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PAEDIATRIC SPINAL SURGERY AND PERIOPERATIVE MANAGEMENT

Tommi Yrjälä

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To Nella-Marie, Joonatan and Jenni-Marie

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ABSTRACT

The aim of this dissertation is to improve perioperative management of adolescent patients undergoing posterior spinal fusion surgery. Posterior spinal fusion surgery is one of the most common major surgical procedures in adolescents. It is the main surgical procedure performed in adolescents with adolescent idiopathic scoliosis, Scheuermann kyphosis, or spondylolisthesis.

The first part of this thesis was a randomised, double-blinded, and placebo-controlled clinical trial of 64 patients. The purpose of the first study was to determine whether perioperative pregabalin reduces the persistent pain in adolescent patients after posterior spinal fusion for spinal deformities compared to placebo. The second and third part of this thesis were retrospective analyses of a prospectively collected paediatric spine register. In the second study, 159 consecutive adolescent idiopathic scoliosis patients undergoing posterior spinal fusion were screened to determine the predictors of postoperative urinary retention. The third part of this thesis included 158 adolescent idiopathic scoliosis, 19 Scheuermann kyphosis, and 36 spondylolisthesis patients undergoing posterior spinal fusion surgery, with the aim of evaluating the predictors of acute and chronic pain.

In our first study, we showed that pregabalin did not affect the chronic postoperative pain two years after surgery, and there is no reason to combine pregabalin to a multimodal treatment protocol in adolescents undergoing posterior spinal fusion. In our second study, we revealed that postoperative opioid consumption after posterior spinal fusion was associated with an increased risk of postoperative urinary retention in adolescent idiopathic scoliosis patients, and multimodal pain management to reduce the opioid amount may be beneficial. The third publication of this thesis demonstrated that after posterior spinal fusion, acute postoperative pain was associated with more extensive tissue trauma (adolescent idiopathic scoliosis and Scheuermann kyphosis), and chronic pain was related to the disease pathology (spondylolisthesis). Multimodal analgesia may reduce the persistent pain, but an optimal treatment protocol is still not established, and more studies are needed.

KEYWORDS: adolescent idiopathic scoliosis, Scheuermann kyphosis, spondylolisthesis, postoperative urinary retention, postoperative pain

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TIIVISTELMÄ

Tämän väitöskirjan tavoitteena on parantaa nuorten selän luudutusleikkaus potilaiden perioperatiivista hoitoa. Selän luudutusleikkaus on yksi yleisimpiä laajaa kirurgiaa vaativista toimenpiteistä nuorilla. Se on yleisin kirurginen toimenpide, joka tehdään nuorille, joilla on idiopaattinen skolioosi, Scheuermannin kyfoosi tai spondylolisteesi. Suomessa tehdään vuosittain n. 250 selän luudutusleikkausta nuorille.

Tämän väitöskirjan ensimmäinen osatutkimus oli satunnaistettu, kaksoissokkoutettu ja lumekontrolloitu kliininen tutkimus 64 potilaalla. Ensimmäisen tutkimuksen tarkoituksena oli selvittää, vähentääkö perioperatiivinen pregabaliini kroonista kipua nuorilla selän luudutusleikkauksen jälkeen verrattuna lumelääkkeeseen. Toinen ja kolmas tutkimus olivat retrospektiivisiä analyysejä prospektiivisesti kerätystä lasten selkärekisteristä. Toisessa tutkimuksessa tarkastettiin rekisteristä 159 peräkkäisen selkäluudutetun nuoren idiopaattisen skolioosipotilaan tiedot. Tarkoituksena oli löytää virtsaummen esiintyvyys ja riskitekijät. Kolmannessa tutkimuksessa oli 158 nuorta idiopaattista skolioosi-, 19 Scheuermannin kyfoosi- ja 36 spondylolisteesipotilasta, joille oli tehty selän luudutusleikkaus. Tavoitteenamme oli selvittää, miten eri sairaudet vaikuttavat leikkauksen jälkeiseen akuuttiin ja krooniseen kipuun.

Ensimmäisessä tutkimuksessamme osoitimme, että pregabaliini ei vaikuttanut krooniseen leikkauksen jälkeiseen kipuun kaksi vuotta luudutusleikkauksen jälkeen, eikä ole mitään syytä yhdistää pregabaliinia multimodaaliseen hoitokäytäntöön nuorille selän luudutusleikkauksen jälkeen. Toisessa tutkimuksessamme osoitimme, että nuorilla idiopaattista skolioosia sairastavilla luudutusleikkauksen jälkeinen opioidien kulutus korreloi virtsaummen esiintyvyyden kanssa. Multimodaalisella kivunhoidolla saatetaan vähentää virtsaummen riskiä. Kolmannessa julkaisussa osoitimme, että selän luudutusleikkauksen jälkeinen akuutti kipu liittyi laajempaan kudostraumaan (nuorten idiopaattinen skolioosi ja Scheuermannin kyfoosi), ja krooninen kipu liittyi sairauden patologiaan (spondylolisteesi). Multimodaalinen kivunhoito vähentää akuuttia ja voi vähentää kroonista kipua, mutta optimaalista hoitokäytäntöä ei ole vielä löydetty, ja lisää tutkimuksia tarvitaan.

AVAINSANAT: Nuorten idiopaattinen skolioosi, Scheuermannin kyfoosi, spondylolisteesi, leikkauksen jälkeinen virtsaumpi, leikkauksen jälkeinen kipu

Table of Contents

Abbreviations

AIS	adolescent idiopathic scoliosis
ASA	American Society of Anaesthesiologists
BMI	body mass index
CEA	continous epidural analgesia
CI	confidence interval
EA	epidural analgesia
ERAS	enhanced recovery after surgery
FU	follow-up
GABA	γ-aminobutyric acid
IONM	intraoperative neurophysiologic monitoring
IV	intravenous
kg	kilogram
LOS	length of stay
MAC	minimum alveolar concentration
MAP	mean arterial pressure
MCID	minimum clinically important difference
mg	milligram
MEP	motor evoked potential
NSAID	non-steroidal anti-inflammatory drug
PACU	post anaesthesia care unit
PCA	patient-controlled analgesia
po	per oral
PONV	postoperative nausea and vomiting
POUR	postoperative urinary retention
PSF	posterior spinal fusion
SK	Scheuermann kyphosis
SSEP	somatosensory evoked potential
SRS-24	Scoliosis Research Society 24-item questionnaire
SD	standard deviation
TIVA	total intravenous anaesthesia
VAS	visual analogue scale

List of Original Publications

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

I Helenius L, Yrjälä T, Oksanen H, Pajulo O, Löyttyniemi E, Taittonen M, Helenius I. Pregabalin and Persistent Postoperative Pain Following Posterior Spinal Fusion in Children and Adolescents: A Randomised Clinical Trial. *Journal of Bone and Joint Surgery* 2021; 23: 2200-2206.

II Yrjälä T, Helenius L, Taittonen M, Oksanen H, Keskinen H, Kolari T, Helenius I. Predictors of Postoperative Urinary Retention after Posterior Spinal Fusion for Adolescent Idiopathic Scoliosis. *European Spine Journal* 2021; 30: 3557-3562.

III Yrjälä T, Helenius I, Rissanen T, Ahonen M, Taittonen M, Helenius L. The Extension of Surgery Predicts Acute Postoperative Pain, while Persistent Postoperative Pain is related to the Spinal Pathology in Adolescents undergoing Posterior Spinal Fusion. *Children* 2022; 9:1729.

1 Introduction

Adolescent idiopathic scoliosis (AIS) is defined as an abnormal lateral curvature of the spine in the coronal plane of 10˚ or more according to the Cobb method in children aged between 10 and 18 years (Cobb 1948). Scheuermann kyphosis (SK) is a thoracic spine kyphosis due to a growing disorder resulting in three or more wedged vertebrae (Sorenson 1964). Spondylolisthesis is defined as an anterior displacement of the vertebral body, in children mainly due to bilateral spondylolysis (isthmic spondylolisthesis) or due to a congenital deficiency of the posterior elements (dysplastic spondylolisthesis) (Wiltse et al. 1976). The definite aetiologies of AIS, SK, and spondylolisthesis remain unclear. Most of the adolescent patients with moderate AIS or SK or low-grade spondylolisthesis can be treated conservatively. Nonetheless, those are the main reasons for spinal surgery in adolescents with more severe deformity. The main operative treatment for AIS, SK, and spondylolisthesis is nowadays posterior spinal fusion (PSF), which is the most common major surgical procedure performed in children and adolescents. In Finland, approximately 250 PSF surgeries are performed every year in adolescents. There is a lack of standard perioperative management for patients with paediatric spinal surgery, and this study aims to improve their perioperative treatment.

Pain control after PSF is challenging, with no standard multimodal pain management. Prolonged pain increases financial costs and impairs quality of life, and it is therefore necessary to study acute and chronic pain to improve our perioperative treatment. Multimodal pain management includes combining differently acting pain medicines, such as paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, gabapentinoids, dexmedetomidine, and ketamine (Lee et al. 2020; Jitpakdee and Mandee 2014; Naduvanahalli Vivekanandaswamy et al. 2021). It also includes central neuraxial (epidural and spinal) and peripheral blocks as well as non-pharmacological methods, such as an icepack, support from relatives, music, and sometimes psychological therapy (Lee et al. 2020; Tan et al. 2015). The goal of multimodal pain treatment is to improve patient satisfaction and to reduce opioid-related adverse events, such as urinary retention, respiratory depression, and opioid addiction. Despite the multimodal analgesia, opioids are the mainstay in postoperative pain control after PSF. Although

multimodal pain management has been studied widely, there is still no gold standard for pain treatment after spinal surgery in adolescent patients. Multimodal analgesia studies in adolescent spinal surgery have involved central neuraxial opioids, patients-controlled analgesia, NSAIDs, paracetamol, ketamine, gabapentinoids, local anaesthetics, intravenous lidocaine infusions, erector spinae blocks, muscle relaxants, and dexmedetomidine (Lee et al. 2020; Naduvanahalli Vivekanandaswamy et al. 2021; Sheffer et al. 2017). The first part of this study assessed pregabalin and chronic postoperative pain, and the third part of this thesis aimed to find predictors of acute and chronic pain in adolescent patients after spinal surgery.

2 Review of the Literature

2.1 The spine and adolescent spinal deformities

The most common malformations of the spine in childhood and adolescence are AIS, SK, and spondylolisthesis (Schlenzka 1999; Boachie-Adjei and Lonner 1996). All these diagnoses can also be associated with back pain in the adolescent patients. Other, less common causes of spine malformations or back pain in adolescents include neuromuscular disorders, tumours, and infections. Back pain is common in adolescents, and over half of all adolescents experience back pain. Benign muscle strains and growth pain cause most of the back pain in adolescents and children (srs.org). The treatment for most of the spinal deformities in the paediatric population is conservative (Boachie-Adjei and Lonner 1996). Conservative treatment includes regular follow-up (FU), NSAIDs, physiotherapy, and brace treatment.

The spine consists typically of 33 vertebrae, facet joints, intervertebral discs, and spinal cord and nerves. Cervical spine has seven vertebrae (C1-C7), thoracic spine has 12 vertebrae (Th1-Th12), lumbar spine has 5 vertebrae (L1-L5), sacrum has 5 fused vertebrae (S1-S5), and coccyx has 4 fused vertebrae. The openings in the vertebrae form the spinal canal, where the spinal cord and nerves are protected. The vertebrae of the spine are connected to each other by disc spaces and facet joints. Facet joints are cartilage surfaces through which the lower vertebral branches on the side of the vertebrae attach to the upper vertebral columns. Facet joints enable twisting and turning. Intervertebral discs are located between the vertebrae. They allow the bending and twisting, receive the load on the spine and distribute it over a larger area. Spinal cord is a column of nerves in the spinal canal that extends from the skull to the lower back. In the spine, there are also ligaments and muscles to support the back.

The spine normally has three curvatures in the sagittal plane (cervical, thoracic, and lumbar), and these normal curvature limits need to be known before looking at spinal deformities. In the coronal plane, there should be no deviation from the midline, and under 10-degree curvature is considered to be within normal limits. Lordosis is the forward curvature of the spine (neck and lower back), and kyphosis is the backward curvature of the spine (thoracic). Normal thoracic kyphosis range is

20 to 45 degrees, and lumbar lordosis range is 25 to 60 degrees in paediatric spine (Lenke et al. 2001). There is normally no rotation of the spine (Boachie-Adjei and Lonner 1996).

2.1.1 Adolescent idiopathic scoliosis

AIS is a coronal curvature of the spine measuring 10˚or more according to the Cobb angle (Cobb 1948), appearing in patients over the age of ten years without other associated conditions (Raudenbush et al. 2017). The aetiology of AIS is unknown, but is has been observed that genetic factors influence the incidence of AIS (Weinstein et al. 2008).

The prevalence of AIS worldwide is about 1–3% in the adolescent population. 0.4% of these deformities need treatment and only a fraction require surgical treatment (Weinstein 2019; Konieczny et al. 2013; Hresko 2013; Weinstein et al. 2008; Zhang et al. 2015). In Finland, the prevalence of AIS is 9% in the adolescent population, and 0.2% need to be treated (Helenius I. 2020). AIS is the most common indication for major surgery among children in the United States (Healthcare Cost and Utilization Project 2017). In 2009 in the United States, over 500 million dollars were spent on spinal surgery to correct AIS (Weinstein et al. 2013). Operative treatment of AIS is increasing (Raudenbush et al. 2017; Vigneswaran et al. 2015) and in 2012, the cost associated with operative treatment of AIS was over 1,000 million dollars (Vigneswaran et al. 2015). According to Vigneswaran et al. (2015), inpatient hospital charges for spine surgery in AIS patients have increased considerably in the United States, from 228 million dollars in 1997 to 1,132 million dollars in 2012.

