .001$) than the CTRL group. HR was lower in the DEX group at incision ($p = .02$), one hour after induction ($p = .007$), during wound closure ($p = .003$) and at PACU ($p < .001$). The weight-adjusted dexmedetomidine dose (1.30 μg/kg) was inversely correlated with MAP change ($r = -0.25$; $p = .03$), but not with change of HR ($r = .01$; $p = .98$). Figure 14 presents the hemodynamics of Study I.

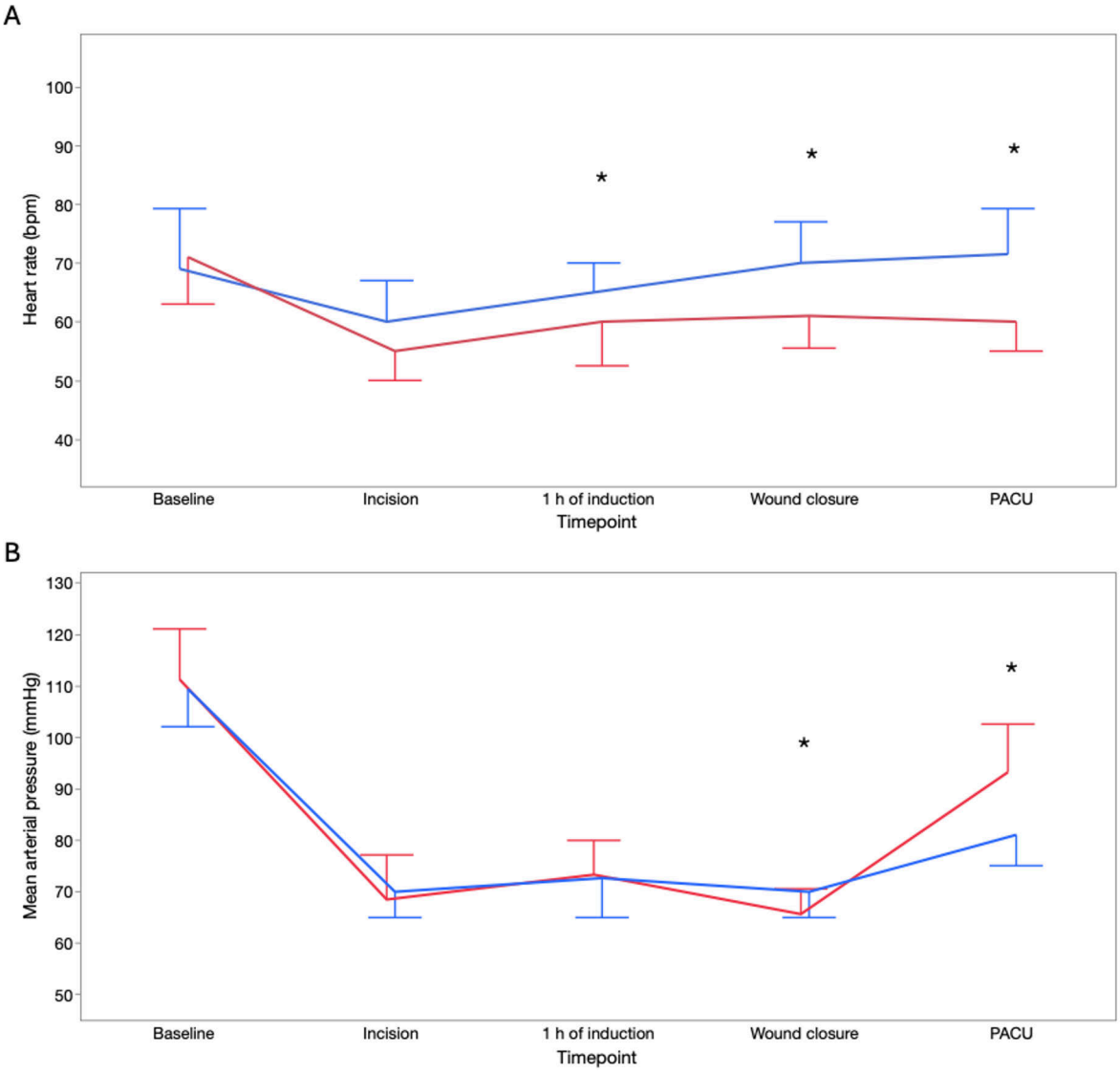


Figure 14. Hemodynamics of Study I patients undergoing TKA under general anesthesia. Median (IQR) heart rate (A) and mean arterial pressure (B). Blue graph represents the dexmedetomidine group and red graph the control group. *The difference between the groups is statistically significant at the timepoint ($p < .05$). Modified from the Original Publication I.

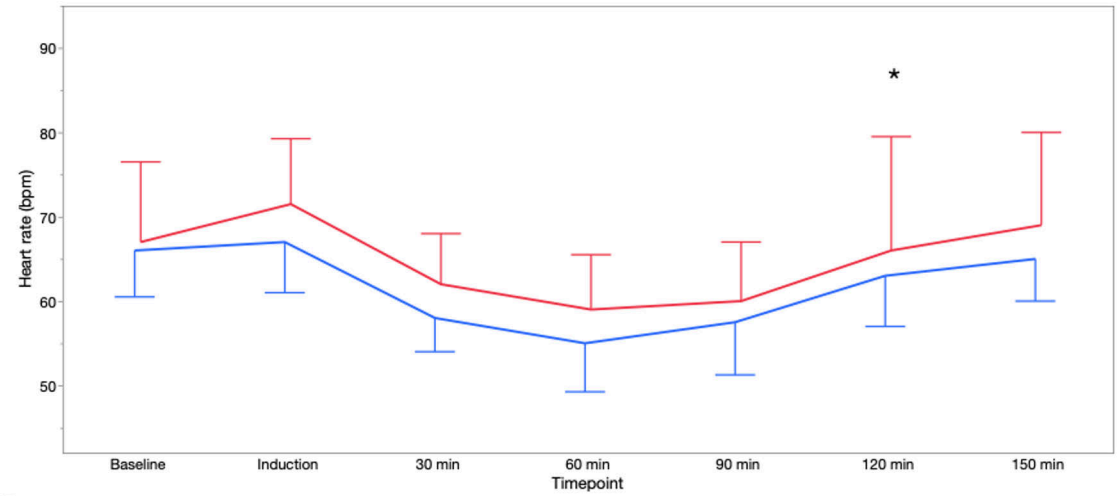
In Study II, intranasal dexmedetomidine was well tolerated. The median (IQR) dose of intravenous ephedrine was 6 mg (0–12 mg). None of the patients required norepinephrine infusion to treat hypotension. No bradycardia was reported.

