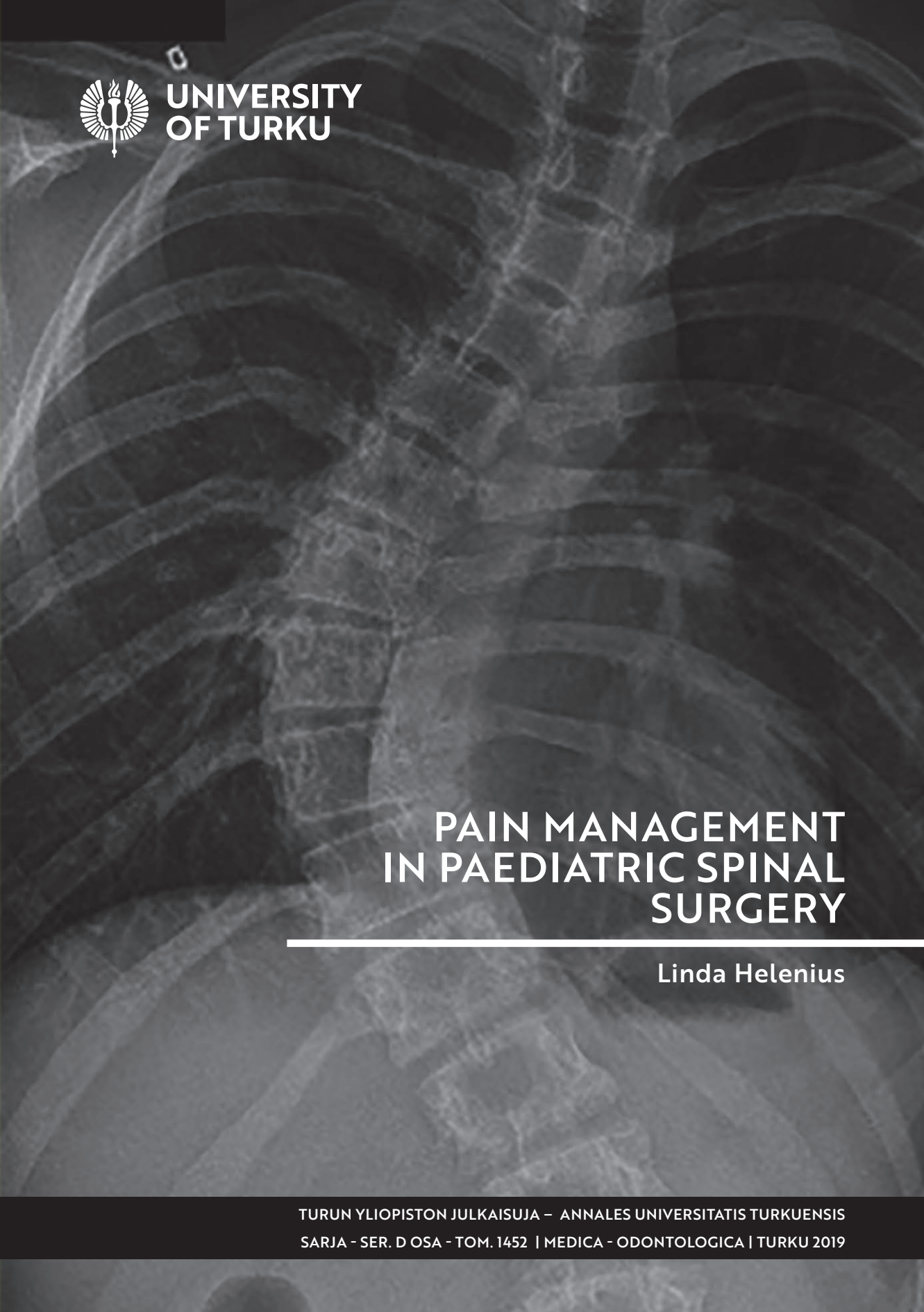

UNIVERSITY OF TURKU

PAIN MANAGEMENT IN PAEDIATRIC SPINAL SURGERY

Linda Helenius

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
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To Ilkka, Robin and Emilia

ABSTRACT

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PAIN MANAGEMENT IN PAEDIATRIC SPINAL SURGERY

University of Turku, Faculty of Medicine, Department of Anaesthesiology, Intensive Care, Emergency Care and Pain Medicine and Department of Paediatric Surgery and Orthopaedics, Doctoral Programme in Clinical Research, Turku University Hospital, Turku, Finland

Annales Universitatis Turkuensis, Medica-Odontologica, Turku Finland 2019

Posterior spinal fusion is one of the most common major surgical procedures performed in children and adolescents. Pain control can be challenging owing to the extensive posterior exposure and major tissue trauma. Therefore, a multimodal pain management is often necessary.

Pregabalin was originally developed for use as an anti-epileptic drug. It has been shown to have antinociceptive and neuroprotective effects, and the use in pre-emptive analgesia has increased worldwide. Pregabalin has been shown to reduce pain scores and opioid consumption after spine surgery in adult population. Thus, the study objective was to evaluate the effect of perioperative pregabalin on postoperative pain scores and oxycodone consumption in adolescents after posterior spinal fusion and to assess the effect of pregabalin on the intraoperative neurophysiological measurements. Multimodal pain management aims to reduce the need for opioids and reduce the adverse effects of high opioid use. One of these adverse effects is postoperative urinary retention. The fourth publication of this thesis evaluates the incidence of urinary retention in adolescents after spinal surgery.

The results of previous studies on the causal relationship between spinal deformities in children and back pain have been controversial. The traditional view is that deformities do not result in back pain. However, more recent studies suggest that spinal asymmetry and scoliosis are risk factors for back pain. Evidence of chronic pain after spinal surgery in children is sparse. The main goal of our third study was to evaluate the preoperative pain and to assess the prevalence of persistent postsurgical pain in children after spinal surgery.

In our study we showed that pregabalin did not affect the intraoperative neuromonitoring, postoperative opioid consumption or pain scores after spinal fusion. Children with scoliosis reported a moderate amount of pain prior to surgery and a reduction in pain after surgery. Compared to the healthy controls the back pain was similar in the surgically treated patients. Almost 50% of adolescents experience impaired bladder emptying after spinal surgery.

Keywords: pregabalin, pre-emptive analgesia, scoliosis, posterior spinal fusion

TIIVISTELMÄ

Linda Helenius

KIVUNHOITO LASTEN JA NUORTEN SELKÄLEIKKAUKSISSA

Turun yliopisto, Lääketieteellinen tiedekunta, Anestesiologia, tehohoito, ensihoito ja kivunhoito sekä lastenkirurgian oppiaineet, Turun kliininen tohtoriohjelma, Turun yliopistollinen keskussairaala, Turku, Finland

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Selän luudutusleikkaus on yksi tavallisimmista suurta kirurgiaa vaativista toimenpiteistä lapsilla ja nuorilla. Suuri kirurginen avaus ja laaja kudosvaurio voi tehdä leikkauksenjälkeisestä kivunhoidosta haastavan. Tämän takia, multimodaalinen kivunhoito on usein tarpeellista.

Pregabaliini on lääke, jota alunperin kehitettiin epilepsian hoitoon. Mutta sillä on todettu myös kipua lievittäviä ja hermoja suojaavia ominaisuuksia, ja lääkkeen käyttö ennaltaehkäisevässä kivunhoidossa on lisääntynyt maailmalla. Aikuispotilailla pregabaliini on osoittautunut olevan opioidien tarvetta ja kipua selkäleikkausten jälkeen vähentävä lääke. Lapsilla ja nuorilla on tehty hyvin vähän tutkimuksia koskien pregabaliinin käyttöä. Tutkimuksen tarkoituksena oli mitata pregabaliinin vaikutusta kivun voimakkuuteen ja opioidilääkityksen tarpeeseen lapsilla ja nuorilla selän luudutusleikkauksen jälkeen. Tavoitteena oli myös selvittää pregabaliinin vaikutusta leikkauksenaikaisen neuromonitoroinnin luotettavuuteen. Multimodaalisen kivunhoidon tavoitteena on vähentää vahvojen kipulääkkeiden tarvetta ja näin ollen vähentää opioidien aiheuttamia sivuvaikutuksia. Yksi näistä sivuvaikutuksista on leikkauksenjälkeinen virtsaumpi. Tämän väitöskirjan neljäs työ selvittää virtsaretention esiintyvyyttä nuorilla selkäleikkauksen jälkeen.

Aiempien tutkimusten tulokset selkäkivun yhteydestä selkärangan virheasentoihin ovat olleet ristiriitaisia. Perinteinen näkemys on ollut, etteivät selän virheasennot aiheuta kipua. Tuoreemmat tutkimukset kuitenkin viittaavat siihen, että selän epäsymmetria ja skolioosi ovat riskitekijöitä selkäkivun esiintymiseen. Selkäleikkauksen jälkeisen pitkäkestoisen kivun esiintymistä lapsilla on hyvin vähän tutkittu. Kolmannen tutkimuksemme tavoite oli arvioida selkäkivun esiintyvyyttä selkäleikkaukseen tulevilla lapsilla ja nuorilla sekä lisäksi tutkia pitkäkestoisen selkäkivun esiintyvyyttä leikkauksen jälkeen.

Tutkimuksemme osoittaa, että pregabaliini ei vaikuta neuromonitoroinnin luotettavuuteen, ei vähennä opioidikulutusta eikä kipua selkäleikkauksen jälkeen. Lapsilla, joilla todettu selän virheasento kärsivät kohtalaisesta kivusta. Leikkaushoito helpottaa kipua ja on leikkauksen jälkeen samanlainen kuin terveillä verrokeilla. Melkein joka toisella nuorella esiintyy virtsaamisvaikeutta selkäleikkauksen jälkeen.

Avainsanat: pregabaliini, ennaltaehkäisevä kivunhoito, idiopaattinen skolioosi, selän luudutusleikkaus

SAMMANDRAG

Linda Helenius

SMÄRTBEHANDLING EFTER RYGGOPERATION HOS BARN OCH UNGA

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Steloperation av ryggen är en av de vanligaste stora operationer, som barn och unga genomgår. På grund av den extensiva öppningen av huden och stor vävnadstrauma kan smärtbehandlingen efter operationen vara utmanande och en multimodal smärtbehandling kan behövas.

Pregabalin är en medicin ursprungligen utvecklad för behandling av epilepsi. Den har visat sig ha smärtlindrande och nervskyddande effekter, och dess användning inom förebyggande smärtbehandling har ökat i många länder. Pregabalin har i studier med vuxna patienter visat minska på smärtgraden och opioid konsumtionen efter ryggoperationer. Målet med vår studie var att utvärdera effekten av perioperativ pregabalin på smärtan omedelbart efter operation och effekten på den totala oxikodon konsumtionen efter steloperation av ryggen hos barn och unga. Vi ville också fastställa pregabalins effekt på de neurofysiologiska mätningarna gjorda under operationen. Målet för multimodal smärtbehandling är att minska behovet av starka värkmediciner och således minska biverkningar orsakade av opioider. Urinretention är en av dessa biverkningar. I den fjärde artikeln i denna avhandling utreder vi förekomsten av urinretention hos unga efter steloperation av ryggen.

Tidigare studier beträffande sambandet mellan deformiteter av ryggraden och ryggsmärta hos barn har uppvisat kontroversiella resultat. Den traditionella synen har varit att felställning inte leder till smärta i ryggen. De nyare studierna antyder att asymmetri av ryggraden och skolios utgör en riskfaktor för ryggsmärta. Litteraturen berörande kronisk smärta hos barn efter ryggoperation är mycket sparsam. Huvudmålet för vår tredje studie var att mäta förekomsten av ryggsmärta före operation och bedöma incidensen av långvarig smärta hos barn och unga efter steloperation av ryggen.

Vår studie visar att pregabalin inte påverkar opioid konsumtionen eller smärtan efter steloperation av ryggen. Vi visade att barn med skolios lider av måttlig smärta och operativ behandling minskar på smärtan. Ryggsmärtan hos operativt behandlade patienter var likadan jämfört med den hos friska kontroller. Nästan hälften av de unga patienterna lider av problem med urinering efter steloperation av ryggen.

Nyckelord: pregabalin, förebyggande smärtbehandling, skolios, steloperation av ryggen.

TABLE OF CONTENTS

ABBREVIATIONS

AIS	adolescent idiopathic scoliosis
ASA	American Society of Anesthesiologists
b.i.d.	bis in die (twice daily)
BIS	bispectral index
BMI	body mass index
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
EEG	electroencephalogram
EMG	electromyography
GABA	γ-aminobutyric acid
HRQoL	health-related quality of life
IV	intravenous
MAP	mean arterial pressure
mg	milligram
MEP	motor evoked potential
NMDA	N-methyl-D-aspartate
NSAID	non-steroidal anti-inflammatory drug
NRS	numerical rating scale
PCA	patient-controlled analgesia
po	per oral
POUR	postoperative urine retention
PSF	posterior spinal fusion
SSEP	sensory evoked potential
SRS-24	scoliosis research society 24-Item questionnaire
SD	standard deviation
TCI	target-controlled infusion
TIVA	total intravenous anaesthesia
tMEP	transcranial electrical motor evoked potential
VAS	visual analogue scale

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by the Roman numerals I-IV.