AIS patients can be asymptomatic or suffer from back pain. Incidence of back pain in AIS patients is 23–54% (Ramirez et al. 1997; Sieberg et al. 2013; Théroux et al. 2015; Djurasovic et al. 2018; Fekete et al. 2019). Other negative consequences of scoliosis include curve progression, pulmonary dysfunction, and negative impacts on self-image (Vigneswaran et al. 2015).

Most patients are under regular FU. When curve progression exceeds 25 degrees, bracing (orthosis) is the first choice of treatment provided that the patient has growth left (less than one year after menarche) (Weinstein et al. 2008). When the spinal curve exceeds 45 degrees, surgery is recommended to prevent further curve progression (Hresko 2013; Weinstein et al. 2008; srs.org). Posterior instrumentation with pedicle screws is the most common procedure performed nowadays for AIS (Weinstein et al. 2008). The primary goals of surgery in AIS are correction of the curve and prevention of its progression (Fekete et al. 2019) (Figure 1). Untreated AIS can lead to pulmonary complications by reducing lung volume, increase the risk of back and radicular pain, and lower self-image by the cosmetic aspect (Weinstein

2019). A study by Helenius et al. (2019) found that 5 years after PSF in AIS patients, the patients had better health-related quality of life and less pain compared to untreated AIS patients. There is paucity of how treatment regimens affect long-term health-related quality of life; and differences in skeletal maturity, the degree of the deformity, as well as changes in indications and surgical methods over time distort any comparison of treatment techniques (Ragborg et al. 2023).

The Lenke classification system is used to define spinal fusion levels in AIS. It is arranged according to curve type 1-6 with a lumbar spine modifier (A-C) and a sagittal thoracic modifier (-, N, +). 1 is main thoracic curve, 2 is double thoracic curve, 3 is double major curve, 4 is triple major curve, 5 is single thoracolumbar/lumbar curve, and 6 is thoracolumbar/lumbar –main thoracic double curve (Lenke et al. 2001).

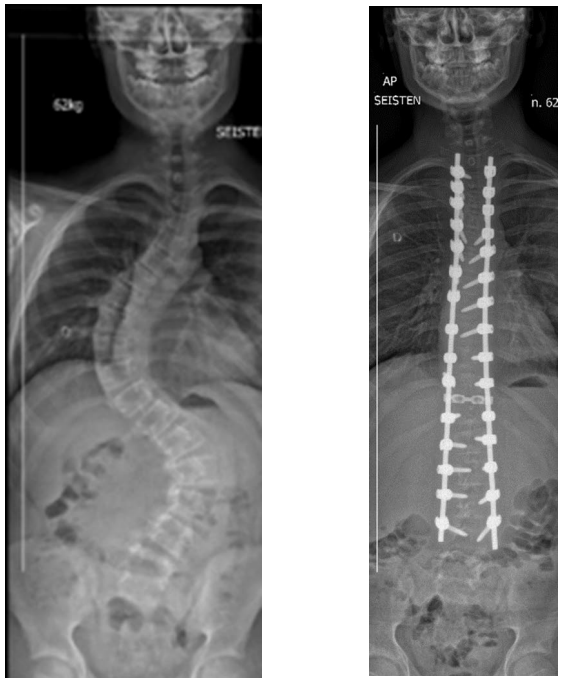

Figure 1. Adolescent idiopathic scoliosis patient before and after correction. Reprinted without identification data, personal register.

2.1.2 Scheuermann kyphosis

SK (Figure 2) is named after Dr Holger Werfel Scheuermann, who first described this rigid thoracic kyphosis in adolescents in 1920 (Scheuermann 1920). In 1964, Sorensen defined the classic diagnostic criteria for SK: three or more wedged (wedging of at least 5 degrees) vertebrae in the thoracic spine (Horn et al. 2019).

Additional imaging findings include endplate irregularities, Schmorl's nodes, and flattening of the intervertebral disc spaces (Boachie-Adjei and Lonner 1996). The aetiology of SK is unknown, but a genetic component has been found (Horn et al. 2019; Arlet and Schlenzka 2005; Boachie-Adjei and Lonner 1996; Wenger and Frick 1999; Schlenzka 1999; Lowe 1990; Palazzo et al. 2014). The incidence of SK is 0.04% to 10% of the general population (Horn et al. 2019; Arlet and Schlenzka 2005; Boachie-Adjei and Lonner 1996; Schlenzka 1999; Sardar et al. 2019; Lowe 1990). In the adolescent population, SK is one the most common reasons for back pain (Horn et al. 2019).

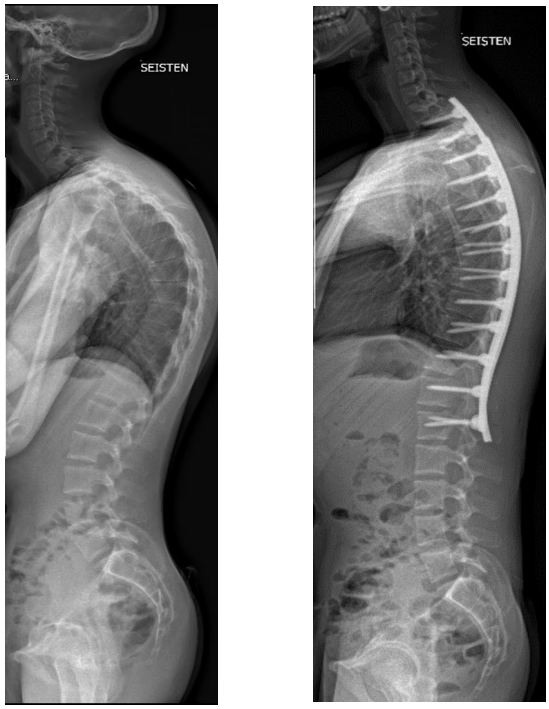

Figure 2. Scheuermann kyphosis before and after surgical management. Reprinted without identification data, personal register.

Conservative treatment with exercises and bracing is the first choice and is typically indicated during the growth period when thoracic kyphosis exceeds 60˚ and the radiological signs of the disease are present (Arlet and Schlenzka 2005; Schlenzka 1999). There is a lack of evidence-based criteria for indication of surgery, except in very rare cases with neurological complications, i.e., radicular pain, progressive weakness of the lower limbs, or paraparesis (Arlet and Schlenzka 2005). In severe kyphosis of more than 75–80˚, surgical treatment may be indicated, especially if the patient suffers from back pain (Arlet and Schlenzka 2005; Sardar et al. 2019; Palazzo

et al. 2014; srs.org). Severe kyphosis of 90˚ or more is associated with decreased pulmonary function (Abbi et al. 2014). Posterior approach procedure is currently the most common type of surgery in SK patients (Horn et al. 2019; Sardar et al. 2019; Tsirikos and Carter 2021).

2.1.3 Spondylolysis and spondylolisthesis

The terms spondylolysis and spondylolisthesis are derived from Greek: *spondylos* means vertebra, *lysis* means to break or defect, and *listhesis* means dislocation or slipping (Lonstein 1999). Spondylolysis is defined as a fracture in the pars interarticularis of the vertebra and occurs mostly in the fifth lumbar vertebrae (Fredrickson et al. 1984; Gagnet et al. 2018; Lonstein 1999). Spondylolysis may lead to spondylolisthesis if spondylolysis is bilateral and does not achieve bony union. The aetiology of spondylolysis is unknown. Spondylolysis is considered to be partially acquired and in some way genetic (Lonstein 1999). The caudal edge of the inferior articular facet of the L4 contacts the pars interarticularis of the L5 during repetitive extension and flexion, which results in microtrauma. This is supported by the higher prevalence of spondylolysis in athletes of specific sports, such as gymnastics, soccer, diving, and ice hockey (Lonstein 1999; Beck and Simpson 2019; Tsirikos and Garrido 2010). Most spondylolysis patients are asymptomatic (Gagnet et al. 2018). When symptoms are present, the most common symptom is low back pain that worsens during exercise. Conservative treatment is the main method and includes NSAIDs, restrictions of sports, physical therapy, and sometimes bracing (Gagnet et al. 2018; Beck and Simpson 2019).

Spondylolisthesis is defined as the forward translocation of one vertebral segment over the one beneath it (Figure 3). Spondylolisthesis occurs most frequently at the L5-S1 segment in adolescents (Cavalier et al. 2006; Beck and Simpson 2019). Spondylolisthesis can be classified according to the Meyerding classification in five grades: grades 1 to 2 are low-grade and grades 3 to 5 are high-grade (Beck and Simpson 2019). Grade 1 is a slip of up to 25%, grade 2 is a slip of 26% to 50%, grade 3 is a slip of 51% to 75%, and grade 4 is a slip of 76% to 100%. Grade 5 (spondyloptosis) is a complete dislocation of L5 in front of the sacrum (slippage over 100%) (Meyerding 1932). The Wiltse classification is another most frequently used spondylolisthesis classification. This classification describes aetiology and morphology and has five (six) major types. Type 1 is dysplastic (congenital malformation of the sacrum or neural arch of L5), 2 is isthmic (stress fracture, elongation, or acute fracture of the pars interarticularis), 3 is degenerative (in older adults), 4 is traumatic, 5 is pathologic (Paget's, metastatic disease), and 6 is iatrogenic (after lumbar spine surgery) (Wiltse et al. 1976). Of them, type 1 dysplastic and type 2 are typical in paediatric patients.

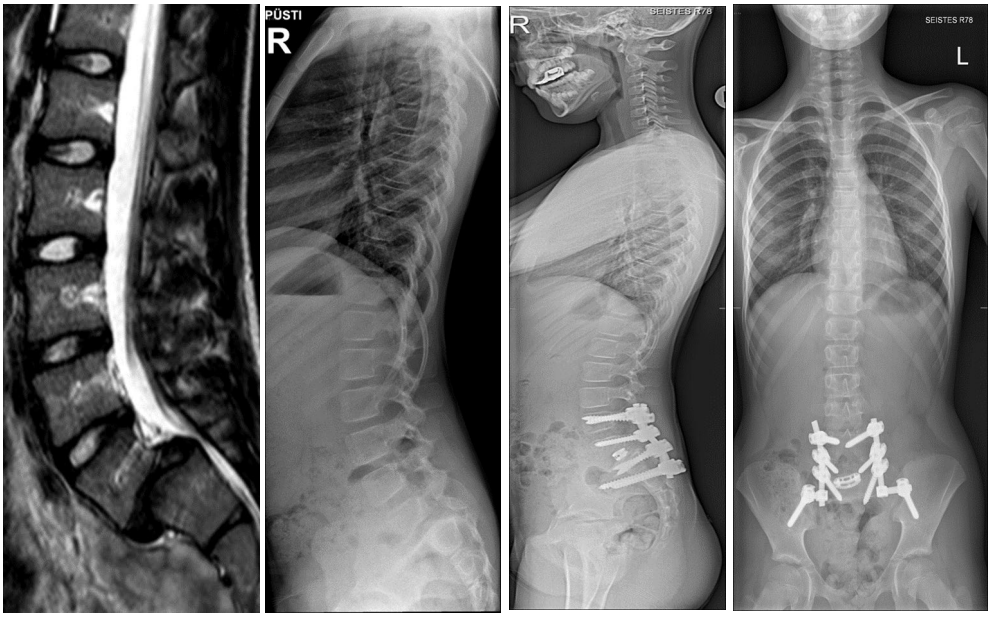

Figure 3. Spondylolisthesis before and after surgical management. Reprinted without identification data, personal register.

The incidence of asymptomatic spondylolysis and spondylolisthesis is 6–11% in the general population (Herman and Pizzutillo 2005; Tsirikos and Garrido 2010). In adolescence, vertebral displacement is usually associated with a stress fracture of the posterior arch of the vertebra. On the contrary in older people, vertebral displacement is usually a result of degenerative changes. The prevalence of asymptomatic degenerative spondylolisthesis increases with age: 3% in 20 years old, 8% in 40 years old, 23% in 60 years old, and 50% in 80 years old (Brinjikji et al. 2015).

Spondylolisthesis is one of the leading causes for low back pain in the adolescent population and may lead to radicular symptoms – even cauda equina may occur in the dysplastic type (Schoenleber et al. 2015; Gagnet et al. 2018; Schlenzka 1999; Herman and Pizzutillo 2005). Low-grade asymptomatic spondylolisthesis does not need any treatment. Low-grade spondylolisthesis with symptoms can be treated conservatively like spondylolysis (Gagnet et al. 2018; Beck and Simpson 2019). Operative treatment is indicated in spondylolisthesis patients when pain persists despite conservative treatment, or in the presence of a neurologic deficit (Schoenleber et al. 2015; Cavalier et al. 2006; Lonstein 1999; Tsirikos and Garrido 2010; Bourassa-Moreau et al. 2019). High-grade spondylolisthesis in growing children can progress and usually needs to be treated surgically (Cavalier et al. 2006; Lonstein 1999; Schlenzka 1999; Herman and Pizzutillo 2005; Tsirikos and Garrido 2010). A study by Lundine et al. (2104) found that 10 of 25 patients with

asymptomatic or minimally symptomatic high-grade spondylolisthesis patients needed surgery after "watchful waiting". The main aim of operative treatment is to provide a solid fusion and to achieve adequate nerve root decompression (Schoenleber et al. 2015; Beck and Simpson 2019). After PSF, there is loss of motion segments, but usually these patients function well (Lonstein 1999).