In Studies III–IV, compared to baseline measurements, MAP decreased in the dexmedetomidine group 36.3 (1.7) mmHg (95% CI 32.9–39.7; $p < .001$) and in the

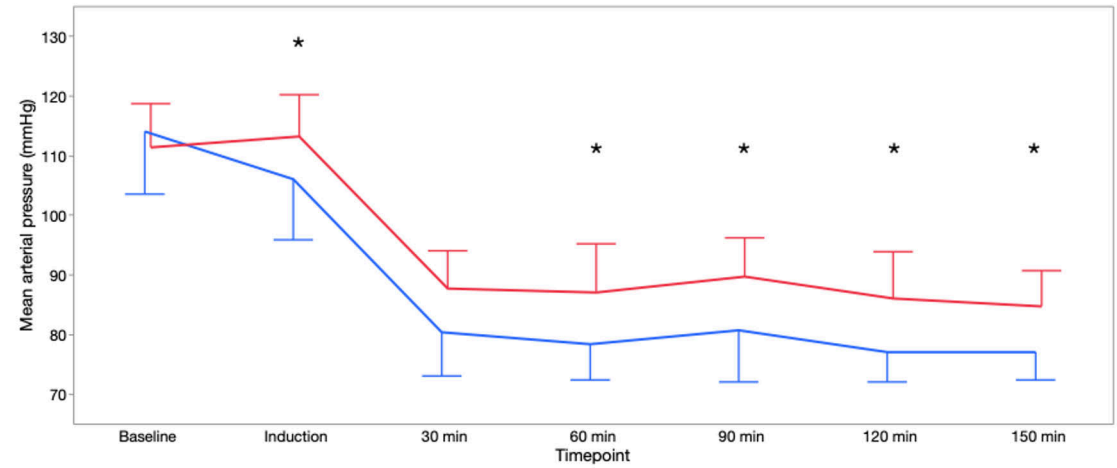
control group 26.5 (1.7) mmHg (95% CI 23.2–29.7) after induction of spinal anesthesia, while HR decreased in the dexmedetomidine group 11.6 (1.3) bpm (95% CI 9.1–14.1; p < .001) and in the control group 9.7 (1.2) bpm (95% CI 7.3–12.2; p < .001). The intraoperative HR (maximal difference -6.1 [2.2] bpm [95% CI -10.5 – -1.7; p=0.007]) and MAP (maximal difference -8.5 [2.5] mmHg [95% CI -13.5 – -3.5; p <.001]) were lower in the dexmedetomidine group than the control group. The incidence of intraoperative bradycardia, tachycardia and hypotension was the same for both groups, but intraoperative hypertension (RRsyst >150 mmHg) was significantly more common in patients who had received placebo (p = .03). Noradrenaline, ephedrine, adrenaline, and labetalol requirements did not differ between the groups. There was no difference in peripheral oxygen saturation (SpO2) or requirement of supplemental oxygen between the groups. Figure 15 presents the hemodynamics and respiratory effects of Studies III–IV.

Figure 15. ► Hemodynamics and respiration data of patients in Studies III–IV undergoing TKA under spinal anesthesia. Median (IQR) heart rate (A), mean arterial pressure (B) and peripheral oxygen saturation (SpO_2) (C). Blue graph represents the dexmedetomidine group and red graph the control group. *The difference between the groups is statistically significant at the timepoint (p < .05). Modified from the Original Publication III-IV.

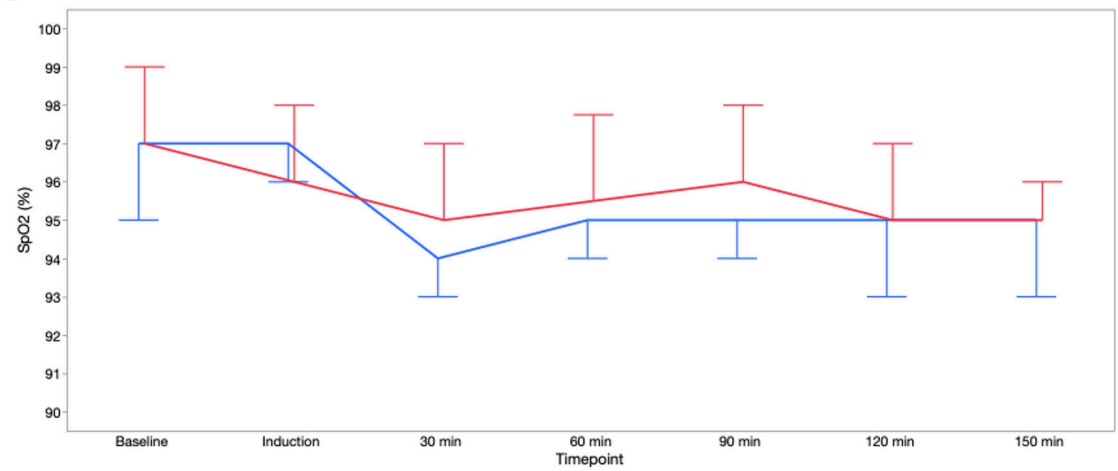
A


Heart rate (bpm)
90
80
70
60
50
*
Baseline
Induction
30 min
60 min
90 min
120 min
150 min
Timepoint