I Helenius L, Puhakka A, Manner T, Pajulo O, Helenius I. Preoperative pregabalin has no effect on intraoperative neurophysiological monitoring in adolescents undergoing posterior spinal fusion for spinal deformities: a double-blind, randomized, placebo-controlled clinical trial. *Eur Spine J* 2018; **27**: 298-304.

II Helenius L, Oksanen H, Lastikka M, Pajulo O, Löyttyniemi E, Manner T, Helenius I. Preemptive Pregabalin in Children and Adolescents Undergoing Posterior Instrumented Spinal Fusion. A double-blind, placebo-controlled, randomized clinical trial. *J Bone Joint Surg Am* Accepted for publication.

III Helenius L, Diarbakerli E, Grauers A, Lastikka M, Oksanen H, Pajulo O, Löyttyniemi E, Manner T, Gerdhem P, Helenius I. Back Pain and Quality of Life after Surgical Treatment for Adolescent Idiopathic Scoliosis at 5-year Follow-up. Comparison with Healthy Controls and Patients with Untreated Idiopathic Scoliosis. *J Bone Joint Surg Am* 2019; **101**: 1460-1466.

IV Keskinen H, Helenius L, Pajulo O, Helenius IJ. Postoperative urinary retention or difficulties to empty the bladder in young patients undergoing posterior spinal fusion for adolescent idiopathic scoliosis. *J Pediatr Surg* 2018; **53**: 1542-1546.

1. INTRODUCTION

Scoliosis is defined as an abnormal lateral curvature of the spine that is associated with vertebral rotation (Cobb 1948). Scoliosis affects 2-3% of the global population (Lonstein 1989, Weinstein et al. 2003). In Finland the prevalence of scoliosis with a Cobb angle of 10° or more might be as high as 9% (Nissinen et al. 1993). The majority of the patients with scoliosis do not require an intervention, and an even smaller number needs surgical treatment. Moderate scoliosis can be treated with a brace, whereas severe scoliosis requires a surgical correction (Weinstein et al. 2013). Typically, surgery is indicated when the curvature of the spine exceeds 45° (Weinstein et al. 2003). The procedure most commonly performed is posterior instrumented spinal fusion.

Adolescent idiopathic scoliosis (AIS) is the most common indication for major surgery among children in the United States (Healthcare Cost and Utilization Project 2017). Posterior transpedicular fixation and segmental correction is effective in aiming at three-dimensional correction of the spinal deformity (Suk et al. 1995). Postoperative pain control is challenging, and a multimodal pain management regimen is often utilised owing to the large tissue trauma caused by excessive spinal muscle exposure (Seki et al. 2018). The purpose of pre-emptive analgesia is to reduce the need for opioids (Zhu et al. 2017). The effect of perioperative pregabalin on postsurgical acute pain and opioid consumption was evaluated in the current study. Our hypothesis was that pregabalin would have a favourable effect on the rate of opioid consumption in patients. A reduction in opioid consumption is associated with a corresponding decrease in opioid-related adverse events (respiratory depression, constipation and urinary retention).

Back pain is common during adolescence and the aetiology is not always clear. The finding of a causal relationship between spinal deformity and back pain in several studies remains controversial. Thus, we aimed to evaluate the incidence of moderate to severe back pain before surgery in patients with adolescent idiopathic scoliosis and measure the degree of persistent postsurgical pain in a 5-year follow-up study.

2. REVIEW OF THE LITERATURE

2.1. Spinal deformities in children

The spine consists of vertebrae that form the spinal column and intervertebral discs. The normal spine has two curves, when viewed from the side. There is a gentle rounding of the upper back known as thoracic kyphosis and an opposite curve in the lower back, referred to as lumbar lordosis. These curves balance the trunk over the pelvis (srs.org).

Spinal deformities in the paediatric age group can be caused by several different conditions, including idiopathic and congenital anomalies, neuromuscular disorders and skeletal dysplasia (Weinstein et al 2003). Congenital deformities, which are acquired before birth, occur when the bones or vertebrae do not develop properly during pregnancy.

Scoliosis is the most common of all spinal deformities and is broadly classified as congenital, neuromuscular, syndromic and idiopathic scoliosis (Morrissy and Weinstein 2006).

Hyperkyphosis is a reference to a pathologically severe posterior curve of the upper spine. Scheuermann kyphosis is a classical form of hyperkyphosis (Sorensen 1964).

Spondylolisthesis is a condition where one vertebra slips over another. The most common cause in adolescents for this condition is an isthmic spondylolysis, e.g. stress fracture of the pars interarticularis (Seitsalo et al. 1990).

In our clinical study we included healthy children and adolescents with idiopathic scoliosis, spondylolisthesis, and Scheuermann kyphosis.

2.1.1. Adolescent idiopathic scoliosis

Scoliosis is defined as a lateral curvature of the spine in the coronal plane over 10° (Cobb 1948). The Cobb angle is used to measure coronal plane deformity on antero-posterior radiographs of the spine. The most common deformity is idiopathic scoliosis, which is diagnosed after the exclusion of congenital and other pathological causes (Weinstein et al 2008). The most typical age for development and progression of idiopathic scoliosis is during the growth spurt before puberty. Adolescent idiopathic scoliosis is diagnosed by definition between 10 to 18 years of age and comprises 65-80% of all scoliosis diagnosed (Weinstein et al. 2008, Altaf et al. 2013). Most cases of idiopathic scoliosis are mild, and the progression of the curve is usually slow after skeletal maturity. However, there is an increased risk for curve progression and need for intervention in certain cases. Scoliosis that is diagnosed at a younger age is associated with a higher risk of curve progression (Lonstein et al. 1994). Thoracic curves progress more than lumbar curves (Bunnell 1986). Likewise, the more

pronounced the curve at presentation, the higher the likelihood of progression (Weinstein et al. 1983).

The scoliosis of most patients is mild and requires no treatment. Intervention is warranted in approximately 10% of cases. Brace treatment is the primary option of care for moderate curves (25-40°) in a growing child (Weinstein et al. 2013). Surgical correction is needed in a minor proportion of cases depending on the magnitude of the curve and skeletal maturity. Surgical treatment is often recommended for patients whose curves are greater than 45° while still growing or for curves that continue to progress greater than 45° once growth has stopped (www.srs.org). The operative treatment is guided by the Lenke classification (Lenke et al. 2001). Currently, pedicle screw posterior spinal fusion is the most common type of surgical correction (Suk et al. 1995).

2.1.2. Spondylolysis and spondylolisthesis

Spondylolysis in adolescents typically involves a stress fracture through the pars interarticularis in the lower lumbar spine owing to a genetic predisposition and overuse. It is a relatively common cause of low back pain in children and adolescents (Altaf et al. 2014). Spondylolisthesis is defined as the anterior displacement of a vertebral body. In children and adolescent spondylolisthesis mainly occurs due to bilateral spondylolysis, isthmic spondylolisthesis (Seitsalo et al 1990). Spondylolisthesis is further divided into low-grade (forward slip <50%) and high-grade (slip ≥50%) subtypes (Meyerding 1932). The majority of children and adolescents with spondylolisthesis has the low-grade subtype. In rare cases, spondylolisthesis origins from congenital abnormal bone formation (dysplastic spondylolisthesis).

The clinical symptoms of isthmic spondylolisthesis are mild in most cases and improve with non-surgical treatment (Seitsalo 1990). In high-grade subtypes, displacement of the vertebrae is more severe, and this may cause a kyphotic balance and compression of the lumbar and sacral nerve roots (Hu et al. 2008, Kim et al. 2018). Surgical treatment should be considered in cases where conservative treatment has been unsuccessful, and/or the displacement of the vertebrae is severe (Bourassa-Moreau et al. 2013). In spinal fusion the slipped vertebra is stabilized and/or reduced with posterior pedicle screw instrumentation (Poussa et al. 2006).

2.1.3. Scheuermann kyphosis

Scheuermann kyphosis is defined as a kyphosis of the thoracic spine as the result of a skeletal disorder with abnormal shape of the vertebrae (Sorensen 1964). The condition is diagnosed using the radiographic criteria of three adjacent wedged vertebrae, each angled by at least 5 degrees. Previously, it was thought that this deformity was more common among males than females, but more recent studies suggest the sex ratio is close to 1 (Damborg et al 2006). The main treatment is conservative and includes

treatment with brace. Surgical correction is considered in severe cases (kyphosis of >70 °) with difficult back pain (Palazzo et al 2014, Polly et al 2019). The procedure most commonly performed is posterior spinal instrumentation.

2.2. Anaesthesia in paediatric spinal fusion surgery

Spinal surgery comprises major surgery with large tissue trauma. Spinal deformity and possible other associated medical conditions can affect the cardiorespiratory systems of the patients. The historical studies of Weinstein indicated that a thoracic scoliosis over 100 degrees causes a clinically relevant decrease in respiratory function (Weinstein et al. 1981). Recently, it has been proposed that 20% of patients with thoracic curves over 60° experience moderate to severe pulmonary impairment (Newton et al. 2005).

2.2.1. Intraoperative neuromonitoring

Surgical correction of the spine may change the position of the neural elements, and the spinal cord is at risk of inadequate perfusion (Bosmia et al 2015). In addition, the misplacement of the transpedicular screws or traction of the spinal cord on the concave side may cause mechanical spinal cord injury. The neural elements are at risk of mechanical injury by screws, injury due to traction on the concave side of the deformity and shortening of the nerves on the convex side of the curve. Neural injury that results in postoperative paralysis or sensory loss is an uncommon but devastating and unpredictable complication of scoliosis surgery (Scoliosis Research Society 2015). In order to decrease the incidence of such injury, intraoperative neurophysiological monitoring including motor evoked potentials (MEPs) and somatosensory evoked potentials (SSEP) is generally accepted as the current standard of care (Schwartz et al. 2007, Glover et al. 2014). Many factors impact the measurements including anaesthetic agents, the depth of anaesthesia, body temperature and blood pressure. A fluent communication between the neurophysiologist, anaesthesiologist and surgeon is critical. Almost all anaesthetic agents affect the intraoperative neurophysiological monitoring with increasing doses. Narcotic agents dampen the synaptic function and suppress the electroencephalogram (EEG). At clinically similar depth of anaesthesia, some anaesthetic agents may produce a greater depression of the evoked responses than others. Neuromuscular blocking agents naturally impact the measurements of motor function (Sloan et al. 2010).

2.2.2. Volatile anaesthetic agents

Commonly used potent inhalational agents (sevoflurane, desflurane and isoflurane) produces a significant anaesthetic effect on the evoked potentials. The inhibitory effect is thought to originate at the cortical synapses and in the spinal anterior horn cells (Wang et al. 2009). Many studies have evaluated the effect of isoflurane on the

evoked responses. Volatile anaesthetics reduce the amplitudes and prolong the latency of intraoperative evoked potentials (Manninen et al. 1985, Heneghan et al. 1987, Newton et al. 1989). Inhalational agents suppress the MEP amplitudes in a dose-dependent manner (Chong et al. 2014). Sevoflurane-maintained anaesthesia, even at low doses, is associated with decreased amplitudes of the motor evoked potentials (Hernandez-Palazon et al. 2015). The literature suggests that compared to other inhalational agents desflurane could show less prominent suppression of the evoked potentials. Desflurane may be used in low concentrations, of up to 0.5 MAC, which still permits intraoperative neuromonitoring (Chong et al. 2014, Holdefer et al. 2014, Martin et al. 2014, Sloan et al. 2015).

2.2.3. Total intravenous anaesthesia

Total intravenous anaesthesia is often chosen for maintenance of anaesthesia in spinal deformity surgery because of the known dose-dependent suppressive effect of inhalational agents on evoked potentials, a.

Propofol is the most widely used anaesthetic agent for induction of anaesthesia. It is also used as a component of total intravenous anaesthesia. Propofol produces a less prominent depression of neurophysiological measurements, it is known to especially preserve the cortical SSEP responses and motor evoked potentials (Pelosi et al. 2001, Clapcich et al. 2004, Liu et al. 2005).

Opioids display minimal effects on the intraoperative neurophysiological measurements (Lee et al. 1994, Samra et al. 2001). Remifentanil is commonly used, in combination with propofol, as an infusion in surgery in which intraoperative monitoring is required. Remifentanil is an ultrashort-acting potent opioid, with a rapid emergence of its effect after end of the infusion. The risk for opioid-induced hyperalgesia is a disadvantage of remifentanil.

Dexmedetomidine is a selective α_2 agonist, with sedative and analgesic effects on spinal cord and in the locus ceruleus (Kamibayashi et al. 2000). Dexmedetomidine was shown to offer a degree of neuroprotection against ischaemic injury in animal studies (Kuhmonen et al. 1997). Concerning the effect of dexmedetomidine on intraoperative monitoring the evidence is still controversial. In several studies, dexmedetomidine has proven to be safe to use and did not alter the evoked potential responses in clinically relevant doses (Anschel et al. 2008, Tobias et al. 2008, Rozet et al. 2015, Li et al. 2016). Conversely, in other research the drug was seen to have a significant effect on the evoked potentials during surgery (Mahmoud et al. 2010, Lee et al. 2019).