2.2 Scoliosis Research Society Outcome Questionnaire and Visual Analogue Scale

The Scoliosis Research Society questionnaire (SRS-24) is a disease specific health-related quality of life questionnaire, which was designed for patients with adolescent idiopathic scoliosis (Haher et al. 1999). The SRS-24 questionnaire is also used for other paediatric spinal surgery patients (Helenius et al. 2005; Virkki et al. 2020). Patients complete the SRS-24 questionnaire preoperatively, at 6 months, and at 2 years postoperatively. The SRS-24 questionnaire has 7 domains: pain, general self-image, general function, general activity, postoperative self-image, postoperative function, and patient satisfaction. The score in each field ranges from 1.0 to 5.0, with higher scores indicating better patient outcomes. A score under 4 in the pain domain is considered to be clinically relevant and indicates moderate to severe pain (Djurasovic et al. 2018). Questions one and two present an answer ranges from 1 to 9, where 1 is no pain and 9 is severe pain. The answer from 1 to 9 is then converted to the 1 to 5 scale (1–2 is 5, 3–4 is 4, 5 is 3, 6–7 is 2 and 8–9 is 1). Question one is: How much pain you have had in the last 6 months? Question two is: What is your worst pain in the previous month? The maximum score of the SRS-24 questionnaire is 120. Questions from 16 to 24 are related to the treatment and can therefore only be answered after surgery. Carreon et al. (2010) determined the minimum clinically important difference (MCID) in Scoliosis Research Society-22 appearance and pain domains after surgical correction of AIS. The MCID in the pain domain was 0.20 and in appearance the MCID was 0.98.

The visual analogue scale (VAS) is a 100 mm long pain rating scale. On the left side is 0 mm meaning no pain and on the right side is 100 mm meaning the worst pain. It was first used by Hayes and Patterson in 1921. The following cutting points of pain have been recommended: 0–4 mm = no pain, 5–44 mm = mild pain, 45–74 mm = moderate pain, and 75–100 mm = severe pain (Hawker et al. 2011).

2.3 Perioperative treatment in paediatric spine surgery

PSF is a major surgery in adolescent patients. Before surgery, patients are afraid of postoperative pain, being awake during operation, and possible complications. The

goal of anaesthesia is to keep the patient unconscious, immobile, and painless during the procedure in order to provide the best possible surgical conditions for the surgeon and maintain normal vitals in the patient.

2.3.1 Intraoperative management

2.3.1.1 Neuromonitoring during surgery

Spinal surgery has special complication risks when operating near the spinal cord and nerve roots and while correcting the spinal deformity. Spinal cord or nerve roots may be damaged in direct contact with the instruments or due to stretching when straightening the spine. The spinal cord can also be damaged due to inadequate spinal cord perfusion. Intraoperative neurophysiological monitoring (IONM) reduces the risk of new neurologic deficits in idiopathic scoliosis correction (Nassef et al. 2021). The idea of neurophysiological monitoring is to detect threatening neural damages before they occur and while the surgical manoeuvres can be reversed (Helenius et al. 2018). During correction of spinal deformities, the standard of care should be IONM (Tsirikos et al. 2020; Kundnani et al. 2010). IONM includes somatosensory evoked potentials (SSEP), motor evoked potentials (MEP), and lumbar nerve root electromyography. In a study by Tsirikos et al. (2020), the multimodal IONM technique had a sensitivity of 100% and a specificity of 99.3% for spinal cord injuries during spinal deformity surgery, which was similar to the results by Kundnani et al. (2010). Anaesthetic management greatly affects IONM. The anaesthesiologist should balance traditional requirements of anaesthesia, analgesia, and non-movement in order to enable detection of IONM changes during the procedure (DiCindio and Schwartz 2005). All inhalational anaesthetic agents disturb IONM with increasing dose, and for that reason total intravenous anaesthesia (TIVA) is the main method for maintaining anaesthesia in spinal deformity surgery (DiCindio and Schwartz 2005). Other factors affecting IONM include body temperature, patient height and weight, hypotension, and even other electrical equipment in the operating room (Helenius et al. 2018). In their study, Chong and colleagues (2014) found that sevoflurane suppresses MEP amplitudes more than desflurane in a dose-dependent manner, though they both depressed MEP amplitudes. Even a low concentration of sevoflurane (Minimum alveolar concentration [MAC] 0.3) significantly depressed MEP amplitudes. Desflurane concentration at a level of 0.5 MAC depressed the MEPs. Studies on dexmedetomidine's impact on IONM are contradictory. In two studies (Holt et al. 2020; Lee et al. 2019), dexmedetomidine had a negative impact on IONM. However, in a randomised controlled trial conducted by Li et al. (2016), the addition of dexmedetomidine to propofol-remifentanil infusions did not have a negative impact on IONM. Propofol preserves cortical SSEP amplitudes better and

provides a deeper level of hypnosis compared to small-dose isoflurane (Clapcich et al. 2004). TIVA should be routinely used to optimise neuromonitoring with MEPs during spine surgery (Wilent et al. 2021). Remifentanil has no significant effect on IONM at therapeutic concentrations (DiCindio and Schwartz 2005). To avoid neurological deficits during surgery, there should be close cooperation between the surgical, anaesthetic, and neurophysiology teams (Tsirikos et al. 2020; DiCindio and Schwartz 2005).

2.3.1.2 Anaesthetic management

Volatile anaesthetic agents (sevoflurane, desflurane, and isoflurane) induce anaesthesia by reinforcing gamma-aminobutyric acid (GABA) acting on GABAa-receptors. Volatile anaesthesia agents are not used in maintenance of anaesthesia in spinal deformity surgery, as they have a dose-dependent negative impact on IONM (Chong et al. 2014), although Martin et al. (2014) determined in a small patient sample (30 adolescents) that use of volatile anaesthesia is feasible even during neurophysiological monitoring. Volatile anaesthetic agents are greenhouse gases, especially desflurane, the use of which is continuously decreasing because of global warming.

Total intravenous anaesthesia with propofol and remifentanil is the gold standard for maintenance of anaesthesia in spinal deformity surgery. Propofol does not affect IONM as much as volatile anaesthetic agents (Clapcich et al. 2004). According to current knowledge, propofol induces anaesthesia by the same mechanism that volatile anaesthesia agents, affecting the GABAa-receptors.

Dexmedetomidine is a highly selective centrally acting α2-adrenergic agonist. It is a sedative drug that also has analgesic effects. It induces sedation by decreasing activity of noradrenergic neurons in the locus coeruleus of the brain stem, which leads to the increase of the downstream activity of inhibitory gamma-aminobutyric acid (GABA) neurons. Dexmedetomidine is not a sufficiently effective anaesthetic for surgery alone but used as an addition to total intravenous anaesthesia. Its disadvantage is the possible negative impact on IONM. Holt et al. (2020) performed a retrospective study of 30 paediatric patients who were administered a dexmedetomidine infusion of 0.5 µg/kg/h, 10 patients who were administered 0.3 µg/kg/h, and 30 control patients. They found that dexmedetomidine infusion at these doses decreases MEP amplitude during paediatric PSF surgery. Also, in a retrospective study by Lee et al. (2019) with 78 patients (40 patients in the dexmedetomidine group and 38 controls) who underwent brain tumour surgery with IONM found that the dexmedetomidine group (0.5 µg/kg/h) required significantly higher intensity and repetition rate of transcranial electric simulation to evoke adequate MEPs. However, in a randomised controlled trial of 71 patients conducted

by Li et al. (2016), adding a dexmedetomidine infusion of 0.5 µg/kg/h to propofol-remifentanil infusions did not have a negative impact on IONM. Dexmedetomidine can be used postoperatively and has been shown to reduce opioid requirements after PSF (Naduvanahalli Vivekanandaswamy et al. 2021).

Remifentanil is a very fast and short-acting opioid: its effects start approximately one minute after administration, and the effect disappears in 5 minutes after stopping the infusion. It is often used in combination with propofol for spinal fusion surgery to facilitate IONM and to enable the wake-up test when necessary (Lee et al. 2020). Theoretically, remifentanil could have negative effects on postoperative pain by triggering opioid induced hyperalgesia (Lee et al. 2020). However, in a retrospective study of 78 AIS patients undergoing PSF (Lo et al. 2021) and in a retrospective study of 142 AIS patients undergoing spine surgery (Aoki et al. 2021), no relationship was found between the dose of intraoperative remifentanil and postoperative opioid consumption. Intraoperative ketamine (Joly et al. 2005) and dexmedetomidine (Wu et al. 2021) have been shown to reduce remifentanil induced hyperalgesia. In a case report by Erb et al. (2005), ketamine had a positive effect on intraoperative evoked potentials compared to propofol in one child. On the contrary, a randomised, placebo-controlled study by Furutani et al. (2021) revealed that a ketamine bolus of 1 mg/kg can reduce MEP amplitudes.

A muscle relaxant can be administered in small doses at induction of anaesthesia, as long as its effect has passed when IONM is running.

2.3.2 Enhanced recovery after surgery

Enhanced recovery after surgery (ERAS) protocols are multimodal strategies to facilitate recovery after surgery and to decrease the length of hospital stay (LOS) (Julien-Marsollier et al. 2020; Yang et al. 2021). The goal of ERAS protocols is to improve patient care and satisfaction and to reduce the financial burden related to increased LOS (Gadiya et al. 2021). ERAS protocols can be divided into preoperative, intraoperative, and postoperative interventions (Koucheki et al. 2021; Gadiya et al. 2021; Debono et al. 2021; Pennington et al. 2021). Preoperative strategies include educating patients and families, physiotherapy, nutrition, mental health assessments, fasting minimisation, and carbohydrate loading (Koucheki et al. 2021; Gadiya et al. 2021; Julien-Marsollier et al. 2020; Yang et al. 2021; Debono et al. 2021; Pennington et al. 2021). Preoperative education of ERAS patients and their parents includes enhanced recovery principles, discharge criteria, FU scheme, and patient expectations in addition to the general information about surgery (Yang et al. 2021). Preoperative nutritional interventions should be used if the patient is considered malnourished (Debono et al. 2021), and the fasting period before operation should be kept as short as possible; clear fluid should be permitted for up

to one (two) hour(s) and solid foods for up to six hours before the surgery. Oral carbohydrate loading may be useful before spine surgery, but the evidence is currently insufficient (Debono et al. 2021). Intraoperative strategies involve standardised prevention and treatment of postoperative nausea and vomiting (PONV) as well as strict perioperative temperature control, multimodal opioid-sparing anaesthesia, and optimal fluid management (Julien-Marsollier et al. 2020; Yang et al. 2021; Debono et al. 2021; Pennington et al. 2021). Two consultant surgeons are used to operate for reducing the surgical time and blood loss. The use of cell salvage to reduce the need for allogenic red blood cell transfusion is recommended (Gadiya et al. 2021; Pennington et al. 2021). Prevention of PONV should be routinely used by dual antiemetic prophylactic therapy, including ondansetron and dexamethasone and necessary metoclopramide if nausea and vomiting occurs (Yang et al. 2021). Normothermia is maintained through pre-warming and active warming of patients intraoperatively as well as continuous intraoperative temperature monitoring (Debono et al. 2021). During surgery, multimodal anaesthesia includes propofol, remifentanil, and dexmedetomidine infusions and avoidance of neuromuscular blocking agents (Yang et al. 2021; Julien-Marsollier et al. 2020). Fluid management during surgery should be restricted, and the use of cell salvage and tranexamic acid bolus/infusion to reduce the need for allogenic red blood cell transfusions should be the standard of care in ERAS protocols (Yang et al. 2021; Julien-Marsollier et al. 2020). Postoperative protocols include rapid physiotherapy, rapid feeding, oral medication as soon as possible, multimodal analgesia to reduce opioid amounts, and early mobilisation as well as removal of urinary catheters and surgical drains (Julien-Marsollier et al. 2020; Lee et al. 2020; Yang et al. 2021; Koucheki et al. 2021; Shah et al. 2020; Gadiya et al. 2021; Debono et al. 2021; Pennington et al. 2021). There is a lack of an optimal standardised ERAS protocol for adolescent patients undergoing PSF. Preliminary data suggests that ERAS protocol implementation may result in better outcomes for paediatric patients with scoliosis (Pennington et al. 2021). In a study by Yang et al. (2020), 80% of the patients felt that their time of discharge was appropriate, and there was no correlation between patient satisfaction and LOS. The disadvantages of and the rapidly developing addiction to opioids are nowadays understood. The ERAS protocols and particularly the multimodal pain management aim to reduce the need for opioids and thus reduce their adverse effects.

2.3.3 Postoperative urinary retention

Postoperative urinary retention (POUR) is one the known adverse effects of opioids. The definition of POUR is an inability to urinate in the presence of a full bladder following surgery or a significant amount of residual volume after voiding (Baldini

et al. 2009; Boulis et al. 2001). However, the definition of POUR varies greatly between studies: it can be defined by length of inability to void (8–12 hours after surgery), by clinical symptoms and catheterisation, or by measurement of the urinary bladder volume or residual urine volume after surgery using ultrasound (Baldini et al. 2009). This great variation in the definition of POUR leads to variation in the incidence of POUR in the published data, which is 5–70% (Baldini et al. 2009). The urinary bladder capacity of adults is generally 300–600 mL (Baldini et al. 2009; Altschul et al. 2017; Keskinen et al. 2018; Sherburne and Sawin 2008; Rosseland et al. 2002; de Boer et al. 2017). For children aged 4 to 12 years, urinary bladder capacity is calculated with the formula (30*[age in years +1]mL) (Austin et al. 2016). POUR has been shown to prolong LOS, to increase the risk of urinary tract infection, and to lead to over distention of the detrusor muscle when left untreated (Baldini et al. 2009; Boulis et al. 2001; Altschul et al. 2017; Knight et al. 2020; Jackson et al. 2019; Golubovsky et al. 2018). POUR affects almost every third patient undergoing PSF for AIS (Keskinen et al. 2018). The aetiology of POUR is multifactorial, with opioids and male gender being known risk factors. It is unclear whether spinal deformity correction itself increases the risk of POUR. There is a lack of clear definition and management of POUR in the paediatric population, and therefore there is great variability in the results and conclusions among studies on POUR.