B


Mean arterial pressure (mmHg)
130
120
110
100
90
80
70
*
*
*
*
*
Baseline
Induction
30 min
60 min
90 min
120 min
150 min
Timepoint

C


SpO2 (%)
100
99
98
97
96
95
94
93
92
91
90
Baseline
Induction
30 min
60 min
90 min
120 min
150 min
Timepoint

In Study V, during the 5 h observation period, dexmedetomidine decreased HR by 10.4 (3.7) bpm (95% CI 2.9–17.8; p = .004) and MAP by 16.2 (4.4) mmHg (95% CI 7.3–25.1; p < .001). Following administration of dexmedetomidine, MAP substantially decreased at 1, 2, and 3 hours (p < 0.01 for all comparisons) and HR at 2 hours when compared to baseline values (p = .03). The greatest impact on blood pressure was noted 1–2 hours following intranasal dexmedetomidine. Two patients required one to two single doses of ephedrine for hypotension. Figure 16 presents the effects of intranasal dexmedetomidine on heart rate, blood pressure, SpO2, and respiratory rate.

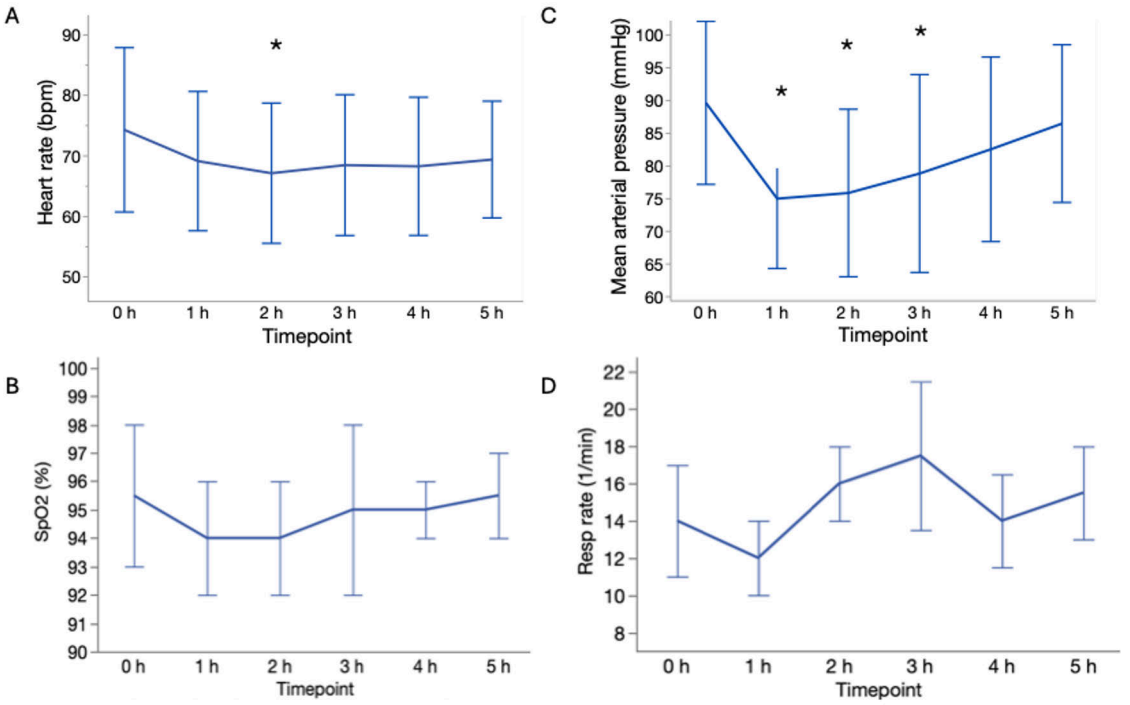


Figure 16. Hemodynamics and respiration data of Study V patients. Median (IQR) heart rate (A), mean arterial pressure (B), peripheral oxygen saturation (C) and respiratory rate (D) 0-5 hours after administration of intranasal dexmedetomidine. *The difference from the baseline value is statistically significant at the time point (p<0.05). Modified from the Original Publication V.

5.6 Other Perioperative Parameters (Studies I, III, IV)

In Study I, the intraoperative entropy levels were comparable between dexmedetomidine and control groups (at incision p = .95, 1h after induction p = .30, at wound closure p = .22). Blood loss was modest in both groups: 100 (50–250) ml in dexmedetomidine group and 100 (50–200) ml in the control group (p = .86).

In Study III the incidence of PONV (p = .310), length of motor block (p = .497), length of stay in PACU (p = .985), and length of hospital stay (p = .861) did not differ between the dexmedetomidine and control groups.

Study IV examined the effects of intranasal dexmedetomidine on intraoperative blood loss and change in hemoglobin and thrombocyte levels. No difference in the amount of surgical bleeding or change in the amount of hemoglobin or thrombocytes existed between the two groups (Table 7).

Table 7. Intraoperative bleeding and changes in hemoglobin and thrombocytes (Study IV).