The action of ketamine, a selective antagonist of the N-methyl-d-aspartate (NMDA) receptor, is different to that of any other anaesthetic agent. Ketamine increases the amplitudes of intraoperative evoked potential responses (Erb et al. 2005).

2.3. Pain management in spinal surgery

Posterior spinal fusion surgery with pedicle screw instrumentation is currently the gold standard surgical care for correction of idiopathic scoliosis. The procedure involves extensive posterior exposure of the spine, segmental pedicle screw instrumentation and correction of the scoliosis. As a consequence of the extensive surgery the postoperative pain management can be challenging. Often a regimen combining different forms of analgesia and drugs is utilized (Borgeat et al 2008).

2.3.1. Pain mechanisms in spinal surgery

The previously mentioned surgical procedure with major tissue trauma induces postoperative pain with nociceptive, neuropathic, and inflammatory components.

The stimuli for nociceptive pain originate in the vertebrae, facet joint capsules, ligaments, fascia, muscles, subcutaneous tissue, and skin. Nociceptors of these structures elicit the sensation of pain. Mechanical irritation, compression or inflammatory signals released by the injured cells activates the pain signal (transduction). The pain sensation travels as an electrical signal in the nerve fibres to the synapse in the dorsal horn of the spinal cord. The nerve fibres involved are of two types. The myelinated A-delta fibres transmitting acute, localized pain, and unmyelinated C fibres that convey slow, dull pain signals. From the dorsal horn the secondary neurons transmit the signal to the central nervous system, specifically to the thalamus and the somatosensory cortex (transmission). In the central nervous system and the spinal cord, the pain signal is subject to modification and modulation. Complex interactions occur between excitatory and inhibitory interneurons at the synapse level in the dorsal horn (gate-control theory, Melzack and Wall 1965). The neural circuits within the dorsal horn are particularly complex and are modulated by both descending inhibition and facilitation from supraspinal structures such as the brainstem and cortex (Julius and Basbaum 2001, Zhuo 2017). The pain signal is processed in thalamus and transmitted to somatosensory cortex, the frontal cortex and the limbic system (perception). Psychological factors such as stress, anxiety and catastrophizing can enhance the acute pain by these modulations (Pogatzki-Zahn et al. 2017, Kalso et al. 2018). Pain is defined by the International Association for the Study of Pain (IASP) as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage' (Loeser and Treede 2008). As previously suggested, within this definition, psychological factors play a role in the experience of pain.

Postoperative pain after spinal deformity surgery also includes a neuropathic component. During the procedure the neural elements, the spinal cord and spinal nerves, are subject to both traction and compression when the curvature of the spine is corrected. The nerves may also suffer from inadequate perfusion and hypoxia, which may induce neuropathic pain after surgery. A loss of sensitivity in certain areas is common after major spinal surgery. Physical damage to the nerves leads to

abnormal signalling, which can appear as motor, sensory or autonomic dysfunction. Allodynia and hyperalgesia can also be present in neuropathic pain as the damaged nerve has a lower threshold for activation. Peripheral nerve injury leads to activation of spinal glia cells, which increases the production of pro-inflammatory substances (Cohen and Mao 2014). These substances act both directly on the neurons and via action in the dorsal root ganglion.

Major skin incision and muscle exposure induces an inflammatory response after tissue injury. Pro-inflammatory agents, such as bradykinin, histamine, cytokines and prostanoids, are released from the damaged cells and mast cells. Neutrophilic granulocytes migrate to the site of injury and release cytokines and growth factors. The inflammatory agents activate the arachidonic acid pathway and generate the production of prostaglandins. The inflammatory mediators act directly on nociceptors and also indirectly by generating other pain-inducing agents. Some inflammatory mediators act on the modulation of pain in dorsal root ganglion. A peripheral sensitization occurs, where inflammatory mediators induce modulation of receptors and ion channels, which leads to mechanical hyperalgesia around the area of incision. The NMDA receptors are thought to play an important role in central sensitization, where the excitability of the dorsal horn neurons increases (Kidd et al. 2001).

2.3.2. Postoperative pain management

Analgesic agents with different mechanism of action are combined for postoperative pain management after spinal surgery in children and adolescents. Effective analgesia is achieved, and the adverse effects of drugs are minimised through the use of multimodal analgesia.

Paracetamol is the primary analgesic agent used. It crosses the blood-brain-barrier and has a mainly central analgesic effect. The exact mechanism of action of this drug is still debated. It is thought that its main effect is mediated through the inhibition of the prostaglandin synthesis in central nervous system. Paracetamol activates the descending serotonergic pathways and its peripheral action is minimal. In a randomized, controlled trial paracetamol improved analgesia, but did not reduce the opioid consumption (Hiller et al. 2012). According to a recent systematic review paracetamol reduces the opioid requirements in children (Wong et al. 2013).

Non-steroidal anti-inflammatory drugs (NSAIDs) such as ketorolac, have been shown to reduce pain scores and morphine consumption after spinal surgery in children (Munro et al. 2002, Rosenberg et al. 2017). The analgesic effect of the NSAIDs is achieved through the inhibition of the cyclooxygenase enzyme and the prevention of prostaglandin synthesis (Seki et al. 2018). There are limitations to the use of NSAIDs after spinal surgery, due to the concerns of negative effects on bone formation. Animal studies have demonstrated that NSAIDs slow down bone formation after spinal fusion (Martin et al. 1999). In human studies a normal dose of NSAIDs after spinal fusion was considered to be safe (Li et al. 2011).

Glucocorticoids are widely used in the anaesthesia to prevent nausea and vomiting (De Oliveira et al. 2013). Corticosteroids also reduce the postoperative pain scores and opioid consumption. In a published meta-analysis, patients receiving single-dose dexamethasone had lower postoperative pain scores and required less opioids (Waldron et al. 2013). The mechanism of action of corticosteroids include inhibition of prostaglandin synthesis and a reduction in vascular permeability. The drug has also been shown to reduce spontaneous discharge in injured neurons (Devor et al. 1985).

Ketamine is used in pain management as it is an NMDA receptor antagonist and is a good analgesic at sub anaesthetic doses. In animal studies, ketamine has been shown to reduce the hyperalgesia induced by remifentanil-infusion (Gu et al. 2009).

2.3.3. Opioids

Opioids exert agonist activity on the μ-, δ- and κ-opioid receptors. These receptors are present in the peripheral tissue and their expression in the primary afferent neurons increases during inflammation. Intravenous patient-controlled analgesia (PCA) with opioids is widely used for the management of moderate to severe pain. PCA has also been shown to be safe and effective in children (Berde et al. 1991). Morphine-based PCA is the most common pain management used after posterior fusion surgery for adolescent idiopathic scoliosis (Olkkola et al. 1988, Palmer et al. 2010). Background infusion with PCA is widely utilised in children, but the data regarding its safety and efficacy are controversial. Background infusion was not shown to provide advantages over only bolus dose administration in AIS patients after scoliosis surgery. There was no difference in patient satisfaction, adverse events and morphine use (Weldon et al. 1993, Hayes et al. 2016). Despite the effective analgesia of opioids, the drugs have several side effects. These unwanted effects include oversedation, respiratory depression, nausea and vomiting, constipation, pruritus, and risk for addiction. Postoperative urinary retention is an adverse effect of opioid treatment. Extensive problems with opioids in the United States, especially following the treatment of postoperative pain, have led to caution regarding their use.

2.3.4. Epidural analgesia after spinal surgery

Epidural infusion is used in many institutions after paediatric spinal fusion surgery (Palmer et al. 2010). However, a standardised method has not been established and the used agents and mode of administration varies (Seki et al 2018). Generally, a solution including both opioids and local anaesthetics is used. The epidural catheter is inserted by the surgeon at the end of the procedure before wound closure. Epidural analgesia is used in conjunction with IV PCA for postoperative pain. Meta-analysis with four randomized studies showed significantly lower pain scores in the epidural group. The patient satisfaction was higher in the epidural group than with intravenous only analgesia group (Taenzer et al. 2010). One epidural catheter has shown in clinical studies to provide better analgesia than intravenous opioids alone (O´Hara et al. 2004,

Sucato et al. 2005, Gauger et al. 2009). Two catheters have been used in some studies, and the data suggest that this approach is superior to one catheter or intravenous opioids in postoperative analgesia (Blumenthal et al. 2005, Klatt et al. 2013). The potential for motor block, which can hide a neurological deficiency and prevent diagnosis of surgical complications, is an unwanted adverse effect of epidural analgesia. Respiratory depression is a potentially lethal but relatively rare adverse effect of epidural local anaesthetic infusions with opioids (Sucato et al. 2005).

2.3.5. Intrathecal morphine

Clinical studies show that intrathecal opioids can reduce postoperative pain scores and opioid consumption, but the effect only lasts for 24 hours (Milbrandt et al. 2009, Li et al. 2018). A single preoperative injection of a moderate dose of morphine has been shown to be safe and effective, but higher doses increases the risk of respiratory depression (Eschertzhuber et al. 2008, Tripi et al. 2008). A recent meta-analysis states that intrathecal morphine produces a potent analgesic effect in the immediate postoperative period and does not increase complications (Musa et al. 2019).

2.3.6. Postoperative urinary retention and adverse effects of opioids

Patient controlled analgesia with intravenous opioids is widely used for pain management in children after major surgery (Cravero et al. 2019). Epidural infusions, including opioids, are also commonly used. Multimodal pain management has gained popularity due to the various side effects of opioid medication and not least the concerns regarding addiction (Harbaugh et al. 2018).

Respiratory depression and oversedation are the most feared side effects of opioids. The risk of respiratory depression has been reported to be as low as 2.3% in adults (McNicol et al. 2015), but in some paediatric studies the risk has been considerably higher 11-19% (Voepel-Lewis et al. 2008, Gauger et al. 2009). Nausea and vomiting are common adverse effects due to anaesthesia or analgesic treatment. The literature regarding opioids effect on emesis in children is sparse and controversial (Cravero et al. 2019).

The postoperative opioid-related decreased bowel motility has been well studied in adult population (Barletta et al. 2011). However, the incidence among children and adolescents is not well documented.

Postoperative urinary retention (POUR) is a perioperative challenge that must be acknowledged. The incidence of POUR was 23% among patients with PCA and 25% in the non-PCA group in a study review on adult population (McNicol et al. 2015). Another review compared different analgesic treatments and stated that the incidence of urinary retention was higher in group with epidural analgesia (29%) compared to that in the intravenous PCA group (13%) (Dolin et al. 2005). Making comparisons between different studies is difficult because the definition of POUR varies. In

children and adolescent urinary retention occurs at least as frequently as in adults. Two studies show an incidence of 29 - 64% of postoperative urinary retention in children (Sherburne et al. 2008, Alfheim et al. 2016). In a study with children after various surgical procedures, the incidence of postoperative urinary retention was 13% (Esmail et al. 1999). The urinary retention can be affected by both surgical factors and other perioperative treatment as in analgesic management. Risk factors for postoperative urinary retention in children include patient-controlled analgesia, excessive analgesia, the liberal use of intravenous fluids and a delay in the time to bladder emptying (Sherburne et al. 2008).

2.4. Pregabalin and pre-emptive analgesia

Pregabalin and gabapentin are alpha-2-delta ligands. Pregabalin was initially developed as an epileptic drug but has gained popularity as a potent drug for the treatment of neuropathic pain. Pregabalin has been demonstrated to have an effect on central sensitisation and, has therefore been recommended for use as a component in multimodal analgesia (Chou et al. 2016).

2.4.1. Pharmacokinetics and pharmacodynamics of pregabalin

Pregabalin has anticonvulsant, analgesic and, anxiolytic properties. The exact mechanism of action remains uncertain especially regarding the analgesic effect. Pregabalin is a chemical analogue of γ-aminobutyric acid (GABA) but exerts no GABA activity. The high affinity binding of pregabalin to the α2δ –subunit of presynaptic voltage-dependent calcium-channels occurs in the peripheral and central nervous system (Sills 2006). This leads to inhibition of calcium influx and a reduction in the release of excitatory neurotransmitters, such as glutamate and substance P. Pregabalin is thought to exert its action in the dorsal horn neurons of the spinal cord by reducing central sensitization. Pregabalin was approved by the European Medicines Agency in 2004 for treatment of neuropathic pain and treatment of partial seizures in adults.

Orally administered pregabalin is absorbed quickly, with maximum plasma concentration achieved within 1 hour. Bioavailability is high, >90% regardless of dosage, and shows linear pharmacokinetics. It differs from gabapentin, which is absorbed slowly and bioavailability dropping with increasing dose. Pregabalin does not bind to plasma proteins. The drug remains unaffected by hepatic enzymes and is renally excreted, it has an elimination half-time of six hours (Bockbrader et al. 2010). The percentage of pregabalin concentration in the cerebrospinal fluid was reported to be 1-30%, with peak concentration attained at eight hours after drug administration (Buvanendran et al. 2010). Pregabalin shows dose-dependent efficacy.