Urinary catheter is placed routinely in every patient undergoing PSF for AIS or SK in our Department of Paediatric and adolescent surgery and orthopaedics at the Turku University Hospital. There is also a lack of research exploring the convenient and clinically optimised time of urinary catheter removal after PSF.

2.4 Adolescent spinal deformities and pain

After a surgical procedure, substantial tissue trauma causes postoperative pain with nociceptive, neuropathic, and inflammatory components (Seki et al. 2018; Helenius 2019). Pain is produced by nociceptors found in the skin, muscles, fascia, ligaments, vertebrae, and facet joint capsules. Spinal surgery involves adjusting and stretching of the spinal cord, nerve roots, and spine. Additionally, these parts may experience hypoxia and insufficient perfusion, which could result in neuropathic pain following surgery. Direct damage or contusion with the instrument on the nerve root caused by the surgeon could also result in neuropathic pain.

Inflammation is always the result of tissue damage. Pro-inflammatory substances such bradykinin, histamine, cytokines, and prostanoids are released by damaged cells. Some of these inflammatory mediators influence the modulation of pain in dorsal root ganglion and directly on nociceptors (Helenius 2019).

Experiencing pain is multifactorial and individual, as all patients are psychophysical social entities and experience pain differently. The experience of the

intensity of pain is influenced by emotional factors, previous pain experiences, and hereditary factors (Olkkola et al. 2021; Kalso et al. 2018).

Back pain in healthy adolescents and children is common, and one-year prevalence rates vary between 7% and 58%. Although children's back pain is usually benign, the pathologies (malignancy and spondylodiscitis) must not be missed (Altaf et al. 2014; Virkki et al. 2021; Calvo-Muñoz et al. 2013). In infection, there might be fever and weakness. In malignancies, the symptoms can be diverse. Malignancies are very rare in children and adolescents, and usually when back pain is present, malignancies are not remembered as a differential diagnostical option (Helenius and Krieg 2021). The lack of clear definition and delimitation of back pain and its frequency, intensity, and duration explains the great variation of back pain prevalence in the studies (Calvo-Muñoz et al. 2013). Low back pain during and after physical activity is typical of acute paediatric spondylolysis (Virkki et al. 2023) and midscapular pain in Scheuermann kyphosis (Suominen et al. 2022).

2.4.1 Preoperative pain

AIS was previously considered to be a painless condition, but it is now known that patients with AIS have more back pain compared to healthy adolescents. Approximately one third of patients undergoing surgery for AIS have significant back pain, a pain score over 3/9 in the SRS-24 questionnaire question 1 (1 = no pain and 9 = severe pain) (Helenius et al. 2019). After deformity correction, back pain is statistically and clinically significantly decreased (Fekete et al. 2019; Helenius et al. 2019; Landman et al. 2011). There is no correlation between preoperative back pain and the coronal curve magnitude (Fekete et al. 2019). Older age, higher BMI, and larger proximal thoracic curve are all associated with higher preoperative pain in AIS patients (Landman et al. 2011).

Most paediatric spondylolisthesis patients have preoperative pain. The main indication for operative treatment in spondylolisthesis is pain as well as prevention of progression in patients with a high-grade slip (Helenius et al. 2008). Similar to spondylolisthesis, pain is also an indication for surgery in SK patients (although not as dominant) and therefore, many SK patients have preoperative pain (Arlet et al. 2005; Wenger et al. 1999; Green et al. 2020).

2.4.2 Acute postoperative pain

AIS patients undergoing PSF experience moderate to severe pain after the operation: the mean pain score in PACU (post anaesthesia care unit) was 5.1 (0–10 VAS) in a study by Tripi et al. (2008). In a study conducted by Hiller et al. (2012), over half of adolescent patients undergoing major spine surgery had a pain score of 6 (0–10 VAS)

or more in PACU. In studies by Van Boerum et al. (2000) and Ricciardelli et al. (2020), the mean pain score after AIS correction was 3–4 (0–10 VAS) over the 48-hour postoperative period. Acute postoperative pain is positively associated with preoperative pain (Chidambaran et al. 2017; Ocay et al. 2020). In a study by Mayell et al. (2014), pain was often in the moderate to severe range for 72 hours after PSF in paediatric patients. There is a lack of studies on acute postoperative pain in SK and spondylolisthesis patients, possibly due to smaller surgical volumes.

2.4.3 Chronic postoperative pain

Chronic postoperative pain is defined as pain in the surgical site that develops or increases in intensity after the operation and lasts over 3 months, well beyond the healing process (Schug et al. 2019). Chronic postoperative pain increases functional disability, psychological distress, and economics costs (Rosenbloom et al. 2019).

Studies of AIS patients after PSF show an incidence of chronic postoperative pain between 12% and 42% (Helenius et al. 2019; Chidambaran et al. 2017; Lee et al. 2020; Hwang et al. 2020). The incidence of chronic postoperative pain varies between the studies due to different definitions of chronic postoperative pain. In the study by Helenius et al. (2019), the incidence of chronic postoperative pain (pain over 3/9 in SRS-24 question one) 5 years after surgery was 14%, and in a study by Chidambaran et al. (2017), the incidence of chronic postoperative pain (pain over 3/10 in the numerical rating scale or pain that affects daily activities or sleep) one year after surgery was 42%. In a study conducted by Hwang et al. (2020), the incidence of chronic postoperative pain (patients having complaints of pain) 6 months after surgery was 12%. The type of pain (nociceptive local, neuropathic) has not been properly specified or classified in the previous studies. In their study, Helenius et al. (2019) mentioned that there were no radicular symptoms to the extremities in any patient and that one patient had numbness over dermatomes T4-T6 on the right side, yet nothing else was mentioned concerning the type of pain. In the study by Chidambaran et al. (2017), half of the patients with persistent pain complained of back pain (other pain locations were neck, shoulder, lower extremities, upper extremities, and chest), and approximately every third patient with chronic postoperative pain had neuropathic type of pain. In the study by Hwang et al. (2020), there was no mention of the type of pain.

There is a paucity in literature regarding chronic postoperative pain after deformity correction in SK and spondylolisthesis patients. There are a few small studies on the subject. In a study conducted by Green et al. (2020) with 27 operatively treated SK patients, improvement was found in the mean SRS-22 pain domain scores from 3.7 preoperatively to 4.4 at 2 years after surgery. A study by Suominen et al. (2022) with 22 operatively treated SK patients revealed

improvement in the mean SRS-24 pain domain scores from 4.0 preoperatively to 4.5 at 2 years postoperatively (p=0.002). Virkki et al. (2019) revealed in their study with 26 operatively treated spondylolisthesis patients that the mean SRS-24 pain domain score increased from 3.3 perioperatively to 3.9 at two years after PSF (p=0.007). Seventy-eight operatively treated spondylolisthesis patients in a study by Bourassa-Moreau et al. (2019) had significant improvement in the mean SRS-22 pain domain scores from 2.9 preoperatively to 3.8 after 2 years FU.

Preoperative pain is a common risk factor for chronic pain after spinal fusion (Chidambaran et al. 2017; Bastrom et al. 2013; Hwang et al. 2020; Connelly et al. 2014; Bailey et al. 2021). Studies have shown that acute postsurgical pain predicts chronic pain in adolescents (Ocay et al. 2020; Chidambaran et al. 2017). On the contrary, the study by Li et al. (2019) found that opioid consumption during the acute postoperative time did not significantly predict pain at 6 months after surgery. Other risk factors for chronic pain after PSF in AIS patients according to literature are older vs. younger age (Oksanen et al. 2019), child anxiety (Bailey et al. 2021; Chidambaran et al. 2017; Connelly et al. 2014), longer operative time (Helenius et al. 2021; Chidambaran et al. 2017), and lower self-image (Landman et al. 2011). The development of chronic postoperative pain seems to be multifactorial (Seki et al. 2018). Multimodal analgesia has been considered as an important component in reducing chronic pain, but there is no optimal multimodal treatment protocol for adolescent spinal surgery (Lee et al. 2020; Ricciardelli et al. 2020). On the other hand, a large meta-analysis by Chaparro et al. (2013) in adults showed that according to current evidence, multimodal analgesia has no effect on chronic postoperative pain.

Helenius et al. (2019) showed that 14% of the AIS patients experienced chronic postoperative pain 5 years after PSF. However, the rate of back pain did not differ compared to the healthy control group. There was a significant difference when comparing operatively treated AIS patients to the untreated AIS patients, as 51% of untreated AIS patient reported moderate to severe pain (Helenius et al. 2019).

2.5 Postoperative pain management after spinal fusion surgery

The surgical correction of AIS, SK, and spondylolisthesis differ in nature. Multiple levels of spinal fusion are required to address the deformity in AIS and SK with large tissue trauma, while one- or two-level spinal fusion with or without pelvic instrumentation is adequate to reduce or stabilise spondylolisthesis. Ideally, AIS and SK patients undergo surgery without nerve root manipulation. Wide nerve root decompression and retraction is needed in patients with spondylolisthesis (Molinari et al. 1999; Poussa et al. 2006). Additionally, reduction of high-grade

spondylolisthesis improves possibilities of spinal union, but increases tension on L5 nerve roots (Poussa et al. 2006; Petraco et al. 1996; Longo et al. 2014).

Multimodal analgesia with NSAIDs, paracetamol, central neuraxial blocks, local anaesthesia, and neuromodulator agents to reduce opioid amount should be used as part of a rapid recovery pathway to facilitate faster recovery in patients undergoing PSF (Shah et al. 2020; Lee et al. 2020). Despite the adverse effects, opioids are still the mainstay in postoperative pain control after spine surgery (Shah et al. 2020; Sheffer et al. 2017; Lee et al. 2020). The idea of a multimodal analgesia is to provide superior analgesia and minimise the adverse effects (Sheffer et al. 2017).

2.5.1 Paracetamol

Paracetamol is a basic analgetic drug administered after almost every surgery and has been found to reduce the need for opioids. The mechanism of action of paracetamol is not well defined, but it is assumed that the mechanism is possibly mediated via central nervous system COX 3 inhibition (Sheffer et al. 2017). In the study by Hiller et al. (2012), the IV-administered paracetamol improved postoperative analgesia but did not decrease the opioid consumption during 24 hours after spine surgery in adolescents. Paracetamol's maximum daily dose is 75 mg/kg, with hepatotoxicity occurring at 150 mg/kg/d (Sheffer et al. 2017).

2.5.2 Non-steroidal anti-inflammatory drugs

NSAIDs are a group of pain medicines which also decreases inflammation and fever. NSAIDs reduce the synthesis of prostanoid neurotransmitters (prostacyclin, thromboxane, prostaglandins), even at low concentrations, by inhibiting the enzyme cyclo-oxygenase. NSAIDs' therapeutic effects are attributed to the lack of these neurotransmitters. NSAIDs have shown potential to reduce postoperative opioid requirements in the paediatric population (Shah et al. 2020). In their meta-analysis, Michelet et al. (2012) found that coadministration of NSAIDs and opioids in children reduces postoperative pain and decreases both postoperative opioid requirements and opioid adverse effects. NSAIDs have still not gained popularity after PSF because of the potential risk of pseudo arthrosis and postoperative bleeding. Low-dose ketorolac reduces the morphine requirements and improves analgesia after PSF without increasing the incidence of non-steroidal anti-inflammatory side-effects (Munro et al. 2002). Ketorolac does not increase the risk of bleeding complications or reoperation in children after spinal surgery (Vitale et al. 2003). Ketorolac is recommended to use after PSF as supplemental pain management without the increased risk of developing a pseudo arthrosis (Sucato et al. 2008). Ketorolac is associated with significantly lower odds of prolonged LOS and prolonged duration

of IV opioid use (Rosenberg et al. 2017). According to current knowledge, NSAIDs, especially ketorolac, should be used after PSF in adolescent patients.

2.5.3 Opioids

Opioids are a group of analgesic agents affecting μ-, δ-, and κ-opioid receptors. The effect of opioids is mainly based on their activating effect on μ-opioid receptors in the central and peripheral nervous systems (Pathan and Williams 2012). Opioids are the most effective pain medicines and therefore generally used to treat severe pain after surgery. Opioids have multiple adverse effects, including somnolence, nausea, vomiting, pruritus, constipation, urinary retention, tolerance, physical dependence, and the most serious side effect of respiratory depression (Munro et al. 2002; Vitale et al. 2003; Jitpakdee and Mandee 2014). Most of the opioid-related adverse effects are dose dependent, and by decreasing the opioid dose it is possible to reduce the adverse effects (Jitpakdee and Mandee 2014). Other methods to prevent opioid-related adverse effects in children are $5HT_3$-antagonists and dexamethasone for PONV, naloxone for pruritus, and laxatives and early ambulation for prevention of constipation (Jitpakdee and Mandee 2014). Nonetheless, opioids are the most effective analgetic agents in pain control and remain as a mainstay in postoperative pain control after spine surgery (Shah et al. 2020; Sheffer et al. 2017; Lee et al. 2020). Currently, there is no consensus on which opioid or dose is optimal, but minimising opioid adverse effects is a ubiquitous goal (Shah et al. 2020). IV opioid administration via PCA (patient-controlled analgesia) is widely used after major surgical procedures. In PCA, the patient receives an additional analgetic dose by pressing a button. For safety reasons, there are pre-determined background infusion limits, as well as a set single dose concentration, lock time until the next dose, and a set number of single doses per hour. The safety limits are set by medical staff, in order to avoid an overdose.