Parameter	DEX (N=49)	CTRL (N=52)	P-value
Intraoperative blood loss (ml)	100 (50–150)	100 (50–138)	0.66
Change in Hb (Pre-op vs 1POP)	-22 (-29– -17)	-22 (-30– -17)	0.52
Change in Tromb (Pre-op vs 1POP)	-25 (-51– -6)	-33 (-46– -12)	0.55

Data is reported as median and interquartile range. Modified from the Original Publication V.

5.7 Patient Satisfaction (Study III)

Patient satisfaction was measured in Study III. A higher proportion of patients in the DEX group were satisfied with pain management in the ward (p = .004). Other measures regarding patient satisfaction did not differ between the groups (Figure 17).

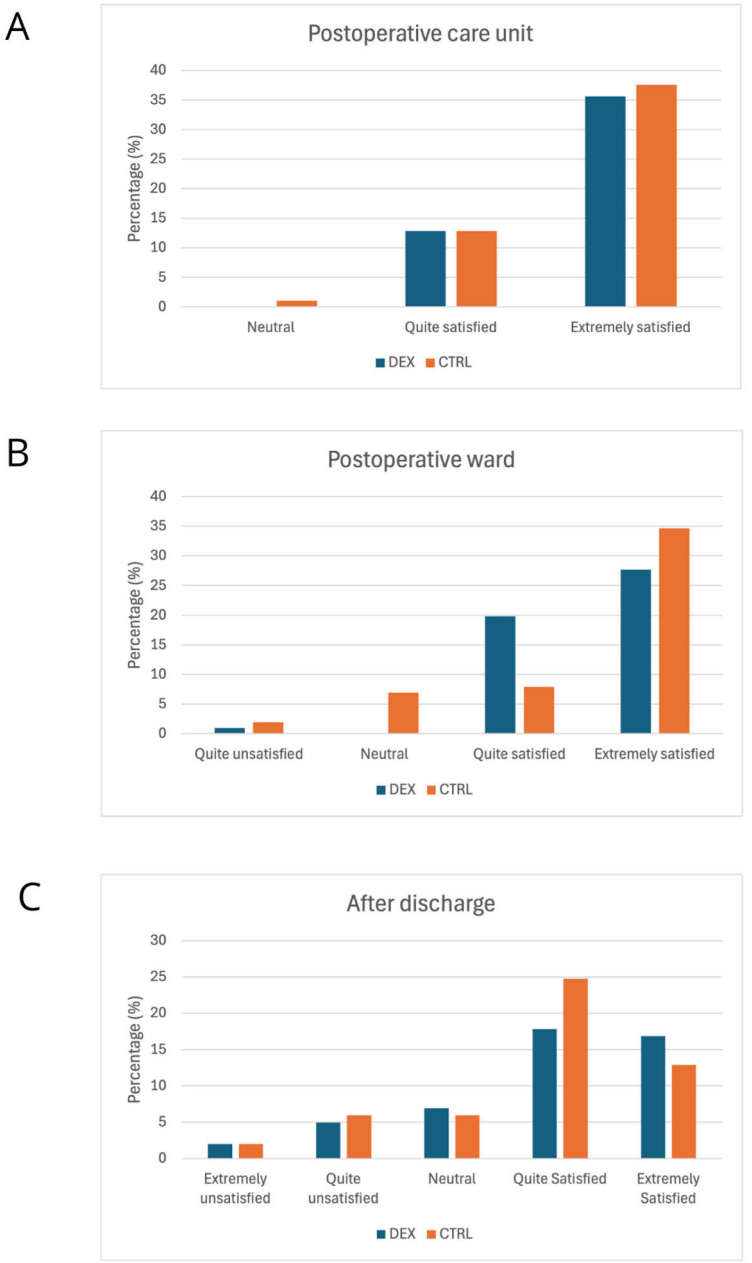


Figure 17. Patient satisfaction with pain management in Study III. A) Pain management in the post-anesthesia care unit. B) Pain management in the ward. C) Pain management at home. Data is shown as the percentage of patients. Abbreviations: DEX; dexmedetomidine group, CTRL; control group. Author's own drawing.

5.8 Safety/adverse Effects (Studies I–V)

Intranasal dexmedetomidine was generally well tolerated, and adverse effects were infrequent in studies.

In Study I, patients in the dexmedetomidine group had lower HR and MAP, but the need for vasoactive medications did not differ between the dexmedetomidine and control groups. Intranasal dexmedetomidine did not affect the PACU time compared to the control group.

In Study II, no adverse events were recorded. All the patients were under general anesthesia, and hypotension is a common adverse effect of anesthesia, regardless of dexmedetomidine administration. During the study, there was no substantial bradycardia necessitating atropine treatment.

In Studies III and IV, dexmedetomidine was not associated with severe adverse effects. No difference existed in perioperative hypotension, hypertension, bradycardia, or tachycardia between the groups, but intraoperative hypertension was more common in patients who received a placebo.

In Study V, during the observation period, three individuals were hypotensive, and two of them required intravenous ephedrine boluses to manage their hypotension. No other adverse events were recorded.

6 Discussion

6.1 Analgesic and Opioid-sparing Effect of Intranasally Administered Dexmedetomidine (Studies I, III, V)

Our results suggest that a single dose of perioperative intranasal dexmedetomidine effectively reduces postoperative pain and opioid consumption in orthopedic patients. The analgesic and opioid-sparing effects were more apparent in patients under general anesthesia (Study I) than in those under spinal anesthesia (Study III). In Study V, cumulative 6 h opioid consumption was markedly lower after administration of intranasal dexmedetomidine compared to the time before dexmedetomine dosing.