The adverse effects of pregabalin can in some cases be challenging. Dizziness (50%) is the most commonly reported side effect of pregabalin. Other common adverse effects are somnolence (50%), headache (29%), dry mouth and blurred vision

(Tassone et al. 2007). The side effects of dizziness and delirium can prevent pregabalin use especially in adults. In children and adolescents, the experience of adverse effects may be smaller. In a study with 107 adolescents having pregabalin treatment for fibromyalgia the incidence of dizziness was 30% and headache 19% (Arnold et al. 2016).

2.4.2. Preventive analgesia and postoperative pain

Transmission of pain signals induced by tissue damage leads to sensitisation of the peripheral and central pain pathways. Pre-emptive analgesia is the administration of analgesic treatment with the aim of blocking pain signal transmission before, during, and after surgical procedure. Many of the drugs used in preventive analgesia act by reducing the central sensitisation process in the dorsal horn (Woolf and Chong 1993).

2.4.3. Reduction of peripheral sensitisation

Peripheral sensitisation of the primary afferent neurons leads to primary hyperalgesia, which is an important component of postoperative pain. Non-steroidal anti-inflammatory drugs reduce peripheral hyperalgesia by diminishing prostaglandin concentration (Pogatzky-Zahn et al. 2017). Glucocorticoids are anti-inflammatory drugs, that have been shown to reduce postoperative pain scores and opioid requirements (De Oliveira et al. 2011). Corticosteroids act by inhibiting the prostaglandin synthesis, similar to NSAIDs. In rat models with nerve injury, corticosteroids have reduced nerve excitability (Devor et al. 1985, Watanabe and Bruera 1994).

2.4.4. Inhibition of central sensitisation

Ketamine is a non-competitive antagonist of the NMDA receptor. It has two optic isomers, R- and S-Ketamine. S-Ketamine has more potent analgesic and anaesthetic effects. Ketamine has an analgesic effect at subanaesthetic doses. NMDA receptors are situated in the dorsal horn of the spinal cord and participate in the modulation of the pain signal (Joshi and White 2001). Receptor antagonists like ketamine prevent central hyperexcitability. This may play a role in the prevention of persistent postsurgical pain. Studies on the paediatric population have been collected in two meta-analyses (Dahmani et al. 2011, Cho et al. 2014). In the first meta-analysis ketamine was associated with lower pain scores and opioid consumption during the first two hours after surgery, but no difference later postoperatively. In the second meta-analysis on tonsillectomy patients, the ketamine group had lower analgesic requirements in the first 24 hours. The results from studies evaluating ketamine in patients undergoing spinal deformity surgery are controversial. Intraoperative ketamine infusion failed to reduce opioid consumption or pain scores in three studies (Engelhardt et al. 2008, Pestieau et al. 2014, Perello et al. 2017). A low-dose perioperative ketamine infusion decreased the cumulative morphine requirement by

20% after surgery (Minoshima et al. 2015). Evidence is lacking regarding the ability of ketamine to reduce the incidence of persistent postoperative pain (PPP) after paediatric spinal surgery. Prolonged ketamine-infusion did not lead to reduction in the incidence of PPP in children undergoing posterior spinal fusion in one study (Perello et al. 2017).

Gabapentinoids, such as gabapentin and pregabalin, are mainly used in treatment of neuropathic pain. The drugs have also been shown to affect the central sensitisation and are therefore indicated for treatment of fibromyalgia. In two meta-analyses, it was concluded that gabapentin and pregabalin were effective in reducing pain intensity, opioid consumption and opioid-related adverse effects after surgery (Tiippana et al. 2007, Mishriky et al. 2015). Sedation, dizziness and visual disturbance were more common in pregabalin-treated subjects compared to placebo-treated participants (Mishriky et al. 2015). The same results were obtained in a meta-analysis focusing on gabapentinoids effect on acute pain following spinal surgery in adults. Gabapentinoids reduce postoperative pain, morphine consumption, and reduce opioid-related adverse effects (Liu et al. 2017). The benefits of perioperative gabapentin for postoperative pain management seems to be almost absent according to a more recent systematic review (Fabritius et al. 2016). In paediatric patients, studies are very sparse. The effect of gabapentin on postoperative pain after spinal surgery in children has been evaluated in three studies. A single dose preoperative gabapentin did not reduce pain intensity or opioid requirement (Mayell et al. 2014). In a randomized trial, preoperative gabapentin and 5 days postoperative treatment, showed a reduction in morphine consumption (Rusy et al. 2010). In the most recent retrospective study, perioperative gabapentin reduced opioid consumption by 25% (Choudhry et al. 2017). No studies are available on pregabalin and paediatric spinal surgery.

The evidence is very sparse regarding the impact of gabapentinoids on the development of persistent postoperative pain, and the follow-up period in these studies is often short. Based on moderate-quality evidence in a recently published review article, no preventive effect of pregabalin on chronic postsurgical pain could be demonstrated (Martinez et al. 2017).

Alpha-2 agonists, as clonidine and dexmedetomidine, can also be used in multimodal analgesia. The antinociceptive effect of these drugs is a result of stimulation of the alpha2-adrenoreceptors, which are located in the central nervous system and spinal cord. According to a meta-analysis on adult population, perioperative systemic alpha-2 agonists decrease postoperative opioid requirement, pain intensity, and reduce postoperative nausea. Dexmedetomidine reduced morphine consumption up to 24 hours after surgery by 30%. Common adverse effects included bradycardia and arterial hypotension. The review showed that the impact of alpha-2 agonists on chronic pain remains unclear and further studies are warranted in this regard (Blaudszun et al. 2012). Two meta-analyses on the intraoperative use of dexmedetomidine in children have been published and reveal that dexmedetomidine reduces postoperative opioid requirements and pain scores (Schnabel et al. 2013, Bellon et al. 2016).

2.5. Adolescent idiopathic scoliosis and back pain

The reports on back pain and its correlation with spinal deformities are somewhat contradictory. The subject can be difficult to study, as the pain sensation is a very subjective feeling and is modulated by many psychological factors. The studies reported are also very heterogenic in design. Overall, the prevalence of low back pain is very common among healthy individuals.

2.5.1. Back pain in healthy adolescents

In a meta-analysis that was published in 2013, the lifetime mean prevalence of low back pain in healthy adolescents was reported to be nearly 40% (Calvo-Munoz et al. 2013). The mean prevalence of back pain was found to be 33% during the 12 months period, according to data obtained from 13 studies. In a study performed in Finland, the prevalence of back pain was lower. In this study, 18% of the 14 and 16-years old adolescents reported experience of low back pain interfering leisure activities during the preceding 12 months (Taimela et al. 1997). Low back pain is common in adolescence and the prevalence increases with age but is mostly mild and self-limiting (Balague et al. 2003). Studies show that the prevalence among females is higher than among males (Kovacs et al. 2003).

2.5.2. Spinal deformity and back pain

Spinal deformity is a major risk factor for back pain in adolescence, although historically scoliosis has been considered to be a painless condition. Studies evaluating back pain in patients with adolescent idiopathic scoliosis report an incidence of 23 - 54% (Ramirez et al. 1997, Sieberg et al. 2013, Théroux et al. 2015). In the work by Ramirez, the pain intensity was not specified for the 23% of patients who reported pain. Sieberg, on the other hand, included only patients reporting moderate to severe back pain and found the incidence to be 35%. In an epidemiological study in Japan with 30 000 healthy students and 51 students with scoliosis, the scoliosis patients were found to have twofold risk of back pain compared to the healthy controls (Sato et al. 2011). Predictors of back pain in surgical candidates for adolescent idiopathic scoliosis was evaluated and it was found that older age at diagnosis, no use of brace, and rigid lumbar curve predicted worse back pain (Smorgick et al. 2013). There are several limitations to the studies on back pain and scoliosis. The definition of low back pain is often unclear, and the intensity of pain is not always evaluated. The methods and design of studies vary, and longitudinal monitoring is lacking.

Spondylolisthesis is known to be a condition associated with back pain in adolescents (Tsirikos and Garrido 2010, Berger et al. 2019). Isthmic and dysplastic spondylolisthesis are the two main types seen in children and adolescents (Wiltse 1969). The intensity of the low back pain often correlates with the degree of vertebral

displacement (Smith and Hu 1999). Pain symptom increases after physical activity or prolonged standing. The prevalence of spondylolysis in athletes with back pain has been reported to be 47% (Micheli et al. 1995).

2.6. Persistent postoperative pain after spinal fusion in children

The literature on persistent postoperative pain in children is limited. Very little is known about its prevalence, about predisposing factors and its impact on quality of life (Nikolajsen and Brix 2014). The definition of chronic postsurgical pain in children is unclear. In adults, the definition of chronic postsurgical pain has been suggested to be: pain persisting at least three months after surgery, pain not present before surgery, pain localized to the surgical site or referred area, and that other causes of pain are excluded (Macrae et al. 2008).

A few studies can be found reporting on persistent pain after spinal fusion surgery in children, but comparison across studies is difficult because of heterogeneity in design and methodology. Many studies only use the SRS domain scores to evaluate existence of pain, which is a very rough measure of pain with no data on intensity. These studies report a prevalence of persistent postoperative pain in 6 - 27% of the surgically treated patients at two-year follow-up (Merola et al. 2002, Upasani et al. 2008, Djurasovic et al. 2017). In the study by Sieberg, 190 surgically treated patients with adolescent idiopathic scoliosis completed 2-year follow-up and 15% reported pain in the moderate to severe range (Sieberg et al. 2013). Forty-two per cent of 110 patients reported having NRS > 4 at the time or over the previous month one year after surgery, (Chidambaran et al. 2017).

Predicting risk factors for development of persistent postoperative pain in adolescents have been identified (Sieberg et al. 2013, Chidambaran et al. 2017). Higher pain scores in the immediate postoperative period, anxiety of the child and the duration of surgery were found to be predictive of worse outcome regarding persistent pain (Chidambaran et al. 2017). Higher preoperative level of pain and anxiety have been reported as risk factors for chronic pain (Connelly et al. 2014). A similar finding was reported in another study in which higher immediate postoperative pain scores predicted a twofold risk for chronic pain at 12 months after surgery. Anxiety sensitivity predicted maintenance of moderate chronic pain in children (Pagé et al. 2013).

2.6.1. From acute to chronic pain

Studies on adult population have identified risk factors for persistent pain after musculoskeletal injury. Risk factors include high initial pain scores, older age, pain catastrophizing and psychological factors, such as anxiety and depression (Rosenbloom et al. 2013, Rosenbloom et al. 2016).

The mechanisms that are responsible for the development of persistent postoperative pain have not been fully elucidated but are thought to involve peripheral and central neural modulation (Chapman and Vierck 2016). The surgical lesion to peripheral axons leads to spontaneous signalling and lowered stimulus threshold causing so called hyperalgesia or allodynia. Persistent harmful signalling of peripheral nociceptors induced by inflammation, neurotrophic factors and neurotransmitters may play a role in pain chronification. It is also thought to occur neuroplastic changes in the spinal dorsal horn and higher central nervous system generating noxious pain signalling. Changes in the inhibitory pathways in the spinal cord and descending modulation may be involved in transition from acute to chronic pain. Finally, maladaptive remodelling in brain connectivity and structure has been a target for research.

3. AIMS OF THE STUDY

The objective of this thesis, consisting of four studies, was to develop and optimize the perioperative management of posterior spinal fusion surgery in adolescents with idiopathic scoliosis, spondylolisthesis and Morbus Scheuermann. Additionally, the aim was to evaluate the prevalence of persistent postoperative pain in adolescents after spinal deformity surgery.

The specific aims of these studies were:

1. To evaluate the effect of preoperative pregabalin on intraoperative neurophysiological measurements
2. To evaluate the effect of pregabalin on the immediate postoperative pain and opioid consumption after spinal fusion surgery
3. To determine the prevalence of persistent postoperative pain five years after posterior spinal fusion in patients with adolescent idiopathic scoliosis
4. To assess the incidence of postoperative urinary retention in patients after spinal surgery for idiopathic scoliosis

4. MATERIALS AND METHODS

The study protocols were approved by the Ethics Committee of the Hospital District of Southwest Finland. The National Agency for Medicine approved the protocol with drug intervention. The clinical trial was registered in the public trials registry, ClinicalTrials.gov, prior to initiation of patient recruitment. Written informed consent was obtained from every patient and their parents.

4.1. Randomised clinical trial comparing pregabalin and placebo (Study I and II)

The first and second publication of this thesis is based on a randomised, double-blind, placebo-controlled clinical trial. In this trial we evaluated the effect of pregabalin on intraoperative neurophysiological measurements and immediate postoperative pain and opioid consumption after posterior spinal fusion in children.

4.1.1. Study sample

Seventy-seven consecutive patients were evaluated for enrollment during the period between August 2015 and September 2018. Sixty-four adolescents (31 randomly allocated to control group with placebo and 33 to active treatment group with pregabalin) undergoing instrumented spinal fusion surgery gave their consent to participate in the study. There was not known how pregabalin affects the intraoperative neurophysiological measurements. In order to evaluate the safety of the study intervention, a data analysis of the neurophysiological measurements was performed after recruitment of the first 31 patients.