2.5.4 Pregabalin and gabapentin

Pregabalin and gabapentin are structural analogues of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter in the central nervous system (Lee et al. 2020; Sheffer et al. 2017). They are used to treat neuropathic pain. Neuropathic pain is caused by damage or disease in the somatosensory system. Neuropathic pain can be divided into central or peripheral neuropathic pain. Neuropathic pain has a neuroanatomically logical location and findings that point to an abnormal function of the somatosensory system. Gabapentinoids are widely studied for postoperative pain treatment, and the results indicate reasons both for and against their use. Gabapentinoids have several common adverse effects, including dizziness,

headache, drowsiness, and potential abuse. In a study by Mayell et al. (2014), a single 600 mg dose of preoperative gabapentin did not reduce the morphine requirements compared to placebo after PSF in paediatric patients. On the contrary in a study by Rusy et al. (2010), a preoperative gabapentin dose of 15 mg/kg and a postoperative dose of 5 mg/kg three times daily for 5 days significantly reduced the morphine consumption and decreased pain scores in the first 48 hours after PSF in adolescents compared to placebo. Helenius et al. (2020) studied the effect of pre-emptive pregabalin in children undergoing PSF. In their study, the use of perioperative pregabalin (2 mg/kg twice daily preoperatively and for 5 days after surgery) did not reduce the pain scores nor the postoperative opioid consumption after PSF in adolescent patients compared to placebo. Currently, there is no evidence supporting the use of perioperative gabapentinoids for adolescent patients undergoing PSF (Lee et al. 2020; Helenius et al. 2020).

2.5.5 Ketamine

Ketamine is an N-methyl-D-aspartate receptor non-competitive antagonist and likely also affects opioid receptors. Ketamine induces dissociative anaesthesia and has analgesic effects. The common disadvantages of ketamine are nightmares, hallucinations, agitation, increased salivation, and tachycardia. A small dose of intraoperative ketamine is widely used to reduce postoperative pain, although there is a lack of convincing studies. There is no current evidence supporting the routine use of ketamine to reduce pain and opioid consumption in AIS patients undergoing surgery (Lee et al. 2020). However, the study by Ricciardelli et al. (2020) found that a perioperative ketamine infusion of 0.2 mg/kg/h for 48 hours after PSF in adolescent patients reduced the median total morphine consumption during the 48-hour postoperative period, though they did not reach significance for the primary endpoint which was patient satisfaction. On the contrary, in a double-blinded prospective controlled trial by Pestieau et al. (2014), a perioperative 72-hour low-dose ketamine infusion did not reduce the opioid consumption or pain scores after paediatric scoliosis surgery.

2.5.6 Central neuraxial and peripheral blocks

Postoperative pain after PSF can be treated safely with epidural analgesia (EA), but inhibition of motor function and sensory in lower extremities and respiratory depression are possible adverse events (O'Hara et al. 2004; Sucato et al. 2005; Millbrandt et al. 2009; Schenk et al. 2006), and for that reason, it is not used in every hospital routinely. Compared to IV medication after paediatric scoliosis surgery, the efficacy or safety of the central neuraxial blocks have not been proven superior (Shah

et al. 2020; O'Hara et al. 2004). In their study, Sucato et al. (2005) found that continuous epidural analgesia (CEA) with hydromorphone (20 µg/mL) and bupivacaine 0.1% at an initial rate of 0.1–0.2 mL/kg/h provided improved pain control within the first 48 hours after surgical treatment of AIS compared to PCA, but CEA was often discontinued because of adverse effects, including respiratory depression, oversedation, and sensory changes in the lower extremities. In a study by Millbrandt et al. (2009), there was also a significant increase in the transient neurological changes and respiratory depression in the CEA group with hydromorphone (20 µg/mL) and bupivacaine 0.1% at an initial rate of 0.1–0.2 mL/kg/h and need for a temporary or permanent interruption of the epidural infusion. A study by Schenk et al. (2006) showed that patient-controlled epidural analgesia (PCEA) with ropivacaine 0.125% and sufentanil 1.0 µg/mL at a rate of 14 mL/h with patient-controlled bolus of 5 mL provided superior analgesia and patient satisfaction when compared with PCA after spinal fusion surgery, but 46% of the patients in the PCEA group had transient sensory deficits attributable to the local anaesthetic. Boerum et al. (2000) reported that EA with 0.1% bupivacaine with morphine administered at 0.05 mg morphine/kg/h is safe and effective after PSF in AIS patients, but they found no statistically significant difference in pain control compared to PCA groups. EA does not increase the postoperative wound infection risk (Boerum et al. 2000).

Paraspinal blocks are recent advances in the perioperative pain management of paediatric spine patients, but their use is currently limited and scientific knowledge sparse (Diwan et al. 2020; Stondell and Roberto 2022; Chin et al. 2020). When Akesen et al. (2022) conducted a retrospective study with 57 AIS patients undergoing scoliosis surgery (27 patients in the intervention group receiving bilateral bilevel (T4 and T10) erector spinae plane block with 0.25% bupivacaine and dexamethasone to a total volume of 40 mL versus 30 patients in control group), they found that 24-hour cumulative postoperative morphine consumption was significantly lower in the study group and patient satisfaction scores were significantly higher.

3 Aims

The aim of this thesis, consisting of three studies, was to improve the perioperative management of paediatric spinal surgery in adolescent idiopathic scoliosis, Scheuermann kyphosis, and spondylolisthesis patients.

The specific aims of this thesis were:

1. To evaluate the effect of perioperative pregabalin on the incidence of chronic postoperative pain two years after posterior spinal fusion surgery in adolescents.

2. To determine the incidence and predictors of postoperative urinary retention in adolescent idiopathic scoliosis patients after posterior spinal fusion.

3. To investigate the predictors of acute and chronic postoperative pain in patients undergoing posterior spinal fusion surgery for adolescent idiopathic scoliosis, Scheuermann kyphosis, and spondylolisthesis.

4 Materials and Methods

The studies were approved by the Ethics Committee of the Turku University Hospital District. The drug intervention protocol was approved by the National Agency for Medicine. Every patient and their parents gave their written informed consent for participation in the studies. All the operations were performed in the Turku University Hospital. Study I was registered in ClinicalTrials.gov (NCT02464813) before starting the study.

This thesis is comprised of three series of paediatric spine patients, and the studies have partly the same patients (Table 1).

Table 1. Clinical characteristics of study groups I–III.

	Study I	**Study II**	**Study III**
Number of participants	64	159	213
Age (years)	15.6 (11–21)	15.6 (10–21)	15.6 (10–21)
Gender (M:F)	22 : 42	45 : 114	67 : 146
Height (m)	1.67 (0.10)	1.67 (0.9)	1.67 (0.10)
Weight (kg)	58.9 (14.5)	58.3 (13.4)	60.1 (16.3)
BMI (kg/m^2)	21.1 (4.4)	20.9 (3.9)	21.4 (4.5)
Diagnosis			
AIS	51	159	158
SK	4	0	19
Spondylolisthesis	8	0	36
Osteoid osteoma	1	0	0
Number of fused levels	10.3 (3.4)	11.3 (1.9)	9.9 (3.7)
Surgical time (min)	171 (37)	176 (45)	185 (49)
Intraoperative blood loss (mL)	487 (355)	528 (349)	506 (327)
Total oxycodone dose during hospital stay (mg/kg)	3.24 (1.18)	3.79 (2.36)	3.60 (2.40)
Daily oxycodone dose during hospital stay (mg/kg/d)	0.49 (0.14)	0.51 (0.25)	0.49 (0.24)
48-hour postoperative oxycodone dose (mg/kg)	1.53 (0.52)	1.67 (0.78)	1.64 (0.81)

Data presented as mean (SD) or as counts.

4.1 Randomised, double-blinded, clinical trial comparing the effect of pregabalin and placebo on the incidence of chronic postoperative pain (Study I)

The first study of this thesis was a randomised, double-blinded, placebo controlled single-centre clinical trial determining the effects of perioperative pregabalin on the incidence of chronic postoperative pain in adolescents undergoing PSF surgery. The two primary outcomes were cumulative opioid amount in the first 48 hours following surgery (published previously) and the incidence of chronic postoperative pain over the course of the two-year FU period. According to the American Pain Society recommendation, gabapentinoids are recommended as a part of multimodal postoperative pain management in adult patients undergoing spine surgery (Chou et al. 2016). All procedures were performed by two experienced orthopaedic spine surgeons.

4.1.1 Study participants

Between August 2015 and September 2018, 64 of 77 consecutive patients, aged 10 to 21 years gave their consent to participate and were recruited in the study. Thirty-one patients were randomised to the placebo group and the other 33 patients were randomised to the pregabalin group by the Department of Pharmacy at the Turku University Hospital. The groups were not identical regarding the preoperative diagnoses. In the pregabalin group, there were 25 AIS, 4 SK, 3 spondylolisthesis, and 1 osteoid osteoma patients compared to the placebo group with 26 AIS and 5 spondylolisthesis patients. Inclusion criteria were adolescents (10–21 years) with AIS, SK, osteoid osteoma, or spondylolisthesis and scheduled for PSF surgery, American Society of Anaesthesiologists classification (ASA) physical status I or II, written informed consent, and no contraindications for pregabalin use. The exclusion criteria were ASA of III or more, or if the patient had any other comorbidities, preoperative opioid use, or need for anterior surgery.

4.1.2 Study design

The Department of Pharmacy at the Turku University Hospital accomplished the 1:1 randomisation according to a predetermined list with blocks of 20 patients. The study drugs (pregabalin and placebo) were manufactured and the capsules delivered to the paediatric surgical ward in the Turku University Hospital by the Department of Pharmacy. All persons involved in the study (patients, parents, nurses, doctors, and researchers) were blinded to group assignment during the study and FU. In the intervention group, the patients received pregabalin 2 mg/kg p.o., rounded up to the

nearest 25 mg, on the preoperative evening. The second preoperative dose of pregabalin was administered to the patient 2 hours before the induction of anaesthesia. The highest daily dose of pregabalin was 150 mg twice daily. The study drug protocol was continued for 5 days postoperatively. In the placebo group, the patients were administered the same number of identical-looking capsules at similar times.

Anaesthesia was standardised, and induction and maintenance were performed using propofol and remifentanil target-controlled infusions. Bispectral index goal was set between 40 and 60. Dexmedetomidine infusion was included in standard anaesthesia, and after a loading dose of 1 µg/kg over 10 minutes, the infusion was continued at a constant rate of 1 µg/kg/h throughout the operation. None of the patients received a muscle relaxant. Betamethasone 0.2 mg/kg ad 8 mg IV was given to all patients before anaesthesia induction. Mean arterial pressure (MAP) target was between 65 and 75 mmHg, and a noradrenaline infusion was used if necessary to keep MAP in the target area.

PCA (CADD-Legacy PCA Pump, Model 6300; Smiths Medical) was used in every patient. The standard PCA settings included an on-demand oxycodone bolus of 0.03 mg/kg/dose every 10 minutes with an hourly maximum of three doses, without basal infusion. PCA was continued for 48 hours after operation. Paracetamol 20 mg/kg three times daily p.o. was given to all patients. Etoricoxib 2–3 mg/kg p.o. was used as a rescue analgesia if paracetamol and oxycodone were not sufficient.

Pain assessment was performed by using the SRS-24 questionnaire and pain drawing with VAS. The SRS-24 questionnaire was completed by all study patients preoperatively and at two years after operation; there were no dropouts. The first SRS-24 question (pain rating from 1 to 9, higher number indicating more pain) was also analysed separately. A pain score over 4/9 was considered to represent moderate to severe pain.

The primary outcome variables of this study were cumulative opioid consumption during the first 48 hours after surgery and the incidence of chronic postoperative pain 2 years after the operation. The data regarding post-surgery opioid consumption has been analysed and published previously.

4.2 Predictors of postoperative urinary retention (Study II)

The second study of this thesis was retrospective in nature with a prospectively collected spine register including data on urinary retention. The aim of this study was to evaluate the predictors of POUR in AIS patients undergoing PSF in the Turku University Hospital.

4.2.1 Study participants

Subjects in this study were AIS patients aged 10–21 years who were treated with a PSF in the Turku University Hospital between May 2010 and April 2020. A total of 166 consecutive patients were screened. Seven patients were excluded from the study, leaving 159 patients for the final analyses. Reasons for exclusion were a lack of opioid consumption in two patients' records, two patients needing early re-operation, one patient needing anterior surgery, one patient having chronic renal failure, and one patient having a neurological developmental delay.

4.2.2 Study design

Urinary retention has been routinely measured by trained nurses using the ultrasound scanner (PadScan HD3, Caresono) in our university hospital in every paediatric and adolescent patient after spine surgery since 2009. In every patient, the measurement was made at least twice on two separate occasions. Residual volume is first measured after the first voiding following urinary catheter removal or if the patient has difficulties in voiding after catheter removal. When patients were able to void normally and the residual volume after voiding was twice under 100 mL, the residual volume measuring was discontinued. After the catheter removal, the definition of POUR was a documented full bladder with ultrasound, i.e., over 300 mL residual volume and inability to void. If the patients were unable to void with the presence of full bladder, retention was treated by emptying the bladder with a straight catheter, after which the urinary volume was measured. Removal of the urinary catheter was routinely performed in the morning of postoperative day 2–4 depending on each patient's clinical condition.