Previous research shows that dexmedetomidine decreases postoperative opioid consumption after orthopedic surgery when administered intravenously (Donatiello et al. 2022; Chan et al. 2016). Moreover, intranasally administered dexmedetomidine lowers postoperative opioid consumption in patients undergoing THA under general anesthesia (Uusalo et al. 2019). Our results are consistent with these findings, but while the reduction in opioid consumption was apparent in patients under general anesthesia (Study I), it was not statistically significant when patients were under spinal anesthesia (Study III). Patients in Study I received a larger dose of dexmedetomidine (100 μg) than patients in Study III (1μg/kg, mean dose 80 μg). Another explanation for the discrepancy between the studies is that larger opioid requirements in anesthetized patients may have brought out opioid consumption differences in favor of dexmedetomidine. Previous research together with our findings suggests that TKA patients receiving general anesthesia appear to require more postoperative opioids than those receiving spinal anesthesia (Koutp et al. 2024; Yap et al. 2022). While higher opioid administration during surgery has been suggested to induce hyperalgesia, one study with patients under general anesthesia found that increased intraoperative opioid use was associated with lower postoperative pain (Mercado et al. 2023). Better intraoperative pain management during spinal anesthesia could therefore explain better postoperative pain management. The discrepancy between the findings of Study I and Study III can be partially attributed to differences in study design. Study I was a retrospective case-

control study, whereas Study III was a prospective RCT. Additionally, despite power calculations conducted before Study III, the trial may have been underpowered due to a higher-than-expected dropout rate.

The study subjects in all our studies were mostly female, which could have influenced the outcomes, although this appears improbable. Nevertheless, certain factors related to sex differences in pain perception and response to treatment should be considered. Osteoarthritis is more common in women and tends to be more severe (Hawker et al. 2000). Women are generally more sensitive to pain than men (Ruau et al. 2012). It has been proposed that dexmedetomidine's opioid-sparing impact may be stronger in male patients (Li et al. 2016) since estrogen may impair alpha-2 adrenoceptor-mediated analgesia (Thompson et al. 2008). In Studies I and III, there was no difference in the female-male ratio between the dexmedetomidine and control groups; hence, it is unlikely that sex differences affected the comparison between the groups. However, the overall predominance of female subjects could still affect the generalizability of our findings to other surgical populations.

The optimal dose of intranasal dexmedetomidine to be used as an analgesic adjuvant is unclear. The dosage of dexmedetomidine Study III used was quite small (1 μg/kg) which could have affected the results. While a higher dose could lead to a better analgesic effect, it might also increase the risk of more pronounced hemodynamic side effects. Aside from hemodynamic side effects, we did not use a higher dose because the volume that can be effectively administered intranasally is limited. We used a dexmedetomidine solution intended for intravenous use with a concentration of 100 μg/ml, and 100 μg of dexmedetomidine was the maximum amount we expected to be administered effectively (0.5 ml in each nostril). Since repeated doses would allow a larger total dose, we could have administered an extra dose later to reach a larger cumulative dose without affecting absorption with an excessively high volume.

6.2 Anxiolytic Effect of Intranasal Dexmedetomidine (Study III)

Our findings suggest that premedication with intranasal dexmedetomidine reduces the need for additional intraoperative sedation but not patient-reported preoperative anxiety.

Preoperative anxiety has many negative consequences: It can lower the pain threshold (Rhudy et al. 2000), increase the need for analgesics after surgery (Ip et al. 2009), and lead to unstable hemodynamics perioperatively (Tadesse et al. 2022). Intranasal dexmedetomidine has been increasingly popular as an anxiolytic premedication for children before general anesthesia and magnetic resonance imaging (Karlsson et al. 2023; Cai et al. 2024; Yao et al. 2022). In adults, the subject

is less studied, but some studies are reporting that intranasal dexmedetomidine can alleviate preoperative anxiety in adults (Zeng et al. 2022).

Anxiety is a highly subjective emotion, but physiological responses like tachycardia and hypertension can be observed objectively. However, objective measures of anxiety, such as plasma catecholamines and skin conduction, correlate poorly with subjective measures (Wetsch et al. 2009). Women tend to report more anxiety than men. It has been speculated that the reason might be because women are more willing to admit feeling anxious (Kassahun et al. 2022). Male patients, who are more likely to deny their stress, may exhibit a vasovagal response more frequently, which can be a physical manifestation of underlying anxiety.

Benzodiazepines and propofol have been used regularly as sedatives in arthroplasty surgery alongside spinal anesthesia. Several studies have disputed premedication with benzodiazepines, as they seem not to affect the quantity of anxiety (Jeon et al. 2018; Bucx et al. 2016) nor improve patient satisfaction (Maurice-Szamburski et al. 2015). Dexmedetomidine reduces anxiety, whereas midazolam keeps the patient from responding to stimuli that are not subdued. Intraoperative dexmedetomidine sedation lowers the incidence of postoperative delirium compared with propofol sedation in elderly patients undergoing lower limb surgery under spinal anesthesia (Park et al. 2021). Dexmedetomidine has also been associated with better patient satisfaction rates than midazolam sedation (Barends et al. 2017).

The wait time in the hospital before surgery is a potential confounding factor we did not account for. It has been reported that the relative position on the operating list influences the level of preoperative anxiety (Panda et al. 1996). Another confounding factor that we did not account for in Study III was the using non-pharmacological interventions to treat anxiety, such as listening to music with headphones.

6.3 Patient Satisfaction (Study III)

In Study III, patients in both groups were generally content with how their pain was treated following the surgery, but a higher proportion of patients in the dexmedetomidine group were satisfied with pain management at the ward. Our results suggest that adding dexmedetomidine to a multimodal analgesic regime may enhance short-term patient satisfaction.