Inclusion criteria were:

- Adolescents (10 - 21 years of age) with adolescent idiopathic scoliosis, spondylolisthesis or Morbus Scheuermann.
- Scheduled for posterior spinal fusion surgery
- ASA physical status I-II
- Written informed consent
- No contraindication for pregabalin use

Exclusion criteria were:

- Other spinal pathology or other associated medical condition
- Neuromuscular scoliosis
- Major neurological developmental delay
- Need for anterior surgery or for vertebral column resection
- Preoperative opioid use
- Inability to use PCA

Table I. Patient demographics and surgical characteristics.
Data are presented as mean and standard deviation.

Variable	Placebo (n = 31)	Pregabalin (n = 32)
Age (years)	15.5 (2.0)	15.8 (2.3)
Weight (kg)	61.2 (15.2)	57.3 (12.9)
Height	1.67 (0.1)	1.67 (0.1)
BMI	21.9 (5.1)	20.4 (3.4)
Male:female ratio	10 : 21	11 : 21
Main curve (degree)		
Preoperative	52.5 (10.1)	52.5 (7.2)
Postoperative	12.9 (4.6)	11.5 (5.0)
Lenke		
1, 2, 3, 4, 5, 6	11, 8, 4, 1, 0, 3	9, 10, 1, 2, 2, 1
Mb Scheuermann	0	4
Spondylolisthesis	5	3
Levels fused, n	10.3 (3.6)	10.5 (2.9)
Posterior column osteotomy, n	9	14
Surgical time (h)	2.9 (0.7)	2.8 (0.5)
Intraoperative blood loss (mL)	520 (331)	470 (369)

All procedures were performed by the same experienced orthopaedic spine surgeon. The primary outcome variable of the study was cumulative oxycodone consumption during the first 48 postoperative hours and total hourly oxycodone consumption. The secondary outcome variables included postoperative pain (verbal numeric rating scale 0-10) during the first 48 hours, use of rescue analgesia, and length of hospital stay. Secondary variables included also quality of intraoperative neurophysiological monitoring and incidence of postoperative pain at 12 months and 24 months after surgery.

4.1.2. Study design

The randomisation to the study groups (1:1) was done by the Department of Pharmacy at our university hospital based on a predetermined list with blocks of 20 patients. The Department of Pharmacy manufactured the study drugs and the drugs were delivered to the ward for each study subject according to randomisation. The study drugs were similar in appearance. The investigators, patients, parents, nursing staff, and surgeons were blinded to group assignment. Patients in the pregabalin group received an oral 2 mg/kg dose of pregabalin rounded up to next 25 mg on the preoperative evening, 12 hours before induction of anaesthesia. The patients received the second dose preoperatively approximately two hours before induction of anaesthesia. Maximum dose of pregabalin for any patient was 150 mg b.i.d. Patients in the placebo group received the same amount of similar looking capsules at similar timing.

Induction and maintenance of anaesthesia was standardized. Anaesthesia induction was done using propofol and remifentanil. Both drugs were infused using a device designed for target-controlled infusions (TCI). A TCI device uses a set of pharmacokinetic programmed parameters for computing a predetermined plasma or effect site concentration for drug infusion. Katarian kinetic model was used for propofol dose calculation and Minto kinetic model for remifentanil (Kataria et al. 1994, Minto et al. 1997). Muscle relaxant was not used in any of the patients during any time. Anaesthesia was maintained with propofol-TCI and remifentanil-TCI titrated to maintain the bispectral index (BIS) within predetermined limits. Dexmedetomidine was used in all patients for additive hypnosis and analgesia. After a loading dose (1 µg/kg over 10 min) of dexmedetomidine the patients were turned prone and baseline neurophysiological measurements were completed. After the loading dose, dexmedetomidine infusion was continued at a constant rate of 1 µg/kg/h throughout the procedure and with reduced dose after surgery until the first postoperative morning. All patients received betamethasone 0.2 mg/kg, vancomycin 10 mg/kg and cefuroxime 60 mg/kg as antibiotic prophylaxis and tranexamic acid bolus of 30 mg/kg IV (max 1500mg). Tranexamic acid administration was continued with an infusion rate of 10 mg/kg/h until wound closure. Vital signs were monitored and kept within the following limits: mean arterial pressure between 65-75 mmHg with noradrenaline infusion if needed, body temperature 36.0 – 37.0 °C and BIS 40-60. Neurophysiological measurements were done every 20 min and at specific time points. These were 1. Baseline, 2. After dexmedetomidine loading dose and 15 min of maintenance infusion, 3. Exposure completed, 4. Pedicle screw insertion completed, 5. Correction of spine completed, and 6. Wound closed.

4.1.3. Surgical technique

All patients were operated using a posterior approach only. Pedicle screws were inserted at every level and direct vertebral column derotation (Solera 6.0, Medtronic Spinal and Biologics, Memphis, TN, USA) was used to correct adolescent idiopathic scoliosis (Mattila et al. 2013). Cantilever manoeuvre with posterior column osteotomies was used to correct Scheuermann kyphosis (Geck et al. 2007). Patients with spondylolisthesis had wide nerve root (L5, S1) and cauda equine decompression. Pedicle screws were inserted into L5 and S1 to reduce the spondylolisthesis. Transforaminal lumbar intercorporeal fusion cage was inserted in addition to standard posterolateral spinal arthrodesis.

4.1.4. Pain management

Before surgery, all patients were instructed on the use of the patient-controlled analgesia (PCA) system (CADD-Legacy PCA Pump Model 6300; Smiths Medical). Patients received IV oxycodone 0.1 mg/kg (max 5mg) before discontinuation of remifentanil-infusion at the end of surgery. Standard oxycodone PCA was initiated in the postoperative care unit (ICU), with on demand oxycodone-bolus of 0.03

mg/kg/dose every 10 minutes and an hourly maximum of 0.1 mg/kg, with no basal infusion. An ICU nurse gave boluses from the PCA when needed, based on signs as tachycardia and hypertension, until the patient was able to use the device him/herself. Oxycodone PCA was continued for 48 hours in all patients. All patients received oral paracetamol 20 mg/kg x 3. Oral etoricoxib 2-3 mg/kg was used as rescue analgesia. Rescue analgesia was initiated if the patient reported high pain scores despite appropriate PCA. Oral opioid analgesics were initiated 48 h after end of surgery. All patients received lactuloses doses and sodiumpicosulfate for prophylaxis of constipation. All adverse effects were registered and treated appropriately according to normal clinical practice.

Data collected included vital signs, verbal numeric rating scale in rest and in movement (von Baeyer 2009), sedation scores, opioid consumption, and adverse effects (specifically nausea, dizziness, constipation and pruritus). During the first 8 hours postoperatively, these parameters were measured hourly, then every 4 h up to 24 h after surgery, and at 48 h and 72 h postoperatively. Opioid consumption was recorded and analysed in 8 h intervals (mg/kg/h) and as cumulative amount per day (mg/kg). Demographic data collected included age, weight, height, body mass index, and gender. Orthopaedic data included Lenke classification, preoperative and postoperative Cobb angle, intraoperative blood loss and levels fused. Wound infection and need for re-operation was registered.

4.2. Prevalence of persistent postoperative pain after spinal surgery (Study III)

In this study we evaluated the prevalence of persistent back pain in adolescents following spinal correction surgery. Low back pain is a common symptom also in otherwise healthy adolescents and therefore we compared the results of the surgically treated cohort to untreated scoliosis patients and healthy controls.

4.2.1. Study sample

This study included 55 consecutive patients prospectively enrolled from a single academic medical centre. These patients (aged between 12 and 19 years) were surgically treated for adolescent idiopathic scoliosis between January 2009 to February 2013 with a minimum of 5-year follow-up. They underwent posterior spinal fusion with bilateral segmental pedicle screw instrumentation. All procedures were performed by the same senior orthopaedic spine surgeon.

4.2.2. Study design

After a minimum of 5-year after spinal surgery, the 55 patients were asked to complete and return SRS-24 questionnaire including numerical pain rating scale, query on possible reoperation and pain drawing. Perioperative data, radiographic data, and

SRS-24 outcomes from preoperative to 2-year follow-up were collected prospectively into a research register. The pain drawing included an outline of a human body with anterior and posterior views, enabling localization and categorization of the pain (sharp pain, ache, numbness, insensitivity). If the patient did not return the questionnaires, an interview was made by phone in order to complete the SRS-24 questionnaire. The postoperative opioid consumption was obtained from intensive care unit charts and patient charts.

Standard standing posteroanterior and lateral radiographs were taken of the entire spine preoperatively, at six-month and at two-year follow-up in the surgically treated cohort. Bending radiographs were obtained to evaluate flexibility of the curves preoperatively. Radiographic variables collected included Cobb angles of the proximal thoracic, main thoracic, and lumbar curves. Sagittal measures included thoracic kyphosis (T5-T12), lumbar lordosis (T12-S1) and segmental kyphosis (T2-T5; T10-L2) or lordosis. The curves were classified according to the Lenke classification.

Table II Subject demographics (mean ± SD)

Variable	**Treated AIS at 5-yr FU** (n = 49)	**Untreated controls** (n = 49)	**Healthy controls** (n = 49)
Age at last FU (yr)	22.2 ± 2.1	22.1 ± 2.7	22.0 ± 5.1
Males : females	12 : 37	12 : 37	12 : 37
Major curve			
Preoperative	53.2 ± 7.3	27.7 ± 10.1	NA
6mo postop	12.5 ± 5.3	NA	NA
2yr postop	11.7 ± 6.0	NA	NA
Correction	0.78 ± 0.9	NA	NA
Levels fused (n)	11.0 ± 1.4	NA	NA
Blood loss (mL)	647 ± 397	NA	NA
Operative time (h)	3.75 ± 1.1	NA	NA
48h opioid consumption(mg/kg)	1.95 ± 0.9	NA	NA
Lenke 1	21		
2	13		
3	6		
4	4		
5	0		
6	5		

Thoracic rib hump during forward bending test was measured preoperatively, at 6-month and 2-years FU. The correction percentages of the main thoracic curve were calculated. The radiographic measurements were done by an independent observer.

The SRS-24 is a disease-specific health-related quality of life (HRQoL) questionnaire used to measure the current state of the patient with AIS and the effects of scoliosis surgery, consisting of twenty-four questions with a maximum score of 120 (Haher et al. 1999). The questionnaire has seven domains: pain, general self-image, function from back condition, general level of activity, postoperative self-image, postoperative function, and satisfaction. Each domain score ranges from 1 to 5, with higher scores indicating better patient outcomes. A score less than 4 in the SRS-24 pain domain (1=severe pain; 5=pain free) was considered clinically relevant. Numerical pain rating score 4 or more (1=no pain; 9=severe pain) was considered moderate to severe pain. The Numerical Rating Scale has been validated as a pain measure in children aged 7-17 years (von Baeyer 2009).

4.2.3. Healthy and untreated control groups

Untreated individuals with adolescent idiopathic scoliosis and healthy control subjects were obtained from a previous study (Diarbakerli et al. 2017 and 2018).

The untreated control subjects had been observed at a different orthopaedic department in another Nordic country than the surgical cohort and were included in study between November 2010 and June 2015. Inclusion criteria were a Cobb angle of at least 10° and scoliosis that was of idiopathic origin. The individuals had been diagnosed between 10 and 17 years of age. These 347 subjects had not been brace-treated. The data on Cobb angle of major curve was collected from the last available radiograph (at a mean age of 19.4 years).

The 272 healthy controls were selected from a population register in Sweden and were invited to complete and return SRS-questionnaire between the years 2012 and 2015.

Using these research registers, we randomly matched the surgically treated patients to 49 untreated individuals for age (± 2 years), gender, type of idiopathic scoliosis (adolescent), and 49 healthy controls for age (± 2 years) and gender. The age was matched to the operatively treated age at final follow-up. The control groups of untreated and healthy individuals had filled out the SRS-22r. The SRS-22r questionnaire is an improved and modified version of the original SRS-24 questionnaire (Asher et al. 2003).

To able comparison of surgically treated patients at 5-year follow-up with untreated patients and healthy controls without scoliosis, we used the preoperative first 15 questions on SRS-24, which are either exactly the same or close to questions in the SRS-22r questionnaire (questions #1, 2, 4, 5, 6, 8, 9, 11, 12, 14, 15, 17-20). These questions were used to form the four preoperative domains of the SRS-24 questionnaire: pain domain (SRS-24 questions 1, 3, 6, 8, 11; SRS-22r questions 1, 4,

8, 11, 14), general self-image (SRS-24 questions 5, 14, 15; SRS-22r questions 6, 19, 20), general function (SRS-24 questions 7, 12, 13; SRS-22r questions 9, 15, 18), and general activity (SRS-24 questions 4, 9, 10; SRS-22r questions 5, 12, 17). The postoperative question from pain domain was excluded. Finally, the mean total score of the eight exactly same questions with similar scoring in both questionnaires were compared across groups: questions 1 through 8 for SRS-24, and 1, 2, 4, 5, 6, 8, 9, 11 for SRS-22r.

4.3. Incidence of postoperative urinary retention (Study IV)

The fourth publication in this thesis addressed the incidence of postoperative urinary retention among adolescents after spinal surgery for idiopathic scoliosis in a prospective study with a retrospective analysis of its treatment.