The anaesthetic management of paediatric spine patients is standardised and has been used since 2009, including TIVA with propofol, remifentanil, and dexmedetomidine infusions. The perioperative fluid management was not standardised. Most of the patients (78%) received PCA with oxycodone as pain management for first 48 postoperative hours. The standard oxycodone PCA was set with an on-demand oxycodone bolus of 0.03 mg/kg/dose maximally every 10 minutes with an hourly maximum of three doses, without basal infusion. The remaining 22% of patients were administered IV and oral oxycodone. Oral oxycodone doses were calculated to equivalent IV doses with the following formula: 0.6 x p.o. dose = IV dose (Poyhia et al. 1992; Kalso 2005). All patients were administered oral paracetamol 15–20 mg/kg three times daily. Eighty-five (53%) patients received NSAIDs on the catheter removal day.

4.3 Predictors and incidence of chronic postoperative pain after posterior spinal fusion in adolescents (Study III)

The third publication in this thesis was retrospective with prospectively collected data and evaluated the incidence and predictors of acute and chronic postoperative pain in adolescent AIS, SK, and spondylolisthesis patients undergoing PSF.

4.3.1 Study participants

This study included 221 consecutive patients from our paediatric spine register data surgically treated between March 2010 and March 2020. Inclusion criteria were surgically operated AIS, SK, and spondylolisthesis patients (10–21 years) in the Turku University Hospital between March 2010 and March 2020. Exclusion criteria were ASA classification three or more, other comorbidities, need for early reoperation, lack of data on postoperative opioid consumption, and need for anterior surgery. Eight patients from the AIS group were excluded from the study: 2 patients lacked the data of postoperative opioid consumption; 2 patients had early re-operation for a neurologic deficit; 1 patient needed combined anteroposterior approach; 1 patient had chronic renal insufficiency; 1 patient had neurological comorbidity; 1 patient was operated for both AIS and spondylolisthesis. After exclusion, 213 patients remained for further analyses. Most of the patients (158) were treated for AIS; only 19 patients were treated for SK, and the remaining 36 patients had a procedure for spondylolisthesis.

4.3.2 Study design

Patients completed the SRS-24 outcome questionnaire preoperatively, at six months postoperatively, and at 24 months postoperatively. Pain was analysed using the SRS-24 questionnaire, and acute postoperative pain was analysed based on opioid consumption. The first SRS-24 question (pain rating from 1 to 9, higher number indicating more pain) was also analysed separately. A pain score over 4/9 was considered moderate to severe pain. As in the previous studies mentioned, anaesthetic management is standardised in our hospital in adolescent patients undergoing PSF surgery. The two experienced orthopaedic spine surgeons operated the patients. Between AIS, SK, and spondylolisthesis patients, the extension of the surgery varies. Long posterior instrumentation is necessary for the repair of AIS and SK, whereas lumbar fusion at one or two levels is used to treat spondylolisthesis. In spondylolisthesis patients, the neural components were extensively decompressed for nerve roots (L5, S1) and cauda equinae.

Most of the patients (71%) had PCA with oxycodone for the first 48 postoperative hours, and the remaining patients (29%) received IV and oral oxycodone as needed. Oral oxycodone doses were calculated to equivalent IV doses (0.6* p.o. dose = IV dose) (Poyhia et al. 1992; Kalso 2005). Oral paracetamol 15–20 mg/kg three times daily was administered to all patients. One hundred and forty-nine (70%) patients received two or more doses of NSAIDs postoperatively in the hospital.

A uniform protocol was followed when mobilising the patients. Patients were instructed to stand up and walk a short distance on the first postoperative day. On the second postoperative day, the patients were encouraged to walk around the ward.

4.4 Statistical analyses

In study I, which assessed perioperative pregabalin's effect on persistent postoperative pain after PSF for paediatric spinal deformity, statistical comparisons were made using the intention-to-treat analysis principle. The sample-size calculation was based on a long-term study of AIS patients undergoing PSF (Helenius et al. 2019). In that study patients undergoing surgery the mean SRS-24 pain domain score was 4.3 (SD 0.5). According to those parameters, to find a difference of 0.4 in the SRS-24 pain domain score (effect size 0.8) between the groups (at an alpha 0.05 and a power of 0.80), a sample size of 25 patients per group was needed. The Mann-Whitney U test was used for comparing baseline characteristics, preoperative mean Oswestry Disability Index, total opioid consumption at 48 hours, and VAS pain scores for each time point between groups. Using the Friedman's test, the difference in VAS pain scores over time was analysed. Linear mixed models for repeated measures were used because the SRS-24 scores were normally distributed. The treatment group, baseline pain, 48-hour opioid amount, fusion below L1, and number of fused vertebrae were utilised as explanatory variables in a linear model of pain 2 years postoperatively. The Shapiro-Wilk test together with visually checking was used to evaluate normal distribution of variables.

Study II evaluated predictors for POUR in adolescents undergoing PSF for AIS. Continuous variables which followed the normal distribution were presented with mean and standard deviation (SD). Skewed distributions were summarised with median and lower (Q1) and upper (Q3) quartiles. Age was presented with mean and range. Counts and percentages were used to summarise the categorical variables. Fisher's exact test or analysis of variance was performed for testing background characteristics. Pearson correlation coefficients were calculated when examining association between continuous variables. Binomial logistic regression was used to analyse differences between groups. Odds ratios with 95% confidence intervals (CI)

were reported. Univariate analysis was first performed. Then all factors were added to the multivariate models and from these models, non-significant factors were gradually omitted.

Study III determined predictors and incidence of acute and chronic postoperative pain in AIS, SK, and spondylolisthesis patients undergoing PSF. Associations between the opioid consumption and other variables, including study group, gender, surgical time, estimated blood loss, and preoperative pain, were summarised with descriptive statistics. The Spearman correlation test was used for continuous variables, and the Kruskal-Wallis test was used for categorical variables. The Spearman correlation and Kruskal-Wallis tests were also used to study associations between chronic pain and explanatory variables (study group, gender, surgical time, estimated blood loss, and preoperative pain). The Kruskal-Wallis and Dwass-Steel-Critchlow-Fligner pairwise tests were used to view study group effects with surgical outcomes (surgical time, estimated blood loss, and LOS). A mixed model for repeated measures was used to evaluate differences between the groups in preoperative SRS-24 (total, pain, self-image) scores and postoperative SRS-24 (total, pain, self-image) scores at 2 years. The Kruskal-Wallis test was used to examine the differences between study groups in the SRS-24 function and activity domain scores. The normality of variables was checked visually and with the Shapiro-Wilk test.

All statistical tests were performed as two-sided with a significance level set at 0.05. All statistical analyses were performed with SAS system, version 9.4 for Windows (SAS Institute INC., Cary, NC, USA).

5 Results

5.1 The effect of pregabalin on the incidence of chronic postoperative pain

Sixty-four patients were recruited in the study between August 2015 and September 2018. Thirty-one patients were randomised to the placebo group (26 AIS and 5 spondylolisthesis patients), and the remaining 33 patients were in the pregabalin group (25 AIS, 4 SK, 3 spondylolisthesis, and 1 osteoid osteoma patient). All study participants met the minimum FU of two years and had complete radiographical and clinical data at two years postoperatively. None of the patients needed opioids after discharge. The study groups were similar regarding patient demographics and surgical characteristics (Table 2). In the pregabalin group, one patient needed reoperation during the 2-year FU for distal adding-on. Between the study groups, there were no differences in intraoperative anaesthesia or analgesia drug consumption.

In both groups, there was significant improvement in mean SRS-24 pain domain scores. In the pregabalin group, the mean pain domain scores improved from 3.8 to 4.3 at two years postoperatively. In the placebo group, the mean improvement was from 3.8 to 4.0. There were no differences between the study groups at any time points, $p = 0.317$ (Table 3). After the two-year FU in both study groups, 8 patients reported moderate to severe pain (> 4/9) on question 1 of the SRS-24 questionnaire.

There was significant improvement in median VAS pain scores after the two-year FU, $p = 0.001$ in both groups and no differences between the groups (Table 4). In the pregabalin group, the median preoperative VAS 2.6 improved to 0.3 after the two-year FU time, and in the placebo group, the improvement was from 2.0 to 0.35. Neither preoperative pain, 48-hour opioid consumption nor number of fused vertebrae predicted worse pain at 2 years postoperatively in a multivariable analysis.

In a subgroup analysis of 51 AIS patients, there were no significant differences in SRS-24 pain domain scores nor in the total SRS-24 scores. In a subgroup analysis of spondylolisthesis patients, there were no significant differences between the groups.

Table 2. Patient demographics and surgical characteristics. (Original publication I)

	Placebo (n=31)	**Pregabalin (n=33)**
Age (years)	15.5 (2.0)	15.7 (2.3)
Height (m)	1.67 (0.1)	1.66 (0.1)
Weight (kg)	61.2 (15.2)	56.7 (13.2)
BMI (kg/m^2)	21.9 (5.1)	20.3 (3.4)
Male : Female	10 : 21	12 : 21
Main curve		
preoperative	52.8 (9.9)	52.5 (7.2)
postoperative	12.7 (4.6)	11.2 (5.0)
Lenke 1, 2, 3, 4, 5, 6	10, 8, 4, 1, 0, 3	9, 10, 1, 2, 2, 1
Scheuermann kyphosis	0	4
Spondylolisthesis	5	3
Number of fused levels	10.3 (3.6)	10.3 (3.1)
Surgical time (h)	2.9 (0.7)	2.8 (0.5)
Intraoperative blood loss (mL)	515 (331)	460 (369)

The values are presented as mean (SD) or as count.

Table 3. SRS-24 domain scores. (Original publication I)

SRS-24 domain	Pregabalin (n=33)	Placebo (n=31)	P value
Pain			0.317
preop	3.84 (3.54, 4.15)	3.79 (3.45, 4.13)	
6 months postop	4.11 (3.86, 4.37)	4.14 (3.75, 4.53)	
1 year postop	4.31 (4.09, 4.53)	4.07 (3.71, 4.44)	
2 years postop	4.32 (4.06, 4.57)	3.99 (3.67, 4.31)	
Self-image			0.397
preop	3.91 (3.60, 4,22)	4.05 (3.82, 4.28)	
6 months postop	4.20 (3.89, 4.50)	4.11 (3.89, 4.33)	
1 year postop	4.23 (3.96, 4.50)	3.88 (3.59, 4.17)	
2 years postop	4.26 (4.01, 4.52)	4.10 (3.87, 4.33)	
Function			0.549
preop	3.97 (3.73, 4.20)	4.06 (3.91, 4.21)	
6 months postop	3.92 (3.71, 4.13)	3.97 (3.71, 4.22)	
1 year postop	4.18 (4.06, 4.30)	4.27 (4.13, 4.40)	
2 years postop	4.10 (3.93, 4.28)	4.16 (3.98, 4.34)	
Activity			0.209
preop	4.29 (3.98, 4.61)	3.97 (3.48, 4.45)	
6 months postop	3.60 (3.13, 4.06)	3.54 (3.01, 4.07)	
1 year postop	4.73 (4.54, 4.92)	4.48 (4.15, 4.81)	
2 years postop	4.57 (4.28, 4.87)	4.38 (3.99, 4.77)	
Satisfaction			0.139
preop	4.39 (4.08, 4.70)	4.09 (3.78, 4.41)	
1 year postop	4.33 (4.09, 4.58)	3.92 (3.55, 4.29)	
2 years postop	4.27 (4.02, 4.52)	4.14 (3.87, 4.41)	
Total score			0.678
preop	3.99 (3.80, 4.18)	3.97 (3.76, 4.17)	
1 year postop	4.14 (3.93, 4.35)	3.92 (3.71, 4.14)	
2 years postop	4.09 (3.90, 4.29)	3.94 (3.74, 4.14)	

Data presented in mean with 95% CI in parentheses.

Table 4. Back pain by visual analogue scale (VAS 0–10). (Original publication I)

	Pregabalin group	Placebo group	P value
Preoperative	2.60 (0–7.7)	2.00 (0–9.6)	0.371
6-month follow-up	1.00 (0–6.4)	0.75 (0–5.3)	0.683
1-year follow-up	1.00 (0–8.0)	0.58 (0–6.8)	0.789
2-year follow-up	0.3 (0–8.5)	0.35 (0–7.3)	0.836

Data shown as median (range).

5.2 Postoperative urinary retention

Study II was a retrospective study of 159 consecutive AIS patients undergoing PSF. Mean age at the time of surgery was 15.6 years (range 10–21 years), and most of the patients were females (114 [72%]). Median intraoperative blood loss was 430 mL (Q1:280, Q3:660), and the mean (SD) surgery time was 176 min (45 min). The mean (SD) number of fused vertebrae levels was 11.3 (1.9). Data on fluid management was not available from all patient charts and was not taken into consideration.

Urinary catheters were removed at a mean of 2.7 days (range 1–5 days) after surgery. Fifty-three (33%) patients had POUR, i.e., they were unable to void with documented full bladder or the residual volume after voiding was greater than 300 mL (shown by ultrasound). The mean residual volume was 555 mL (range 320–1,400 mL) with those who needed the intermittent catheterisation. After urinary catheter removal, the mean time for the first intermittent catheterisation was 6 hours (range 2–16 hours). Sixteen patients requiring intermittent catheterisation needed it only once, and 37 patients needed catheterisation more than one time. Median need for intermittent catheterisation was three times (range 1–16). Hospital stay was longer in patients with POUR, mean (SD) 7.8 (1.9) days compared to patients without POUR 6.8 (1.4) days ($p < 0.001$).