Although patient satisfaction is complex, two crucial components are unmet patient expectations and residual pain (Myles et al. 2000; Bourne et al. 2010). Still, it is disputed whether patient satisfaction and pain intensity ratings are related (Phillips et al. 2013). Increased opioid use in the PACU has been linked to decreased patient satisfaction (Maher et al. 2016); however, reported pain intensity does not

seem to correspond with satisfaction, and patients are satisfied with pain management regardless of pain severity (Carlson et al. 2003, Lahtinen et al. 2023). It appears the effectiveness of pain medication could be an important factor affecting satisfaction (Ward et al. 1996). This is consistent with our findings, as our patients had discomfort in the ward but were satisfied with the pain treatment overall. We did not inquire about their expectations; therefore, we could not determine if any differences existed between the groups.

There was no difference in patient satisfaction between the groups in the PACU, at home, or in total. Since the spinal anesthetic had not yet worn off, patients in the PACU did not feel much discomfort yet. The fact that almost all patients in both groups were quite or extremely satisfied with pain management in the PACU supports this assumption. Logically, patients were equally satisfied with pain management at home because, based on dexmedetomidine's elimination half-life, its effects should have already faded. However, we do not know about dexmedetomidine's long-term effects. Dexmedetomidine was not linked to higher overall satisfaction with pain management, which could be because evaluations of pain severity made close to the time when satisfaction was assessed have greater weight than evaluations made previously (Carlson et al. 2003).

No widely accepted "gold standard" method exists for assessing patient satisfaction. Numerous studies have used the American Pain Society Patient Outcome Questionnaire (APS-POQ) or its variations to assess patient satisfaction with pain management (Carlson et al. 2003, Lahtinen et al. 2023). Our satisfaction questionnaire was like this one, although it was less comprehensive and used a 5-point Likert scale rather than a scale of 0 to 10. The results of the patient satisfaction questionnaire may be skewed toward being too positive since patients are often reluctant to criticize the care they received. Patients may regard forthright criticism of medical practitioners as disrespectful, which can lead to distorted responses (Plan et al. 2012). Of course, this should not affect the comparison of the two groups, but it might affect the generalizability of the results. Patients may have also avoided the extreme values, as central tendency bias is one of the well-known problems with using the Likert scale. Our satisfaction questionnaire was not anonymous, although a member of the research team who was not involved in patient care made most of the phone calls. The lack of anonymity may have prevented patients from being entirely honest about their experiences.

Patients are satisfied when they believe they receive personalized treatment, are respected, and are treated in a caring environment (Skaug et al. 2023). Some of the patients in this study mentioned that feeling safe and cared for was important to them. Hospital personnel regularly observed and contacted patients participating in the study more often than typical patients undergoing TKA.

6.4 Hemodynamic and Respiratory Effects of Intranasal Dexmedetomidine (Studies I–V)

The most common adverse effects after dexmedetomidine administration are reduced heart rate and blood pressure. We found that intranasal dexmedetomidine was generally well tolerated concerning hemodynamic measures. As expected, heart rate and blood pressure lowered after intranasal dexmedetomidine administration, but the observed hemodynamic alterations were mild in all sub-studies.

The fear of hemodynamic alterations has limited dexmedetomidine's use as an anesthetic adjunct. It has been proposed that the hemodynamic effects of dexmedetomidine may be attenuated if extravascular dosing methods are used because it leads to lower peak plasma concentrations and has a more gradual onset of action than in intravenous administration (Iirola et al. 2011; Uusalo et al. 2018; Chamadia et al. 2020). Our findings are consistent with previous research. In Study II, dexmedetomidine concentrations remained higher after 4 hours following intranasal administration than intravenous administration, but patients remained hemodynamically stable, most likely due to the lack of abrupt concentration changes. Risk factors for hemodynamic instability associated with dexmedetomidine include obesity, female sex, low baseline blood pressure, and old age (Ice et al. 2016; Doo et al. 2021). Additionally, the concurrent use of a beta blockers, high preoperative heart rate, long duration of surgery, and use of loading dose while commencing the infusion are potential risk factors for hemodynamic instability (Ickeringill et al. 2004, Baek et al. 2023). Patients with severe knee osteoarthritis are often older, female, and have a higher BMI (Silverwood et al. 2015). Although these risk factors were common in our research population, intranasal dexmedetomidine was well tolerated.

Although intravenous dexmedetomidine is linked to temporary hypertension, it may also stabilize hemodynamics and reduce the need for antihypertensive medication (Sezen et al. 2014). Intranasal dexmedetomidine was associated with a lower incidence of intraoperative hypertension compared to the control group, but it did not significantly alter the need for labetalol in Study IV. However, it is noteworthy that only patients in the control group received labetalol.

In Studies I and II patients were under general anesthesia and received several other medications besides dexmedetomidine that lower blood pressure and heart rate, whereas in Studies III–V, patients received spinal anesthesia, which also affects hemodynamic parameters. These anesthesia-related effects on hemodynamics must be considered when assessing the effects of intranasal dexmedetomidine in each study. Another factor to consider is that 'baseline' may not be the actual baseline at rest, and anxiety may cause patients to have higher HR and MAP before the start of the study than during the recovery.

Although extravascular dosing is allegedly a safer option, in some studies intranasal dexmedetomidine has been deemed to be unsuitable for the elderly due to hemodynamic changes (Barends et al. 2020; Xu et al. 2022). Unlike these previous studies, our Study V, which investigated using intranasal dexmedetomidine in patients over the age of 70, we discovered that it was well tolerated even in the elderly. However, our results conclude that when using intranasal dexmedetomidine, careful patient selection and monitoring of hemodynamic parameters for at least 3 hours after administration are necessary. Dexmedetomidine pharmacokinetics do not change with age, but clearance is reduced in older adults and the sedative effect may be prolonged (Iirola et al. 2012). A lower dose may suffice for older adults, likely leading to fewer hemodynamic side effects. Although staff should be aware of potential side effects and be ready to address them, fear of hemodynamic alterations should not be a reason to avoid using intranasal dexmedetomidine categorically. The patients in our Study V were all treated in an intermediate ward that has enhanced care and monitoring possibilities.