4.3.1. Study sample

One hundred and eleven consecutive patients were enrolled in the study between March 2009 and August 2016.

Inclusion criteria were:

- Adolescents aged 11-21 years with idiopathic scoliosis
- Scheduled for instrumented posterior spinal fusion
- ASA physical status I-II

Exclusion criteria were:

- Other spinal pathology or other associated medical condition
- Neuromuscular scoliosis
- Major neurological developmental delay
- Need for anterior surgery or for vertebral column resection

4.3.2. Study design

Urinary retention has historically been measured by nurse staff using urinary bladder catheterization. The ultrasound technique for residual measurement was implemented in our unit in 2009. In the first twenty patients, the urinary residual measured by ultrasound scan was verified by urinary catheterization. These values showed to be very similar and routine catheterization was discontinued.

A urinary catheter was inserted for all patients after induction of anaesthesia. The urinary catheter was removed postoperatively at ward. The residual volume of the urinary bladder was measured using ultrasound scan in every patient at least twice on two separate occasions during the postoperative period after posterior spinal fusion.

Intermittent catheterization was continued until the residual volume was measured to be less than 100 ml two times.

Postoperative urinary retention was defined as an inability to empty the bladder after catheter removal and a documented residual volume of 300 ml or more. Difficulty to empty bladder and a need for intermittent catheterizations was defined as a significant residual volume of the urinary bladder.

The postoperative pain management of all the patients included intravenous oxycodone. The patient-controlled analgesia was set with an on-demand oxycodone bolus of 0.03 mg/kg, not administered more often than every 10 minutes and an hourly maximum of 0.1 mg/kg, without basal infusion. Oxycodone PCA was continued in all patients for two days.

4.4. Statistical analysis

In study I, assessing pregabalin´s effect on intraoperative monitoring a cohort of ten patients per group was estimated to be sufficient. The sample-size requirement was calculated with use of study power of 80%, a type-I error (alpha) of 0.05, and an estimated effect size of 1.5. Effect size evaluation was based on a previous report on intraoperative monitoring, with mean latency of SSEP 33 (SD 3) ms and an estimate that 10% increase in latency would be clinically relevant. Two-sided student t-test was used to calculate the level of significance for continuous variables. For categorical variables chi square-test was used (IBM SPSS statistics v21.0). If the data was not normally distributed a logarithmic transformation was made. Mean changes over time of MEP and SSEP latency were evaluated with hierarchical linear mixed models, where group, time and their interaction were in the model, as well as temperature, BIS and MAP as covariates. These models were done separately for both feet.

In study II, statistical comparisons were performed using intention-to-treat analysis principle. Baseline characteristics and length of hospital stay were compared with Mann-Whitney U-test (except gender with Chi-Square test) and number of subjects having adverse events and need for rescue analgesia with chi square - test. Cumulative oxycodone consumption at 24 hours and at 48 hours (mg/kg) was analysed using covariance analysis where number of level fused was handled as covariate and group was categorical factor. The analysis of the oxycodone consumption in mg/kg/h at the five time points was analysed using linear mixed model. To study whether pain scores changes over time, a linear mixed model with repeated measures was used, including one within-factor (time), and several between-factor (group, levels fused). Compound symmetry covariance structure was used for time. Normal distribution of the variables was evaluated from studentized residuals visually together with Shapiro-Wilk test.

The sample-size calculation was based on a previous study in similar set-up as the current study (Rusy et al. 2010). It shows that a sample size of 30 subjects per group is required to detect 30% difference in opioid use between the groups at an alpha-level of 0.05 and a power of 0.80.

In study III, the change in health-related quality of life after spinal surgery was assessed. The prevalence of back pain was compared to healthy controls and patients with untreated scoliosis. Age, gender and group differences were tested with multi-way ANOVA and group comparisons were adjusted with Tukey-Kramer method. Normal distribution assumption was checked visually together with Shapiro Wilk's test. To study whether mean change of different SRS domain scores occurred over the study, we used a hierarchical linear mixed model (HLLM) with repeated measurements. Compound symmetry covariance structure was used for time. After main analyses, pairwise comparison between time points were conducted. Pearson correlation coefficients were calculated when examining association between two numerical variables. Change in categorized pain scores were compared with two time points with McNemar's test. Data are presented as mean and standard deviation (SD) or 95% confidence interval (CI), medians and lower and upper quartiles or frequencies, as appropriate. All statistical tests were performed as 2-tailed.

In study IV, evaluating postoperative urinary retention, the statistical significances of the unadjusted differences between frequency distributions were tested with Pearson's chi square test. The adjusted calculations were performed using a binary logistic regression analysis. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated to quantify the significant associations.

In all studies the statistical analyses were performed using SAS System, version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA). Significance level was set to 0.05 (two-tailed).

5. RESULTS

5.1. The effect of pregabalin on neurophysiological monitoring

Thirty-one patients gave their consent for study participation. The placebo group consisted of 16 patients and the pregabalin group of 15 patients. Two patients in the pregabalin group were excluded from final data, one patient with osteoid osteoma not fulfilling inclusion criteria and one patient diagnosed with hereditary polyneuropathy. One patient in the placebo group was excluded from final data, due to technical problems in monitoring.

The groups were similar with regard to age, height and weight. The spinal deformities of the patients were AIS (25 patients), spondylolisthesis (2 patients) and Mb Scheuermann (1 patient). The groups were similar regarding body mass index, gender, main scoliosis curve and length of instrumentation. There was a similar distribution of Lenke classifications in each group. Surgical time and blood loss during surgery was equal in both groups.

Spinal cord monitoring was successful in all patients but one and no patient showed any marked changes in MEP, SSEP responses or lumbar EMG activity during surgery. No neural deficits were observed postoperatively. There were no complications or adverse effects during the correction manoeuvres.

There were no statistically significant differences between the study groups regarding the latency of bilateral SSEPs (N32 and P37). The mean differences of these latencies and their 95% confidence intervals included zero at all time points. Temperature correlated strongly to the SSEP latency ($p<0.001$ for all four correlations), but there were no differences between the study groups.

The latency of MEPs showed no statistically significant differences between the groups. The mean differences of these latencies and their 95% confidence intervals included zero at all time points. A significant increase in MEP latency was observed after dexmedetomidine loading particularly in placebo group ($p=0.008$).

Table III. Motor evoked potential threshold current.
Data presented as mean and 95%CI

MEP	Baseline	Dex load complete	Exposure complete	Screw insertion complete	Correction complete	Wound closed
Placebo	65 (56, 76)	85 (73, 100)	94 (81, 110)	92 (79, 107)	91 (78, 106)	92 (79, 107)
Pregabalin	66 (56, 78)	81 (69, 96)	88 (74, 103)	88 (75, 103)	85 (73, 100)	86 (73, 101)
Ratio (95%CI)	0.98 (0.98, 1.23)	1.05 (0.85,1.31)	1.08 (0.87, 1.34)	1.05 (0.84, 1.31)	1.07 (0.86, 1.33)	1.07 (0.86, 1.33)
P-value	0.880	0.640	0.480	0.650	0.530	0.540

The threshold current required to elicit MEPs did not differ between the study groups. The ratios (due to logarithmic transformation) and their 95% confidence intervals of threshold current between the study groups included one at all time points (Table III). The threshold current changed in a similar manner in both groups over the time points. There were no differences between the groups regarding body temperature, depth of anaesthesia as measured by BIS, or mean arterial pressure.

Pregabalin group with 13 patients and placebo group with 15 patients were included and analysed.

5.2. Effect of pregabalin on postoperative pain and opioid consumption

After completion of the study protocol, one patient was excluded from final data due to not fulfilling the inclusion criteria (excision of osteoid osteoma). The study cohort consisted of 63 patients, 32 patients randomised to pregabalin group (25 AIS, 4 Mb Scheuermann, and 3 Spondylolisthesis), and 31 patients in the placebo group (26 AIS, 5 Spondylolisthesis). There were no statistical differences between the two groups regarding demographic and clinical characteristics. The groups were also similar regarding surgical characteristics as in preoperative major Cobb angle, levels fused, surgical duration, and intraoperative blood loss.

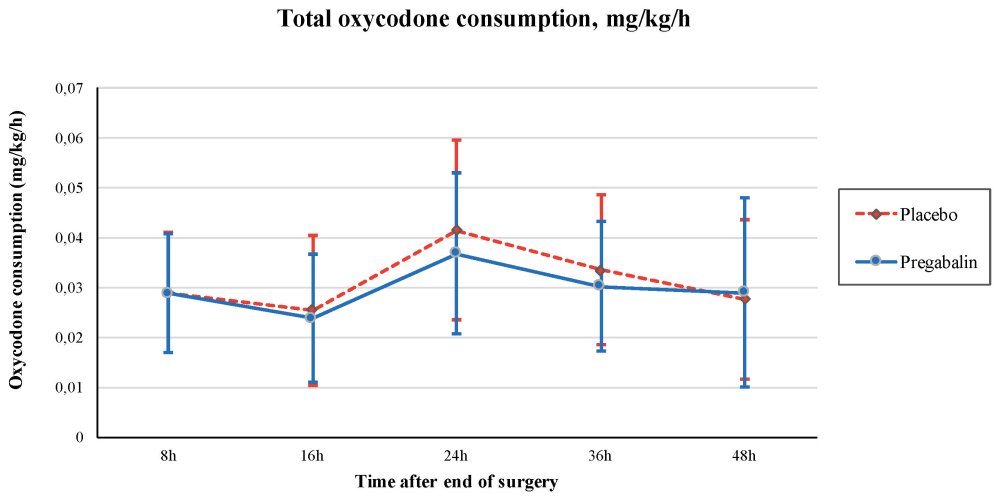

Figure 1. Oxycodone consumption per kg over time. Data presented in mean and SD.

Oxycodone consumption was calculated and registered for every 8 h in all patients. There was no significant difference between the two groups measured in cumulative oxycodone consumption per kilogram for 48 hours after end of surgery adjusted for levels fused. The median consumption in mg/kg (95%CI) for pregabalin group 1.44 (1.32 - 1.67) vs placebo group 1.50 (1.39 - 1.79), p=0.345 (Table IV). We also

calculated the hourly oxycodone consumption in mg/kg/h, comparing the groups over time showed no statistical difference, p=0.752 (Figure 2). No statistical difference existed in the use of rescue analgesia between the groups (p=0.20).

The postoperative pain scores at rest (one hour to 48 hours) did not differ statistically between the study groups over time (p=0.196) as shown in Figure 2. Neither did the pain scores in movement differ statistically between groups (p=0.244).

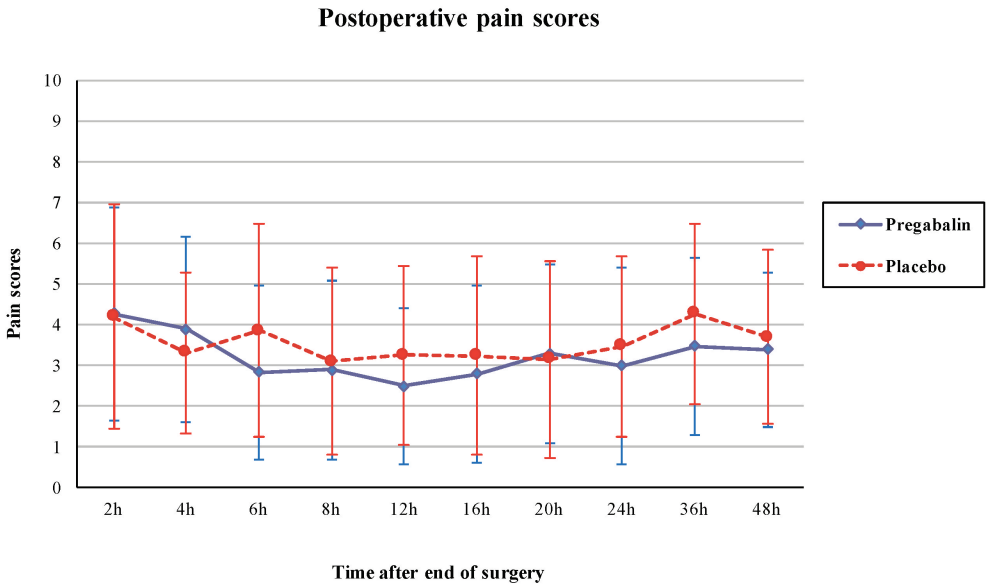

Figure 2. Postoperative pain scores over time. Data presented in mean and SD.

No differences were found between the groups for any measured opioid-related adverse effects. These were somnolence, respiratory depression, nausea and vomiting and pruritus (Table IV).