Higher total opioid consumption during hospital stay was significantly associated with POUR (mean 4.59 mg/kg [95% CI: 3.78, 5.41]) compared to non-POUR patients (mean 3.38 mg/kg [95% CI: 3.02, 3.74]), ($p = 0.002$), as was higher opioid consumption during catheter removal day (mean 0.81 mg/kg [95% CI: 0.66, 0.96] vs. 0.57 mg/kg [95% CI: 0.51, 0.64], $p < 0.001$). Other predictors of POUR were male gender (males 47% vs. females 28%, $p = 0.039$), longer surgical time (mean 188 min [SD 49 min] vs. 171 min [SD 42 min], $p = 0.029$), and greater intraoperative blood loss (median 550 mL [Q1:350, Q3:830] vs. 410 mL [Q1:240, Q3:600], $p = 0.002$). Higher weight was also associated with POUR, whereas BMI was not associated with POUR statistically significantly, $p = 0.08$. The use of NSAIDs during the catheter removal day was not associated with POUR.

In a univariate binomial logistic regression analysis for POUR (Table 5), greater opioid consumption on the catheter removal day had the biggest OR (OR 3.90 [95% CI 1.64, 9.29], $p = 0.002$) for POUR. Other predictors for POUR were greater total opioid consumption during hospital stay, longer surgical time, male gender, and higher weight.

Table 5. Univariate binomial logistic regression analysis for postoperative urinary retention. (Original publication II)

Variables	Odds ratio	95% CI	P value
Gender			
Female	Reference		
Male	2.242	1.098–4.579	0.027
Age (years)	0.939	0.805–1.095	0.422
Weight (kg)	1.028	1.003–1.055	0.029
BMI (kg/m^2)	1.075	0.989–1.169	0.088
Instrumentation to			
T12 or above	Reference		
L1 or below	1.729	0.848–3.525	0.132
Number of vertebrae fused	1.108	0.907–1.354	0.315
Screw replacement	1.331	0.638–2.774	0.446
Surgical time (h)	1.641	1.045–2.577	0.031
Intraoperative blood loss (mL)	1.001	1.000–1.002	0.004
Total oxycodone dose during hospital stay (mg/kg)	1.244	1.070–1.446	0.005
Oxycodone dose on day of catheter removal (mg/kg)	3.902	1.640–9.285	0.002
48 hours postoperative oxycodone (mg/kg)	1.387	0.911–2.112	0.127

Data presented as Odds ratio and 95% CI.

5.3 Acute and chronic pain after posterior spinal fusion

Study III was a retrospective study based on a prospective paediatric spine register of 213 consecutive adolescents (146 females [69%] and 67 males [31%]) with a mean age of 15.6 years (range 10–21 years) at the time of surgery. The patients had PSF surgery for AIS (158 [74.2%]), SK (19 [8.9%]), or spondylolisthesis (36 [16.9%]). Most of the AIS (72.2%) and spondylolisthesis (80.6%) patients were females as opposed to SK patients, where only 15.8% were females. One hundred and ninety (89.2%) of these patients were over the age of 12 years at the time of surgery.

There were statistically significant differences in surgical time, estimated blood loss, and LOS between the study groups (Table 6). The AIS patients' median surgery time was significantly shorter than that of SK and spondylolisthesis patients. The intraoperative blood loss was greatest in SK patients (median 570 mL [Q1:430, Q3:780]), moderate in AIS patients (median 430 mL [Q1:280, Q3:660]), and lowest in spondylolisthesis patients (median 305 mL [Q1:165, Q3:475]) ($p<0.001$). LOS

was shorter in spondylolisthesis patients (median 6 d [Q1:5, Q3:7]) compared to AIS (median 7 d [Q1:6, Q3:8]) and SK patients (median 7 d [Q1:7, Q3:9]) ($p < 0.001$).

Table 6. Patient demographics and surgical characteristics. (Original publication III)

Variables	AIS (n=158)	Scheuermann kyphosis (n=19)	Spondylolisthesis (n=36)	P value
Gender (male:female)	44 : 114	16 : 3	7 : 29	< 0.001
Age (years)	15.6 (2.2)	16.7 (1.3)	14.7 (1.9)	0.002
Weight (kg)	58.3 (13.5)	80.6 (27.8)	57.2 (12.5)	< 0.001
BMI (kg/m^2)	20.9 (3.9)	25.7 (7.5)	21.3 (3.7)	0.018
Surgical time (h)	2.95 (0.75)	3.45 (0.53)	3.49 (1.00)	< 0.001
Intraoperative blood loss (mL)	529 (350)	616 (200)	344 (203)	< 0.001
Daily oxycodone dose during hospital stay (mg/kg/d)	0.51 (0.25)	0.52 (0.25)	0.36 (0.17)	< 0.001
Major curve (degrees)				
preop	52 (8.5)	79 (5.6)		
postop	13 (4.6)	48 (8.4)		
Length of hospital stay (d)	7.2 (1.6)	7.8 (1.6)	6.2 (2.1)	< 0.001

Data presented as mean (SD) or as counts.

Preoperative SRS-24 pain scores were significantly lower in the spondylolisthesis patients, meaning more pain (median 3.17 [Q1:2.67, Q3:3.67]) compared to AIS (median 4.08 [Q1:3.5, Q3:4.5]) ($p < 0.001$) and SK (median 4.25 [Q1:3.67, Q3:4.5]) ($p < 0.001$) patients (Table 7).

Table 7. SRS-24 domain scores in the groups. (Original publication III)

SRS-24 domains	AIS	Scheuermann kyphosis	Spondylolisthesis	p value AIS vs SK	p value AIS vs spondylolisthesis
Pain					
preop	3.96 (0.72)	4.02 (0.64)	3.24 (0.86)	0.82	<0.001
6 mo FU	4.25 (0.63)	4.36 (0.49)	3.60 (0.71)	0.46	<0.001
2 yr FU	4.31 (0.60)	4.43 (0.48)	4.04 (0.94)	0.46	0.04
Self-image					
preop	3.83 (0.70)	3.54 (0.92)	4.00 (0.67)	0.05	0.23
6 mo FU	4.05 (0.68)	3.96 (0.50)	4.19 (0.50)	0.84	0.53
2 yr FU	4.14 (0.68)	4.11 (0.61)	4.21 (0.58)	0.88	0.42
Function					
preop	4.03 (0.47)	3.96 (0.44)	3.84 (0.54)	0.67	0.14
6 mo FU	3.95 (0.52)	4.04 (0.69)	3.95 (0.60)	0.56	0.69
2 yr FU	4.13 (0.56)	4.07 (0.42)	4.10 (0.53)	0.56	0.74
Activity					
preop	4.45 (0.81)	4.57 (0.47)	3.52 (1.13)	0.42	<0.001
6 mo FU	3.93 (0.98)	3.84 (1.10)	3.97 (1.00)	0.37	0.38
2 yr FU	4.66 (0.67)	4.44 (0.88)	4.39 (1.09)	0.13	0.24
Total score					
preop	4.05 (0.50)	4.02 (0.49)	3.55 (0.60)	0.69	<0.001
6 mo FU	3.84 (0.45)	3.94 (0.46)	3.88 (0.44)	0.35	0.61
2 yr FU	4.05 (0.42)	4.09 (0.46)	3.93 (0.64)	0.72	0.18

Data presented as mean (SD).

Between the three groups, there was a statistically significant difference in the amount of opioids consumed following surgery. Patients with spondylolisthesis had a considerably smaller median daily postoperative opioid intake of 0.35 mg/kg/d (Q1:0.25, Q3:0.42) compared to AIS 0.47 mg/kg/d (Q1:0.36, Q3:0.60) and SK 0.47 mg/kg/d (Q1:0.34, Q3:0.60) patients ($p<0.001$). Increased opioid use after surgery was not correlated with patient age, gender, BMI, length of surgery, intraoperative blood loss, NSAIDs, or preoperative pain. The number of fused vertebrae did not affect the opioid consumption after PSF in AIS and SK patients ($p=0.57$).

In all three groups, the SRS-24 pain domain revealed a statistically significant improvement from preoperative levels to the 2-year FU. In the AIS patients, this domain improved from a median of 4.08 to 4.57 ($p < 0.001$), in the spondylolisthesis patients from 3.17 to 4.29 ($p < 0.001$), and in the SK group from 4.25 to 4.57 ($p = 0.03$), respectively.

Ninety-two (46.7%) patients had a preoperative SRS pain score under 4 (62 [42.5%] AIS, 5 [27.8%] SK, and 25 [75.8%] spondylolisthesis). Fifty-one (28.7%) patients had an SRS pain score under 4 at six months after surgery (AIS 35, SK 2, and 14 spondylolisthesis). At two years after the procedure, 39 (23.2%) patients had

an SRS pain domain score under 4, of whom 27 (21%) were AIS, 3 (20%) were SK, and 9 (36%) were spondylolisthesis patients.

The patients with spondylolisthesis had the lowest SRS pain scores (median 4.29 [Q1:3.57, Q3:4.86]) at two years after surgery in comparison to AIS (median 4.57 [Q1:4.07, Q3:4.71]) ($p = 0.043$) and SK (median 4.57 [Q1:4.00, Q3:4.71]) ($p = 0.049$) patients. At the two-year FU, there was no statistically significant difference in the SRS pain scores between the AIS and SK patients ($p = 0.46$). Age, gender, BMI, surgical time, blood loss during the operation, NSAIDs, or preoperative pain were not related to more chronic postoperative pain in patients.

Two years after PSF, higher self-image scores in AIS patients had a strong correlation to a lower incidence of persistent postoperative pain ($p < 0.001$), a positive correlation in self-image and pain scores. The correlation between self-image and pain was not seen in the other groups. The median SRS-24 total scores preoperatively were 3.33 (Q1:3.00, Q3:4.13) in spondylolisthesis, 4.13 (Q1:3.80, Q3:4.40) in AIS, and 4.23 (Q1:3.73, Q3:4.27) in SK patients. There was statistically significant improvement in the SRS-24 total scores during the two-year FU in spondylolisthesis patients ($p = 0.001$), but not in AIS or SK patients. Two years after surgery, there were no statistically significant difference in SRS-24 total scores between the three groups.

SRS-24 self-image scores improved after surgery during the two-year FU in all patient groups. There was a significant positive correlation between preoperative pain and self-image scores in SK patients ($p = 0.04$), whereas there was no significant correlation between preoperative pain and self-image scores in AIS ($p = 0.06$) and spondylolisthesis patients ($p = 0.59$).

6 Discussion

The purpose of this thesis was to improve perioperative management of adolescent patients undergoing PSF surgery. AIS, SK, and spondylolisthesis are long-term diseases and affect young people throughout their lives. The aforementioned diseases affect not only children and adolescents but also their parents, causing increased stress and anxiety for them as well (Motyer et al. 2021). AIS, SK, and spondylolisthesis patients have more pain compared to healthy peers, and there is also a psychological burden due to the diseases. It is important to increase these patients' quality of life and employment and to prevent marginalisation. The cost of operative treatment is increasing (Vigneswaran et al. 2015), and there is also a financial reason to develop the treatment protocol of these patients. There is a lack of studies on whether surgery is cost-effective in preventing marginalisation and increasing employment. Studies have shown that PSF improves the health-related quality of life in AIS, SK, and spondylolisthesis patients (Helenius et al. 2019; Tsirikos et al 2021; Virkki et al. 2021; Bourassa-Moreau et al. 2018) and thus could be cost-effective, at least from an individual perspective.

In Finland, there is a good school screening system for adolescent scoliosis, and because of early diagnosis, conservative treatment is possible for all patients to prevent the curve progression and to reduce the need for expensive surgical treatment (Helenius I. 2020). In Denmark, the screening for scoliosis has been stopped, which is why the patients visiting a specialised doctor now have more curved backs than previously (Helenius I. 2020). Since a school screening system finds several scoliosis patients and makes overdiagnoses, fortunately most of the patients do not need treatment and can be managed under follow-up.

Multimodal analgesia and ERAS protocols are nowadays common after all surgical procedures in children and adults as well as in PSF surgery in adolescence. Peripheral blocks, such as erector spinae blocks, are new parts of multimodal analgesia and are being researched. A new surgical technique for AIS is spinal tethering, where surgery is performed with a videoscope through the chest cavity, screws are attached to vertebrae, and a cable is stretched between the screws. Spinal tethering is suitable for only under 10% of AIS patients, since there needs to be enough growth left to correct remaining curvature. A multidisciplinary approach is

needed for enhanced recovery, and the idea is to improve outcomes of surgery by an evidence-based protocol (Gadiya et al. 2021). ERAS protocols include many aspects of perioperative treatment. The first study aimed to improve multimodal analgesia by adding pregabalin with the intent to decrease opioid adverse effects and chronic postoperative pain. The second study of this thesis aimed to reveal predictors of POUR, as the condition is known to increase financial costs and length of hospital stay (Baldini et al. 2009; Boulis et al. 2001; Altschul et al. 2017). To improve perioperative care and multimodal analgesia, we need to know the predictors of acute and chronic pain. Therefore, the third part of this thesis aimed to find predictors of acute and chronic pain after PSF in adolescent patients.

6.1 Strengths and limitations

Study I was a randomised, double-blinded, placebo-controlled single-centre trial with a homogenous group of adolescents undergoing PSF. The Turku University Department of Pharmacy manufactured the study drugs according to a predetermined randomisation list. Surgeons, patients, parents, and investigators were all blinded to group assignment. All patients were operated by two experienced orthopaedic surgeons. Another strength of the study was that there were no dropouts during 2 years of FU. One limitation of the study was a relatively small cohort size. Although a bigger sample size might detect smaller differences between study groups, the difference would scarcely be clinically relevant.