Intravenous dexmedetomidine has no notable effects on respiration and patients remain cooperative; therefore, it could be more suitable than traditionally used anxiolytics (Ebert et al. 2000; Belleville et al. 1992). Although little information exists on respiratory parameters following intranasal administration of dexmedetomidine, it is likely safe to presume it is at least equally safe, if not safer than intravenous. In Study IV, we did not find differences in SpO2 levels or requirement of supplemental oxygen between dexmedetomidine and control groups. In Study V, intranasal administration of dexmedetomidine did not affect respiratory rate or SpO2. However, the arterial partial pressure of carbon dioxide ($PaCO_2$) was not measured, so direct effects on ventilation cannot be determined from our studies. Although dexmedetomidine has little effects on respiration, it lowers hypoxic ventilatory response and enhances airway collapsibility (Lodenius et al. 2016; Lodenius et al. 2019). Therefore, monitoring respiratory parameters after dexmedetomidine administration is necessary.

6.5 Effects of Intranasal Dexmedetomidine on Other Perioperative Parameters (Study IV)

Previous research suggests that dexmedetomidine during surgery reduces intraoperative bleeding (Durmus et al. 2007). However, in Study IV, we discovered no significant differences between the groups in these parameters. Dexmedetomidine likely lowers surgical bleeding because it can lower blood pressure and heart rate. A possible explanation for this discrepancy between our results and previous studies can be that blood pressure alterations were milder after intranasal administration of dexmedetomidine. While lower blood pressure is frequently associated with less

bleeding during surgery, excessively low blood pressure can obscure bleeding sites, potentially leading to undetected bleeding that can become severe later. Some surgeons opted to use a tourniquet, while others operated without one. Despite these differences in surgical technique, the overall blood loss remained low.

Although changes in hemodynamics seem a straightforward reason for reducing surgical bleeding, it has also been proposed that dexmedetomidine might directly affect coagulation by lowering stress levels and decreasing hypercoagulability (Chen et al. 2018). Since there are alpha2-receptors located in platelets, it has been hypothesized that dexmedetomidine may affect coagulation, but this topic has been studied very little. Dexmedetomidine appears to have stimulating and inhibiting effects on human platelets (Kawamoto et al. 2015).

6.6 Pharmacokinetics of Intranasal Dexmedetomidine in Adult Patients under General Anesthesia (Study II)

Our findings suggest the pharmacokinetic profile of intranasal dexmedetomidine may be influenced by the position in which the drug is delivered, concurrent general anesthesia, or both. When intranasal dexmedetomidine is administered during general anesthesia in the supine position, it seemingly results in slower absorption and onset of action.

Compared to earlier pharmacokinetic investigations on adult patients, the absorption half-time (T_{ABS}=120 min; 95% CI 90 to 147 min) was slower. Absorption characteristics differed from previous pharmacokinetic studies on adults (Table 6), highlighting the importance of administration context. In previous studies, dexmedetomidine was administered to awake adults in the upright or semi-recumbent position (Yoo et al. 2015; Iirola et al. 2011; Kuang et al. 2022; Li et al. 2018; Wu et al. 2022). Our study and these earlier pharmacokinetic studies had significant discrepancies: Absorption was markedly slower, and elimination was slower. However, the pharmacokinetics of intranasal dexmedetomidine on anesthetized children (Grogan et al. 2023; Miller et al. 2018) are quite comparable to those in our study.

To our knowledge, pharmacokinetic studies of intranasal medications involving laryngeal masks were not conducted earlier. Thus, we can only speculate how a laryngeal mask may affect the drug dispersion. However, the pharmacokinetics of intranasal dexmedetomidine in intubated children (Grogan et al. 2023) are similar to our results, suggesting the administration position may affect absorption rather using a laryngeal mask. Some individual time concentrations demonstrated an early rapid absorption phase and a later slower absorption phase. We do not know exactly where the absorption occurs – nasal mucosa or further down in the nasopharynx or upper

gastrointestinal tract. The relative bioavailability was higher than in previous adult investigations, which argues against absorption from the gastrointestinal system, where bioavailability is reduced due to first-pass metabolism. This could suggest that slow absorption is due to pooling in the nasopharynx and absorption from the oral mucosa, as absorption parameters after buccal administration are similar to those seen in our study (Anttila et al. 2003). A cadaver study by Habib et al. examined drug dispersion after intranasal administration with MAD Nasal atomizer in lying head-back and head-down and forward positions. They found that the lying-head-back position demonstrated much higher overall distribution to all relevant anatomical regions; distribution to the nasopharynx was also notable (Habib et al. 2013). However, we cannot draw conclusions straight based on this study as the lying-head-back position slightly differs from the position in the Study II and because mucociliary function is absent in cadavers. Interindividual absorption variance may also be partly explained by absorption to varying degrees from distinct locations.

Most previous adult pharmacokinetic studies have been conducted on healthy volunteers; only one prior study involved actual patients (Wu et al. 2022). Our patients in Study II were older, heavier, and had more comorbidities. Therefore, our study may better reflect real-life clinical circumstances. Clearance in the current study was standardized for size using allometry.