Table IV. Opioid consumption and adverse effects. Data are presented as median (95%CI).			
	Pregabalin n = 32	**Placebo** n = 31	**P-value**
Oxycodone consumption, mg/kg/h			
0 – 8 h	0.026 (0.002, 0.033)	0.029 (0.024, 0.033)	
8 – 16 h	0.023 (0.019, 0.028)	0.023 (0.020, 0.032)	0.752
16 – 24 h	0.036 (0.032, 0.043)	0.041 (0.035, 0.048)	
24 – 36 h	0.028 (0.025, 0.035)	0.032 (0.029, 0.042)	
36 – 48 h	0.033 (0.024, 0.051)	0.025 (0.023, 0.035)	
Cumulative oxycodone consumption mg/kg			
at 24 h	0.70 (0.63, 0.81)	0.72 (0.66, 0.87)	0.559
at 48 h	1.44 (1.32, 1.67)	1.5 (1.39, 1.79)	0.345
at discharge	2.90 (2.75, 3.51)	3.07 (2.96, 3.88)	0.353
Adverse effects (n)			
0 - 8 h			
Deep sedation	3	1	0.317
Nausea	4	3	0.721
Pruritus	2	4	0.368
8 – 16 h			
Deep sedation	1	0	0.321
Nausea	3	4	0.656
Pruritus	5	2	0.247
16 – 24 h			
Deep sedation	0	0	
Nausea	3	6	0.258
Pruritus	6	7	0.707
24 – 48 h			
Deep sedation	0	0	
Nausea	7	9	0.514
Pruritus	15	10	0.236

Three (2 spondylolisthesis, 1 AIS) patients in the pregabalin group and three (2 spondylolisthesis, 1 AIS) patients in the placebo group reported signs of neuropathic pain immediately postoperatively. For these patients pregabalin treatment was initiated and study drugs withdrawn, or pregabalin treatment was initiated after study drug treatment had ended.

No statistical difference was found in the length of hospital stay between pregabalin and placebo groups, reported in mean(days) and 95%CI, 6.5 (6.0 - 7.0) vs 6.8 (6.4 - 7.2), p= 0.348.

5.3. Persistent postoperative pain

The forty-nine patients with 5-year follow-up had a mean (standard deviation) age at surgery of 15.6 (1.9) years. The mean (SD) Cobb angle of the main curve at the time of surgery was 53 ° (7.4 °) and a remaining curve of 12 ° (6.0 °) at 2-yr FU. There were no significant differences between the treatment group and untreated individuals with idiopathic scoliosis and healthy control group regarding age and gender (Table II). The untreated individuals with idiopathic scoliosis had a mean (range) major curve

of 28 ° (range, 10 ° – 61 °). Eight (16%) of these subjects had a main curve exceeding 40 °.

Mean (range) length of FU for HRQoL (SRS-24 questionnaire) and for reoperation and deep wound infection data was 6.2 years (range, 5 to 9 years). One patient presented with a new transient neurologic deficit (right sided peroneal palsy), necessitating early revision (T12 pedicle screw removal). One patient had a cerebrospinal fluid leak treated during the index surgery. There were no postoperative deep wound infections or more revisions during the follow-up on the entire cohort of 55 patients.

5.3.1. Pain outcomes and quality of life in the surgically treated cohort

The domains for pain, self-image, function, and total scores in SRS-24 improved significantly from preoperative to 5-year follow-up ($p \leq 0.016$). The pain score improved from 4.1 to 4.3 at 5-year follow-up ($p=0.003$). There was no correlation between the pain scores at 5-year follow-up and preoperative major curve, instrumentation below L1 or postoperative rib hump.

Thirty-one per cent (16 of 51) of the patients reported moderate to severe pain during the last 6 months preoperatively using numerical pain rating scale. Postoperatively, 15% (8 of 52) reported moderate to severe pain at 2-year FU ($p=0.155$). Fourteen per cent of the patients (7 of 49) reported moderate to severe pain at 5-year FU ($p=0.052$ as compared to preoperative).

Similarly, 41% (21 of 51) of the patients scored less than 4 in the SRS-24 pain domain preoperatively. The number of patients scoring less than 4 diminished significantly at follow-up, 21% (11 of 52) at 2-yr FU ($p=0.0116$) and 18% (9 of 49) at 5-yr FU ($p=0.039$). The pain domain score improved from preoperative to 5-year follow-up by a mean value of 0.29 (95% CI 0.05 - 0.53) (Table V).

We could not find any correlation between preoperative and 5-yr FU pain scores. The opioid consumption 48h after surgery did not correlate with higher pain scores at 5-yr FU. However, the opioid consumption correlated significantly with the number of levels fused ($r=0.32$, $p=0.023$).

According to the pain drawing, no radicular symptoms to the extremities were reported in pain drawing. One patient reported numbness over the dermatomes T4 – T6 on the right side. None of the patients were using *opioid analgesics* or prescription drugs for back pain 2 years or 5 years after surgery.

Table V. Changes in SRS-24 domains as mean and (SD)					
SRS-24 domains	Preoperative (n = 51)	6 mth FU (n = 53)	2-year FU (n = 52)	5-year FU (n = 49)	P value
Pain	4.00 (0.59)	4.27 (0.52)	4.32 (0.51)	4.30 (0.54)	**0.003**
Self-image	3.80 (0.53)	3.91 (0.64)	3.99 (0.70)	4.17 (0.80)	**0.168**
Function	4.01 (0.46)	4.00 (0.46)	4.10 (0.43)	4.26 (0.25)	**0.0008**
Activity	4.78 (0.44)	4.03 (0.97)	4.72 (0.53)	4.84 (0.31)	0.058
Pop self-image	NA	3.30 (0.51)	3.25 (0.56)	3.20 (0.50)	0.276
Pop function	NA	1.98 (0.97)	2.61 (0.79)	2.88 (0.82)	**<0.001**
Satisfaction	NA	4.18 (0.76)	4.23 (0.77)	4.31 (0.53)	0.076

Data presented in mean and standard deviation (SD)
P value, comparison between preop and 5-yr FU, in pop domains compared to 6 months values.

5.3.2. Comparison of pain and HRQoL to untreated and healthy controls

The mean scores in the pain domain were significantly better in the surgically treated patients as compared to untreated individuals with idiopathic scoliosis ($p<0.001$). There was no significant difference between the surgically treated patient's pain scores at 5-year and the healthy controls (Figure 3).

The scores for general self-image and activity scores were significantly higher in the surgically treated ($p<0.014$) and healthy controls ($p<0.001$) as compared to untreated individuals with idiopathic scoliosis. The mean scores of the eight exactly same questions with similar scoring in both questionnaires showed significantly reduced scores in the untreated group as compared to surgically treated patients ($p<0.001$). The healthy controls showed statistically better score in the general function as compared to the surgically treated patients ($p<0.001$) (Figure 3).

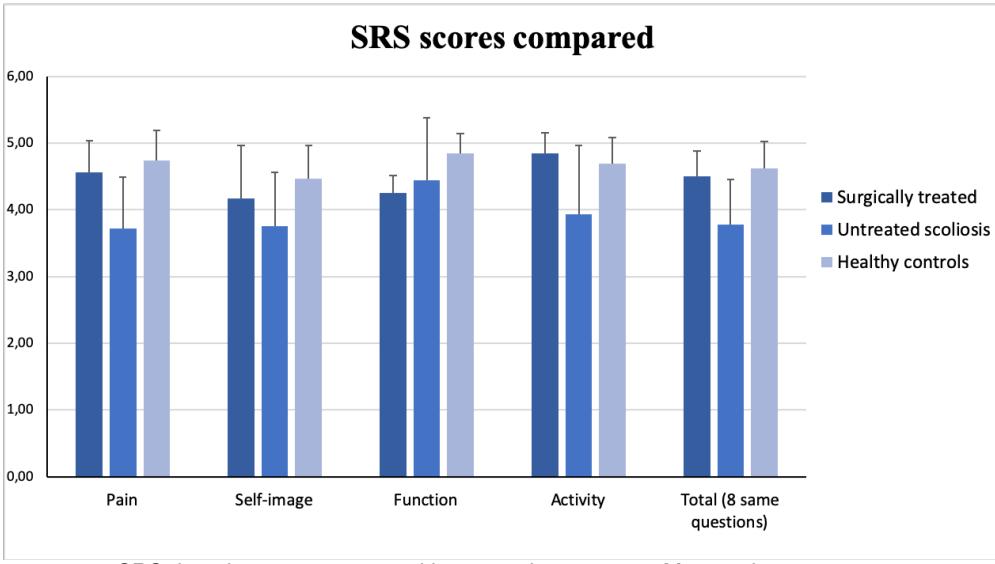

Figure 3. SRS domain scores compared between three groups. Mean-values.

Table VI. Comparison of changes in mean SRS domain scores.				
SRS domains	Surgically treated, change from preoperative to 5 years (n=49)	Untreated patients with scoliosis compared to surgically treated (n=49)	Healthy controls without scoliosis compared to surgically treated (n=49)	MCID
Pain	0.90 (0.79)	- 0.79	0.18	**0.20**
Self-image	0.43 (0.96)	- 0.40	0.30	**0.98**
Activity	0.09 (0.46)	- 0.81	- 0.15	**0.08**

Carreon LY, Sanders JO, Diab M, Sucato DJ, Sturm PF, Glassman SD; Spinal Deformity Study Group. The minimum clinically important difference in Scoliosis Research Society-22 Appearance, Activity, And Pain domains after surgical correction of adolescent idiopathic scoliosis. Spine (Phila Pa 1976). 2010; 35: 2079-83.

Minimum Clinically Important Difference (MCID) is a threshold of improvement that is considered clinically significant. MCID values for the SRS-22 domains (pain, self-image and activity) for patients with adolescent idiopathic scoliosis have been determined in a previous study (Carreon et al. 2010). In Table VI, we show the mean (SD) improvement of SRS domains in surgically treated patients from preoperative to 5-year follow-up. And the changes in means between untreated patients and healthy control groups.

5.4. Postoperative urinary retention

The study cohort consisted of 111 consecutive surgically treated patients (81 female and 30 male) with an average age of 16 years (11-21 years). The mean major preoperative curve of the patients measured in Cobb angle was 53 ° (45 - 83 °) and were corrected with surgery to 12 ° (0 - 28 °). One patient experienced a transient spinal cord deficit, as a result of probe entering spinal canal via a fractured pedicle screw channel. No permanent neural deficit was recorded.

The urinary catheters were removed at a mean of 2.9 (1 - 6) days after surgery. Fifty-one patients (46%) had postoperative urinary retention (POUR) or difficulty to empty bladder, diagnosed using criteria previously described. These fifty-one patients required intermittent catheterization for a mean of two days. Of these 51 patients, 30 (27%) met the criteria for POUR and had a residual of 300ml or more.

Two (1.8%) patients experienced urinary tract infection postoperatively. Patients with urinary retention had a significantly higher mean intraoperative blood loss (mean 626 ml vs. 464 ml; $p = 0.020$) and longer operation time (mean 3.3 h vs. 2.8 h; $p = 0.009$) as compared with those not having urinary retention. In multivariate analyses the main risk factor for urinary retention was male gender, (OR 3.2, 95% CI 1.1–9.2, $p = 0.028$).

6. DISCUSSION

The purpose of our studies was to develop and improve the perioperative management and pain control in adolescents and children after posterior instrumented spinal fusion. In the paediatric population spinal deformities are the most common indication for spinal surgery. Scoliosis correction surgery is major surgery including extensive spinal muscle exposure, segmental pedicle screw instrumentation and arthrodesis. Because of the large tissue trauma and manipulation of the neural elements the postoperative pain management can be challenging. Therefore, multimodal analgesia is commonly used. This includes combination of pre-emptive analgesia, regional analgesia when appropriate, basic analgesics and stronger analgesics like opioids. The aim of pre-emptive analgesia is to reduce the peripheral and central sensitization of the pain signals induced by the surgical incision and tissue-damage. Opioids are strong analgesics with a potent effect in treatment of postoperative pain after major surgery. Opioids have many adverse effects, and therefore, multimodal analgesia aims to reduce the requirement of opioids. Postoperative urinary retention might be one of the most harmful side effects of opioid medication.

Surgery for spinal deformities may change the position of the nerve roots, and the spinal cord is in risk of inadequate perfusion during surgical correction. Neural injury resulting in postoperative paralysis or sensory loss is an uncommon but devastating and unpredictable complication of scoliosis surgery. In order to decrease the incidence of such injury, intraoperative neurophysiological monitoring including motor (MEPs) and sensory evoked potentials (SSEP) is generally accepted as the current standard of care. Intraoperative neurophysiological monitoring aims to detect possible neural damages in an early stage. The monitoring can alert the surgeon before the damage has happened or when surgical manoeuvres still can be reversed. Somatosensory evoked potentials (SSEP) are measured by stimulating peripheral nerves and monitoring the evoked potentials in different locations of the sensory pathway, primarily on the sensory cerebral cortex. Motor evoked potentials (MEP) are recorded after transcranial electrical stimulation of motor cerebral cortex and the responses are recorded in contraction of selected muscles. The intraoperative neurophysiological parameters are influenced by a number of different factors, such as patient height and weight, body temperature, anaesthetic agents used, the amount of drugs used, depth of anaesthesia, hypotension, and even other electrical equipment in the operating room.

Pregabalin is a new-generation gabapentinoid, which originally was developed for use as an anti-epileptic drug. Pregabalin act on presynaptic voltage-dependent calcium-channels in the peripheral and central nervous system, in the dorsal horn of the spinal cord and in locus ceruleus. The activation of these calcium-channels results in a reduction in the release of neurotransmitters. This is thought to explain its antinociceptive effects. Pregabalin has many features that advocate its use preoperatively, particularly pre-emptive analgesia and a potential neuroprotective effect. However, it also has several adverse effects.