In studies II and III, prospectively collected data from a consecutive series of adolescents undergoing PSF in the Turku University Hospital between years 2010 and 2020 was analysed. One of the limitations was that this prospectively collected data was studied retrospectively. All of the operations were performed by two experienced orthopaedic spinal surgeons. In study II, the data included a substantial cohort of uniform AIS patients – these patients are generally in good health and should not have any issues with urinary bladder function. Depending on the clinical condition of the patient, the urinary catheter was regularly withdrawn in the morning of postoperative day 2–4. This procedure involved recording any voiding issues and measuring the amount of urine that was still in the bladder after the initial void. The most common reason for spinal fusion in adolescents is AIS, whereas only a very small percentage of children with spondylolisthesis and those with SK actually require surgery. As a result, there were considerably more patients in the AIS group than in the SK and spondylolisthesis groups in study III (158 AIS patients, but only 19 SK and 36 spondylolisthesis patients). A common lack in studies of children and adolescents is a small sample population and a retrospective analysis of data, as also in our studies.

Perioperative fluid management was not standardised in the studies, and there is no exact data on it. However, the anaesthetic management of all patients was performed by a small group of paediatric anaesthesiologists, implementing a restrictive fluid management principle. Perioperative fluid management could have an impact on POUR, and the unavailability of data on perioperative fluid management is a limitation of study II. A study by Altschul et al. (2017), however, found no statistically significant increased incidence of POUR with intraoperative fluid administration. Perioperative fluid management can cause overdistension of the bladder, especially in patients under anaesthesia, which inhibits detrusor function (Baldini et al. 2009) and might increase the risk of POUR. In our study, all operated AIS patients had a urinary catheter, so there should not have been any overdistension of bladder in patients under anaesthesia. Pain management was not standardised in studies II and III, and some of the patients had oxycodone PCA, while others were administered IV and oral oxycodone after the operation. The amount and type of NSAIDs was not standardised in studies II and III. The SRS-24 questionnaire is disease specific and designed for scoliosis patients. In study III, pain assessment was done in every patient with the SRS-24 questionnaire, which is designed for AIS patients but has been used also for other spinal surgery patients (Virkki et al. 2020; Helenius et al. 2005).

6.2 Pregabalin and persistent postoperative pain

Multimodal analgesia was developed to improve analgesia, to minimise opioid adverse effects, and to enhance recovery. Opioid consumption has increased considerably in the world, especially in the United States, where there is an opioid crisis with an increasing amount of opioid addiction and abuse. This is a result of a liberal approach to opioid prescription by physicians, due to which there are now a considerable number of opioid dependent citizens in all social classes. Multimodal analgesia consists of many parts, including medical treatment as well as patient education. Gabapentinoids are considered as a part of multimodal analgesia, although the literature both supports and discourages their use for this purpose (Chou et al. 2016; Helenius et al. 2020; Lee et al 2020; Rusy et al. 2010).

In our study, pregabalin did not statistically or clinically significantly affect opioid consumption or opioid adverse effects after PSF surgery or persistent postoperative pain. Based on our study, there is no reason to include pregabalin in multimodal analgesia for adolescent patients after PSF surgery. Based on our research and current knowledge of other studies, pregabalin should not be administered routinely in children for postoperative pain management. An exception to use pregabalin as a part of postoperative multimodal analgesia after PSF might be in spondylolisthesis patients due to the risk of neuropathic pain after surgery, but this

still requires further studies. The use of pregabalin as a part of multimodal analgesia in children is very sparce (Egunsola et al. 2019), and it is not used in our hospital nowadays. Pregabalin has previously been used after surgery as a part of multimodal analgesia in our university hospital in urology patients, artificial joint surgery patients, and adolescent patients undergoing PSF surgery. Currently, the use of pregabalin in our hospital in previously mentioned patients has been discontinued, as there is no evidence of its benefits and many patients experienced pregabalin adverse effects (fatigue, dizziness, and sedation).

In our study, perioperative pregabalin did not decrease postoperative opioid consumption 48 hours postoperatively or persistent pain 2 years after the operation compared to placebo. The study showed that in both groups, the SRS-24 pain domain score improved significantly 2 years after surgery, indicating that PSF reduces back pain in adolescent patients and supports surgical management.

6.3 Postoperative urinary retention

There is a lack of exact definition of POUR, and therefore the incidence of POUR varies greatly between studies. POUR is multifactorial and the aetiology is unknown. Male gender, longer operation time (Keskinen et al. 2018; Knight et al. 2020), and opioid consumption (Baldini et al. 2009; de Boer et al. 2017) are predicting factors of POUR. POUR increases costs and LOS and should be screened and treated when necessary.

In the second study of this thesis, we revealed that every third AIS patient had POUR after PSF. The predictors of POUR in our study were higher opioid consumption in the catheter removal day, higher total opioid consumption during hospital stay, male gender, higher weight, and longer operation time. PSF surgery has effects on the spinal cord and nerve roots, and there is always a risk of special complications when correcting the spinal deformity. The correction of spinal deformity as a risk factor for POUR is unclear. In our study, there was no difference in POUR depending on the number of fusion levels or if the fusion extended into the lumbar spine. Replacing the pedicle screw intraoperatively did not indicate a higher incidence of POUR in our study. According to this finding, direct mechanical compression may not be a major factor in the formation of POUR. Prostate hyperplasia has shown to increase the risk of POUR (Altschul et al. 2017; Golubovsky et al. 2018). Our study revealed that male gender is a predictor of POUR. Patients in our study were adolescents and should not have prostate hyperplasia, thus another factor is needed to explain the greater incidence of POUR in males. Alpha-blockers have been shown to be beneficial in reducing the incidence of urinary retention after surgery both in males and females (Chapman et al. 2021;

Pomajzl and Siref 2022). More research is needed before alpha-blockers can be recommended for children to prevent or treat POUR.

6.4 Predictors of acute and chronic postoperative pain

One of the risk factors for chronic pain after PSF in AIS patients is preoperative pain (Hwang et al. 2020; Bastrom et al. 2013; Connelly et al. 2014; Bailey et al. 2021); other risk factors are child anxiety (Chidambaran et al. 2017; Connelly et al. 2014; Bailey et al. 2021), longer operative time (Chidambaran et al. 2017; Helenius et al. 2021), and poor self-image (Landman et al. 2011). The development of chronic postoperative pain appears to be multifactorial (Seki et al. 2018). Preoperative pain as a risk factor for chronic pain after surgery might explain why spondylolisthesis patients had a higher incidence of chronic pain after PSF compared to AIS and SK patients. In our study, spondylolisthesis patients had the longest operative time, which has also been shown to increase the risk of chronic pain.

Multimodal analgesia is considered to be an important part of reducing chronic pain, but the optimal standard multimodal treatment protocol for adolescent spinal surgery is still not determined (Lee et al. 2020; Ricciardelli et al. 2020). Acute postsurgical pain has shown to predict chronic pain in adolescents (Chidambaran et al. 2017; Ocay et al. 2020), but the study by Li et al. (2019) found that opioid consumption after surgery did not significantly predict pain 6 months after surgery. In our study, spondylolisthesis patients consumed less opioids after PSF compared to AIS and SK patients but still had more chronic pain. Pain catastrophizing is a recently acknowledged risk factor for both pre- and postoperative pain in adolescents undergoing surgery for AIS (Ramo et al. 2022).

Patients with AIS, SK, or spondylolisthesis require PSF for different reasons (Helenius et al. 2008; Bourassa-Moreau et al. 2019). Surgery is performed on patients with AIS or SK for spinal deformity and with spondylolisthesis primarily for low back and/or radicular pain. The nature of surgical methods varies as well. Deformity correction requires several levels of spinal fusion, whereas spondylolisthesis can be reduced or stabilised with one or two levels of spinal fusion, with or without pelvic instrumentation. Ideally, nerve root manipulation is avoided during surgery for AIS and SK patients. Patients with spondylolisthesis require wide nerve root decompression and retraction. Additionally, reducing high-grade spondylolisthesis increases the probability that the spine may fuse but also increases tension on the L5 nerve roots (Longo et al. 2014). According to our research, the degree of intraoperative tissue damage (several levels of fusion) predicted rather well acute postoperative pain and the need for opioids following surgery. The spondylolisthesis patients had less acute postoperative pain compared to the AIS and

SK patients, as the surgery required smaller incision and tissue damage. However, the spondylolisthesis patients had more persistent pain due to disease pathology.

Acute postoperative pain can be reduced by using ultrasound guided peripheral blocks as erector spinae block as a part of multimodal analgesia. Treatment and prevention of persistent postoperative pain in adolescent as in adults is limited according to current knowledge, and further studies are required. Several studies have found predictors of persistent pain, but there is still a paucity of persistent pain treatment and prevention. Acute pain may be reduced with mini-invasive surgery, such as spinal tethering in AIS patients. A prospective randomised trial of peripheral blocks, such as erector spinae blocks, with a long-acting liposomal bupivacaine on paediatric patients undergoing PSF would be ideal in the future.

The incidence of persistent postoperative pain after PSF varies between studies due to differences in pain measurements methods and time periods. The incidence of persistent postoperative pain was 14% in the study by Helenius et al. (2019), where the criterion of persistent postoperative pain was a score of over 3/9 in SRS-24 question one at 5 years after surgery. On the contrary in the study conducted by Chidambaran et al. (2017), the incidence of chronic postoperative pain one year after PSF was 42% and the criterion was pain over 3/10 in a numerical rating scale. Several different pain measurement methods and specific questionnaires (for example the SRS-24 questionnaire) are used for different patient groups around the world. To be able to reliably compare studies with each other, there is a need for validated surveys and the time points at which they are completed. There should also be a precise and comprehensive definition of persistent postsurgical pain after PSF in adolescents, so that the studies could be properly compared. The type of pain (nociceptive local, neuropathic) should also be specified in the studies. The perception of pain, especially persistent pain, is very subjective and is influenced by numerous psychological factors, therefore clinical research on the issue is challenging. In their study, Sanders et al. (2018) found that every third AIS patient had clinically significant emotional or behavioural problems, which might also affect the experience of pain.

6.5 Clinical implications

According to this thesis, there is no reason for pregabalin use after PSF in AIS patients, as it does not impact the incidence of persistent postoperative pain. As previously shown (Helenius et al. 2020) in the same patient group, pregabalin did not have an effect on the acute postoperative pain nor opioid consumption after surgery. Pregabalin has several commonly known adverse effects and does not appear to be beneficial in adolescents after PSF surgery. There are studies for and against pregabalin use for postoperative pain management in adolescents and adults.

It might be a good part of multimodal analgesia in certain patients, but according to current knowledge, not reasonable to include in multimodal analgesia for all patients after surgery. Due to our research, the paediatric and adolescent surgical department of the Turku University Hospital has discontinued administering pregabalin to adolescent patients undergoing PSF surgery. Due to current knowledge, the use of postoperative pregabalin is continuously decreasing in the Turku University Hospital.

In study II, we revealed that opioid consumption during catheter removal day increases the risk of POUR. More studies are needed to improve multimodal analgesia to reduce opioid amount and the adverse effects of opioids, such as POUR. In clinical practice, opioid consumption should be kept to a minimum on the urinary catheter removal day by using multimodal analgesia with paracetamol, NSAIDs, and possibly with small doses of ketamine; and the patients should be screened with an ultrasound to detect POUR and prevent its complications. In our study, the patients with urinary retention had longer LOS, which causes physical and psychological harm to patients and financial costs to society.

Spondylolisthesis patients have more preoperative and persistent postoperative pain after PSF than AIS and SK patients, as revealed in our study III. The pain is reduced in AIS, SK, and spondylolisthesis patients two years after PSF, but spondylolisthesis patients still have more persistent pain compared to AIS and SK patients. According to previous findings, the persistent postoperative pain is not associated with larger tissue damage due to surgery but instead with the disease pathology. Spondylolisthesis patients might benefit from specific multimodal analgesia before and after surgery, including psychotherapy, but more studies are needed for determining this.

Unnecessary medications should be avoided. According to this thesis, pre-emptive pregabalin is not indicated for paediatric spinal surgical patients. Urinary bladder dysfunction is common and should be screened and treated in this patient group. Fortunately, the majority of patients recover with transient urinary tract catheterisation. Further studies should investigate methods to reduce the postoperative opioid consumption, such as using paraspinal blocks. Children and adolescents can be informed about the positive effects of PSF not only on the deformity itself but also on back pain. Patients with persistent pain should be identified early to allow effective multidisciplinary management.

7 Summary/Conclusions

The results of this thesis lead to the following conclusions:

1. Perioperative pregabalin did not affect the incidence of chronic postoperative pain 2 years after posterior spinal fusion in adolescents. Our study does not support the use of pregabalin in a multimodal pain management regimen.

2. The incidence of postoperative urinary retention after posterior spinal fusion in adolescent idiopathic scoliosis patients was 33%. Higher total opioid consumption during hospital stay and especially higher opioid consumption during catheter removal day were associated with the increased risk of postoperative urinary retention in adolescent idiopathic scoliosis patients undergoing posterior spinal fusion surgery. Other predictors of postoperative urinary retention were male gender, longer surgical time, and higher body weight.

3. Surgical invasiveness is associated with more postoperative acute pain, as patients with adolescent idiopathic scoliosis and Scheuermann kyphosis required significantly more opioids than the patients with spondylolisthesis after surgery. In contrast, spondylolisthesis patients have more chronic pain after surgery compared to adolescent idiopathic scoliosis and Scheuermann kyphosis patients, suggesting that disease pathology is more predictive of long-term pain. However, posterior spinal fusion reduces pain two years after surgery in adolescent idiopathic scoliosis, Scheuermann kyphosis, and spondylolisthesis patients.

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