The pharmacokinetic profile may be impacted by changing concentration and, consequently, different liquid volumes. When administering drugs via the intranasal route, drug volumes should be kept to a minimum because mucosal surfaces can become saturated, resulting in runoff and reduced absorption. We used dexmedetomidine formulation 100 µg/ml, which is designed for intravenous use but is often used for intranasal administration in clinical practice. A highly concentrated dexmedetomidine formulation (500 µg/ml) intended for veterinary anesthesia was employed in some of the earlier pharmacokinetic trials (Yoo et al. 2015; Iirola et al. 2011). Also, one study used a specialized formulation designed for intranasal administration (Kuang et al. 2022). Different concentrations may partly explain the discrepancies between the current study and earlier ones.

Another factor that could influence the pharmacokinetic profile in our study is the concurrent administration of anesthetic agents due to pharmacokinetic or pharmacodynamic interactions. However, clearance was similar to that reported in other trials. Dexmedetomidine is largely metabolized via glucuronidation (UGT 2B10, UGT1A4), with a lower contribution from CYP enzymes (mostly CYP2A6). Because of the several metabolizing enzymes and the high clearance capacity of UGT, pharmacokinetic interactions are unlikely, with only a few identified in the literature (Flexman et al. 2014; Stiehl et al. 2016). Since dexmedetomidine is primarily metabolized in the liver, any alteration in hepatic perfusion can affect its

clearance (Dutta et al. 2000). Patients under general anesthesia have generally lower blood pressure, which may impact dexmedetomidine pharmacokinetics by reducing liver circulation.

6.7 Limitations of the Studies (Studies I–V)

The obvious limitations of Study I include its retrospective nature and inherent biases related to the study design. Because of retrospective data collection, data quality may be compromised, with potential confounding factors left unaccounted for. However, anesthesia reports are thoroughly documented, and opioid use is rigorously monitored. Systematic differences may exist between included patients and those excluded from the dataset, introducing selection bias, though the analysis of consecutive patients was employed to minimize this risk. Another limitation to consider is that actual pain scores were not recorded.

The main limitation of Study II was the small number of samples and the short sampling period. Dexmedetomidine was still detected in the final samples; thus, it would have been useful to continue monitoring until concentrations were nearly zero.

One limitation in Study III was that patient-controlled analgesia (PCA) was not used in postoperative pain management. PCA was not an option because patients were to be discharged within 24 hours of surgery, and transitioning to oral administration as quickly as possible was critical. Another important limitation was the lack of a group receiving dexmedetomidine intravenously, which would have allowed a direct comparison of two different administration routes. The efficacy of the trial blinding may have been impacted by comparing dexmedetomidine only to placebo, and adding a third arm with a sedative could have helped with this. The trial had more dropouts than anticipated, and the overall number of patients assessed in the intervention group was fewer than the number the power calculation required. This may slightly reduce the statistical power of our findings and should be considered when interpreting the results.

The main limitation of Study IV was that the analysis was not powered specifically for these outcomes, which may limit statistical robustness. Results must be considered as preliminary as there is no way to directly compare different dosing methods without an intravenous dexmedetomidine group. Invasive blood pressure monitoring would have yielded more precise results.

Small sample size, lack of controls, and retrospective data collection may have affected the results in Study V. Retrospective data introduces the risk of charting omissions and potential selection bias, which may affect the validity of findings. To avoid selection bias, we included consecutive patients receiving intranasal dexmedetomidine. However, patients without hourly monitoring of vital parameters,

patients taking concomitant sedative medication, and patients receiving vasoactive medication before dexmedetomidine administration were excluded from the analyses. While the study provides insights into associations between drug exposure and outcomes, it cannot definitively establish causality. A further limitation was the inadequate recording of pain scores, which prevented us from including them in the analysis. Furthermore, postoperative delirium was not assessed using validated delirium assessment methods such as the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). The study design was exploratory, and our results can be considered merely preliminary.

6.8 Future Studies

Using intranasal dexmedetomidine in a multimodal analgesic regime for orthopedic patients requires further exploration. Determining the appropriate dosage for various patient groups is critical, especially for older persons who would benefit from identifying the lowest therapeutic dose to reduce potential adverse effects while maintaining adequate pain control.

Further research is needed to determine the safety and feasibility of intranasal dexmedetomidine in a ward setting. Prospective trials with larger patient populations would yield more reliable data on its efficacy, safety, and applicability in real-world clinical settings. A randomized controlled study with a group receiving dexmedetomidine intravenously and another receiving it intranasally would allow a direct comparison of the two administration routes.

Another area deserving investigation is the optimal positioning for intranasal drug administration. Limited evidence exists on this topic, and more research is needed to determine the optimal strategies for ensuring effective medicine administration.

Finally, new applications for dexmedetomidine outside its current uses warrant further investigation. Expanding our understanding of its potential roles in pain management and other therapeutic areas may produce better patient outcomes and a broader range of clinical applications.

7 Summary/Conclusions

These studies help us improve the perioperative management of orthopedic patients. The following conclusions can be drawn based on sub-studies:

1. Intranasal dexmedetomidine appears to decrease postoperative opioid consumption in patients undergoing TKA under general anesthesia.

2. Intranasal dexmedetomidine has a high bioavailability and can be administered in the supine position during general anesthesia. Compared to awake patients in an upright position, this administration method shows slower absorption, with consequent concentrations attained after T_{MAX} for several hours.

3. Premedication with intranasal dexmedetomidine may lower postoperative pain and improve short-term patient satisfaction in patients undergoing TKA under spinal anesthesia.

4. Premedication with intranasal dexmedetomidine reduces perioperative HR and blood pressure but appears to be hemodynamically safe in patients undergoing TKA under spinal anesthesia. Reduced HR and blood pressure do not seem to affect the amount of surgical bleeding.

5. Based on preliminary findings, intranasal dexmedetomidine may be used to treat postoperative restlessness, agitation, or pain in geriatric patients undergoing orthopedic surgery. However, blood pressure should be monitored up to 3 hours from dosing in this patient population.

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