Chronic postoperative pain is not widely investigated, and especially among children and adolescents the evidence in literature is sparse. What we know is that low back pain is a very common symptom among otherwise healthy adolescents, and the causal relationship between spinal surgery and back pain is not always easy to define. The occurrence of low back pain has increased in recent years (Calvo-Munoz et al. 2013).

6.1. Pregabalin and neuromonitoring

Our study was a randomised, double-blind, placebo-controlled trial with the aim to evaluate the effect of preoperative pregabalin on the intraoperative neurophysiological measurements. Pregabalin has appeared to produce an inhibitory modulation of neuronal excitability (Chizh et al. 2007). This has raised a question, whether pregabalin might prolong neural conduction and interfere intraoperative spinal cord monitoring. Preoperative use of pregabalin has therefore been limited in spinal deformity surgery. There are no previous studies on the effects of preoperative gabapentinoids (i.e. gabapentin and pregabalin) on intraoperative neurophysiological monitoring.

The strength of our study is a very homogenous group of patients scheduled for posterior instrumented spinal fusion. All procedures were done by the same two senior orthopaedic surgeons. The patients were randomised by the Department of Pharmacy. The patients were treated by standardized anaesthetic total intravenous technique, holding potentially confounding factors (depth of anaesthesia, mean arterial pressure and body temperature) as constant as possible. The neurophysiological measurements were made at specific time points in order to recognize any change during the surgical procedure.

In both study groups body temperature tended to decrease after induction, most likely due to not warming the patient before turning and during preoperative preparations. In statistical analysis temperature correlated strongly to SSEP latency in both groups. This might relate to the slight increase in latency after induction and surgical exposure. Another limitation of the study is the small sample size. According to power analysis with pre-set criteria a minimum of 10 patients in each group was required to demonstrate a clinically significant change in three main outcome parameters (MEP latency, threshold current or SSEP latency).

6.2. Pregabalin and postoperative pain

In our study, perioperative pregabalin did not reduce the postoperative opioid consumption or pain scores in adolescents undergoing posterior spinal fusion compared to placebo group.

To our best knowledge, no studies have been performed in children using perioperative pregabalin for postoperative pain after spinal surgery. Pregabalin is widely used for prevention of postoperative pain in adults but lacks regulatory-

approval for use in children and adolescents. It has been stated in a recent review that the efficacy and safety of gabapentin and pregabalin for the treatment of pain in children and adolescents is not well known. The evidence-based data supporting the use of these drugs is very sparse (Egunsola et al. 2019). In the study by Mann, the safety and tolerability of pregabalin was evaluated in children with refractory partial seizures. Doses up to 10mg/kg/day in children aged 1 month to 16 years, and at doses up to 15 mg/kg/day in those aged <6 years, demonstrated acceptable safety and tolerability (Mann et al. 2014).

There are two randomized, placebo-controlled studies evaluating gabapentin use in paediatric spinal fusion patients. In the first study, 59 paediatric spinal fusion patients were randomized to receive preoperative gabapentin 15 mg/kg or placebo and the medication was continued for 5 days (Rusy et al. 2010). This study showed a reduction in morphine consumption postoperatively compared to the placebo group. In the other study the patients were given one single preoperative dose of gabapentin 600 mg one hour before surgery (Mayell et al. 2014). A single preoperative dose of gabapentin did not show a significant difference in opioid consumption or pain scores in adolescents undergoing idiopathic scoliosis surgery.

Our study was a randomized, double-blind, placebo-controlled clinical trial on 63 children and adolescents with spinal deformity undergoing posterior instrumented spinal fusion and completing the outcome parameters. The study was carried out according to international good clinical practice principles. The strengths of our study are a homogenous group of patients operated by the same experienced senior orthopaedic surgeon. The participation rate in the study was high and no drop outs occurred during study protocol. The study is a single-centre study with reliable data collection.

Based on our study results it seems that pregabalin cannot add value to the multimodal pain management in patients undergoing major spinal surgery. A bigger sample size would have been able to detect smaller differences between the groups, but such small difference would hardly be clinically relevant.

An extensive part of our intraoperative anaesthetic management aims to reduce postoperative pain. Both dexmedetomidine and betamethasone reduce the postoperative pain (Waldron et al. 2013, Wang et al. 2018). The additive effect of this multimodal pain management probably reduces the added value of pregabalin, and an opioid-sparing effect could not be detected. We did not want to reduce the drugs in the multimodal pain management of these study subjects. We aimed to treat the postoperative pain as well as possible. However, this multimodal approach may have reduced the assay sensitivity of this trial.

The negative findings of our study cannot be explained by under dosing. In our study protocol we intentionally decided to use a relatively high dose of pregabalin, in order to receive the maximum effect of the drug.

The neural plasticity of the spinal cord and nerve roots in children and adolescents may partly explain the different results in our study compared to previous adult studies. The ability to reconstruct neural elements and regenerate axons and neural circuits are greater in adolescents and especially in children than in adults. The healing of the inevitable neural damage in scoliosis surgery might be more rapid in children and the effect of pregabalin remains insignificant.

6.3. Persistent postoperative pain

The correction of the paediatric spinal deformities primarily aims to prevent curve progression and deterioration in pulmonary function. In recent years, patient's health-related quality of life, such as pain and satisfaction have increased in importance when evaluating surgical results. Persistent postoperative pain after spinal surgery in adolescents and children is infrequently reported and the literature around this subject is sparse. The surgical techniques have developed and in many of the earlier studies older surgical approaches, such as Harrington distraction rod or hook-based instrumentation have been used (Danielsson et al. 2001). The standard surgical technique today is posterior all-pedicle-screw surgery, but the long-term follow-up data after these surgeries is limited. The overall incidence of paediatric persistent postsurgical pain still remains poorly documented and variation in definition of persistent postsurgical pain makes it even more difficult (Nikolajsen and Brix 2014).

Our study patients with spinal deformity scheduled for posterior spinal fusion surgery reported significant preoperative pain. Thirty-one per cent of the patients rated their pain to be moderate to severe before surgery. Surgical treatment had a favourable effect on the experience of pain. The pain scores improved, and patients reported less pain after surgery both at 2-year and 5-year follow-up as compared to preoperative status. Clinical research of pain experience can be difficult, because the experience of pain is very subjective, and many psychological factors affect the sensation. In a review article, it was stated that evidence is lacking regarding the effect of surgery on the pain prevalence in patients with adolescent idiopathic scoliosis (Rodrigues et al 2017). The review included 16 cohorts with data on pain, and 81% of these reported postoperative improvements in pain 2 years after surgery. However, the improvement was considered clinically important only in one of the cohorts. Minimally clinically important difference (MCID) values has been published for SRS-22r in adolescents, but not for SRS-24. MCID threshold for SRS-22r pain domain has been set at 0.20 (Carreon et al. 2010). In our study the pain domain score improved by a mean value (95%CI) of 0.29 (0.07, 0.52). Also, the change in activity scores of the surgical cohort increased more than the MCID threshold (0.08). The increase in scores for self-image domain, did not reach threshold limits for clinical significance.

The prevalence of persistent postsurgical pain was 14% in our study, when defined as patient report of moderate to severe pain over the previous 6 months at 5 years after surgery. This is comparable to the results published by Sieberg, with an incidence of 17% moderate to severe pain at 5 years post-surgery in 69 patients (Sieberg et al.

2013). This is lower than that reported by Chidambaran. In that study, 42% of the patients reported moderate to severe pain one year after surgery with a sample size of 110 patients (Chidambaran et al. 2017). In both these studies pain reports were collected from patients undergoing spinal fusion surgery, one study used the pain question of SRS-30 and the other study used numerical rating scale. Fortier et al. documented a prevalence rate of 13% of chronic pain in children who had undergone various procedures in the previous year (Fortier et al. 2011). Another study found that 22% of children reported moderate to severe pain after major surgery (Pagé et al. 2013). The studies regarding chronic pain after surgery in children are limited and have often problems with small sample sizes and retrospective data. An association between preoperative pain and postoperative pain has been reported in prior studies (Bastrom et al. 2013, Sieberg et al. 2013). However, no association was found in the present study, nor was any association between opioid consumption 48 hours postoperatively and pain domain scores at 5 years postoperatively. Psychological factors were not evaluated in the present study, although such factors have been shown to affect postoperative pain (Connelly et al. 2014).

Because low back pain is commonly reported among healthy individuals, we wanted to compare the existence of pain in our surgically treated patients with a control group. The results from our homogenous cohort of surgically treated adolescent idiopathic scoliosis patients were compared to untreated patients with idiopathic scoliosis and healthy controls. To our knowledge, there are no previous study comparing pain in surgically treated adolescents to healthy controls in the same kind of setting. Twelve per cent of healthy patients in the control group reported moderate to severe pain over the past 6 months. The rate in the surgically treated group was 14%. This difference is not statistically or clinically significant. In contrast, the difference to the group with untreated individuals with idiopathic scoliosis was statistically and clinically significant. Fifty-one per cent of the untreated patients with idiopathic scoliosis reported moderate to severe pain over the same time period.

The group with untreated patients with scoliosis and healthy controls are obtained from Sweden. This could be a limitation of the study due to different cultural and ethnic background. We believe that the cultural differences are relatively small among the Nordic countries, and therefore the data is reliable and comparable.

The study has many strengths. It is a prospective single centre study with consecutively enrolled patients. They were all operated by the same senior surgeon and the surgical technique was identical, posterior spinal fusion surgery with pedicle screw only. We had very few losses at follow-up and the follow-up was minimum 5 years. We used validated standardized questionnaires and the data comprises of patients own reports and results which are compared to age and gender matched controls. A limitation of this study is the somewhat different questionnaires used (the SRS-24 and SRS-22r); however, we chose to keep the same original SRS-24 questionnaire in the surgical treatment group to provide data from preoperatively to 5 years postoperatively. Another limitation is that the study design had selection bias

because some patients chose surgical treatment and others opted for bracing/nonsurgical treatment, which may result in potential performance bias.

6.4. Postoperative urinary retention

In the fourth study of this thesis we evaluated the manifestation of postoperative urinary retention. We showed that almost half of the adolescents under 21 years of age had problems with postoperative urinary retention or difficulty to empty bladder after posterior spinal fusion. The main risk factors for these difficulties were male gender, long surgical time and larger intraoperative blood loss. The classification of the scoliosis affected the outcome, patients with double major curves had longer operation times and increased blood loss.

There is one previous study assessing postoperative urinary retention in children after orthopaedic surgery (Sherburne and Sawin 2008). In this study the time to empty bladder after orthopaedic surgery in the paediatric population was evaluated. According to the study 29% of the children needed catheterisation. None of the patient had urinary catheter during surgery. In other paediatric studies, the incidence has been reported to be 13 - 64% (Esmail et al. 1999, Alfheim et al. 2016). The incidence of postoperative urinary retention after spinal surgery in adults has been reported to be between 5.6% and 38% (Boulis et al. 2001, Gandhi et al. 2014, Altschul et al. 2016). The definition of postoperative urinary retention is variable, and the surgical procedures vary in the studies. The factors leading to urinary retention can be both of surgical origin (lesions to neural elements) and anaesthetic risks (anaesthetic management during surgery and postoperative pain management). In previous studies anaesthetic factors affecting postoperative urinary retention included intravenous fluid management, different anaesthetic techniques, the medication used and, postoperative analgesia (Baldini et al. 2009). Some studies suggest that the risk of postoperative urinary retention is increased when using patient-controlled analgesia (Petros et al. 1993).

The strength of our study is the prospective design in a homogenous patient population, and ultrasound scan is considered a reliable tool for estimating bladder volume (Baldini et al. 2009). The limitations of the study include non-standardised rules for catheter removal at the time and not fully standardised pain management. The definition of postoperative urinary retention in adults were used in our study, and this might underestimate the occurrence of residual bladder volume in children. In our study we could not estimate the correlation between opioid consumption and urinary retention due to unreliable documentation. This should be evaluated in future studies.

7. SUMMARY AND CONCLUSIONS

These studies help us to improve the perioperative management of children and adolescents after posterior instrumented spinal fusion. The conclusions of our studies are:

1. Preoperative pregabalin does not interfere with the intraoperative spinal cord monitoring and is safe to use as part of multimodal analgesia.

2. Perioperative pregabalin did not reduce the postoperative opioid consumption or pain scores in adolescents undergoing posterior instrumented spinal fusion compared to placebo group.

3. Surgical correction of adolescent idiopathic scoliosis improves back pain and health-related quality of life compared with untreated patients. The prevalence of back pain in the surgically treated patients did not statistically differ from that of healthy individuals. Patients in the surgically treated group had similar health-related quality of life to that of the healthy control group, except for function, which was significantly lower. There was no need for potent analgesic drugs in any patient at 2 and 5 year after surgery

4. Postoperative urinary retention or difficulty to empty the bladder is common (46%) in adolescent spinal surgery. Risk factors include male gender and enhanced intraoperative blood loss. Urinary retention needs active attention and treatment.

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Linda Helenius

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